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*APPLICATION NUMBER:*

**125370**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Review Completion Date February 18, 2011

Established Name Belimumab  
(Proposed) Trade Name Benlysta<sup>®</sup>  
Therapeutic Class Monoclonal Anti-BLyS Antibody  
Applicant Human Genome Sciences, Inc.

Formulation Intravenous  
Dosing Regimen 10 mg/kg (b) (4)  
intravenous (IV) infusion  
Indication Treatment of active, autoantibody-  
positive systemic lupus  
erythematosus (SLE)  
Intended Population Adults

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval for this biological licensing application for belimumab as a treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. The data contained in this application is sufficient to support a finding of efficacy and safety for belimumab when administered as a dosing regimen of 10 mg/kg via intravenous infusion every 2 weeks for the first 3 doses and at 4-week intervals thereafter.

### 1.2 Risk Benefit Assessment

The efficacy of belimumab as a treatment (b) (4) in adult patients with active, autoantibody-positive SLE on standard therapy was assessed in two adequate and well-controlled dose comparison trials, Studies 1056 and 1057, that evaluated the efficacy of two dosing regimens of belimumab when administered as 1mg/kg or 10 mg/kg IV infusions on Days 0, 14, and 28 and then every 28 days compared to placebo in 1,684 patients. In both of these studies, patients treated with belimumab 10mg/kg had higher rates of response than placebo patients as assessed by the composite endpoint, the SLE Responder Index (SRI) while a higher rate of response for the belimumab 1mg/kg group was demonstrated in only Study 1057. Additional support for the modest primary efficacy findings observed in these trials was provided by the results from the prespecified sensitivity analyses and post hoc analyses that employed higher reductions in the SELENA SLEDAI thresholds ( $\geq 5$  through  $\geq 10$ ) used in calculating the composite SRI response score. However, the results of numerous major and ancillary secondary endpoints were less robust, and at times, discordant to those of the primary analysis resulting in a lack of a consistent dose-response effect, the lack of persistence of efficacy as manifested at the Week 76 time point, the inability to demonstrate a consistent and clinically meaningful reduction in concomitant corticosteroids or disease flares, as well as a lack of efficacy in black patients. Other supportive evidence for belimumab's efficacy as add-on therapy in patients with SLE in these trials comes from the higher use of prohibited medications by placebo subjects over the course of these trials as compared to the belimumab treatment groups and from other post hoc exploratory analyses of treatment effect on various organ system manifestations of SLE that appeared to be suggestive of a treatment benefit with belimumab.

Specific safety concerns raised during the review of safety included a higher incidence of deaths, a higher rate of serious adverse events and serious infections, and an increase in psychiatric adverse events that included depression and suicide in patients

treated with belimumab. The types of deaths associated with belimumab treatment were consistent with immunosuppressive therapies (e.g., infection) and with the risks related to underlying and concomitant medical conditions (e.g., cardiovascular disease). Many of the serious adverse events in the belimumab safety database were related to underlying disease activity or were the result of infections. An increase in the risk for serious infections is an expected finding for an immunosuppressive agent such as belimumab that targets B cells, however no associated increases in infections or serious infections in belimumab-treated patients with treatment-associated reductions in immunoglobulins as compared to placebo patients was observed. The increase in psychiatric adverse events including depression and suicidality was an unexpected finding. However, a retrospective assessment of suicidality was conducted by the Applicant in support of the belimumab's safety profile showed no difference in the primary safety population with regard to suicidal behaviors. Additionally, an internal consultant for the Agency found no convincing evidence of a signal for belimumab-related psychiatric experiences on review of these data. The overall risk for anaphylaxis and hypersensitivity reactions associated with belimumab appears to be low; however, this risk may be underestimated due to a number of factors including the high use of concomitant corticosteroids by study subjects, the inconsistent use of prophylactic premedications and the lack of an acceptable methodology to classify these types of events by the Applicant. A number of study subjects also became pregnant while participating in belimumab trials. Review of the pregnancy data contained in the safety database did reveal an increase in fetal loss that may have been due to the presence of anti-cardiolipin antibodies that are known to cause spontaneous abortions in SLE patients.

The heterogeneity in clinical manifestations and disease severity of SLE in addition to the risk for morbidity associated with untreated disease has made it difficult to evaluate the efficacy of potential treatments for this disease. Although a clinically meaningful difference has yet to be determined for the SRI, it represents both a statistically and clinically rigorous endpoint to achieve. In view of this and the inconsistent dose-response effect, the marginal efficacy demonstrated in the pivotal Phase 3 trials, and the various safety concerns (e.g., death, serious infections, serious adverse events and depression/suicidality) identified on review of the safety database submitted in support of belimumab, the risk/benefit assessment favors the 10 mg/kg belimumab dosing regimen administered as an intravenous infusion every 2 weeks for the first 3 doses and at 4-week intervals thereafter.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

The Applicant submitted a Risk Evaluation Minimization Strategy (REMS) for belimumab in their original submission and a revised REMS in an amendment dated November 23, 2010 based on discussions with the Agency. The goals of the Applicant's

proposed revised plan are to inform patients about the serious risks (e.g., risk for death, infections, anaphylaxis, infusion reaction, and psychiatric adverse events including suicide) associated with the use of belimumab for intravenous infusion via a Medication Guide which the Applicant plans to dispense in accordance with 21 CFR 208.24. Since neither a communication plan or elements to assure safe use (ETASU) have been determined to be needed for belimumab, and the proposed Medication Guide does not constitute a REMS but is considered part of the product's labeling as per the February 2011 Draft Guidance for Industry: Medication Guides –Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), no postmarketing risk management activities should be required for belimumab at the present time. However, this requirement may be reconsidered if future postmarketing evidence identifies a safety risk that cannot be managed by labeling.

#### 1.4 Recommendations for Postmarket Requirements and Commitments

As per provisions of the Pediatric Research Equity Act (PREA), the Applicant has submitted a request for a partial waiver not to conduct a trial in children less than 5 years of age on the grounds that studies in children < 5 years are highly impractical due to the low incidence of SLE in this age group as well as a request for a deferral to conduct a study in children ages  $\geq 5$  through  $\leq 17$  years old with SLE. Pursuant to the latter request, this submission contained a proposed pediatric development plan to evaluate the safety and efficacy of belimumab in the pediatric population (b) (4)

[REDACTED]

Based on discussions held at the October 6, 2010 meeting of the Pediatric Review Committee (PeRC), it was agreed that the Applicant's proposed partial waiver for studies in infants and children < 5 years of age and deferral for pediatric studies in children  $\geq 5$  through  $\leq 17$  years of age was acceptable.

In order to better elucidate the safety signals that were identified during the Agency's review of this application, the Applicant should be required to conduct a randomized, controlled, postmarketing safety study to evaluate adverse events of special interest

that include mortality, malignancy, serious and opportunistic infections and depression/suicidality. Additionally, they should be required to submit safety data collected from the ongoing, open-label continuation studies LBSL99, 1066, and 1074 which have a current enrollment of 1,293 patients in support of the product's long term safety. Since SLE affects young women of childbearing potential, the Applicant should also be required to conduct a postmarketing pregnancy registry to further explore belimumab's effects on pregnancy outcomes. In view of belimumab's B-cell modulating effects and the inconclusive data generated from the Applicant's small vaccination substudy, they also need to conduct another study that will assess belimumab's impact on host responses to vaccinations. As a result of the discussions held at the belimumab Arthritis Advisory Committee meeting in November 2010, the Applicant should also be required to conduct a pilot study to assess belimumab's efficacy and safety when administered with concomitant immunosuppressant therapy as a treatment for lupus nephritis as well as a another study to further explore its efficacy and safety in black patients with SLE.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

The established name of the subject product of this application is belimumab and the proposed trade name is Benlysta®. The established name will be used in this review to refer to the product. Belimumab is supplied as a sterile, preservative-free, white to off-white lyophilized powder for intravenous infusion in two, single-use vial configurations with latex-free rubber stoppers. After reconstitution with Sterile Water for Injection, each vial will deliver belimumab at 80mg/mL: a 400 mg/vial with a 5 mL deliverable volume and a 120mg/vial with a 1.5 mL deliverable volume along with 0.16 mg/mL citric acid, 0.4 mg/mL, polysorbate 80, 2.7 mg/mL sodium citrate, and 80 mg/mg/mL sucrose, with a pH of 6.5.

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

Belimumab has a typical antibody structure, composed of two identical H chains and two identical L chains, with a molecular weight of approximately 147 kDa. There is a typical heterogeneity at the H-chain N-terminus due to cyclization of glutamine to pyroglutamic acid and at the C-terminus of the H chain due to incomplete cleavage of

the C-terminal lysine. This leads to a heterogeneous charge profile which does not impact the activity of belimumab. Belimumab also contains a typical heterogeneous N-linked glycosylation profile in the CH2 domain of the H chain. It is expressed in a NSO mouse myeloma cell line and manufactured using typical bioreactor and purification methods for therapeutic monoclonal antibodies.

The proposed indication for belimumab is for the (b) (4) adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard of care.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists the treatments that are currently approved and available for the treatment of SLE:

Table 1 – Currently Available Treatments for the Treatment of SLE

Product	Year of Approval	Indication
Aspirin	1948	Treatment of arthritis and pleurisy of systemic lupus erythematosus
Prednisone	1955	During an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus
Hydroxychloroquine	1955	Treatment of discoid and systemic lupus erythematosus

The effectiveness of these agents varies depending on organ system disease involvement and is also limited by associated toxicities (e.g., hydroxychloroquine causes retinal and cornea deposits, high doses of aspirin cause gastrointestinal bleeding and tinnitus, and prednisone increases the risk for infections and causes glucose intolerance, osteoporosis, glaucoma, hypertension, osteonecrosis, etc...). Hydroxychloroquine is the most common immunomodulating therapy used as a treatment for mild SLE disease manifestations including constitutional, cutaneous, and musculoskeletal. Corticosteroids (prednisone) are used for treatment of both mild SLE disease manifestations (low doses) as well as severe organ involvement such as nephritis, hematologic abnormalities, and central nervous system (CNS) disease (high doses). However, not all patients respond adequately to corticosteroids or can tolerate dose dependent toxicities associated with this drug class. Due to the paucity of approved drugs for this autoimmune disease current standard of care involves the use of off-label immunosuppressive therapy.

## 2.3 Availability of Proposed Active Ingredient in the United States

This product is an unapproved new molecular entity under development for licensing by the Applicant and is currently not marketed in this country.

## 2.4 Important Safety Issues With Consideration to Related Drugs

No other members of the pharmacologic class are currently marketed.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

BBIND 9970 was originally opened in October 2001 in CBER prior to being transferred to CDER's Division of Anesthetic, Analgesics and Rheumatology Products in October 2005. In March 2010, this application was subsequently transferred to the Division of Pulmonary, Allergy and Rheumatology Products. The following are highlights of the regulatory activity that occurred during the development program for belimumab.

- March 26, 2003 – Fast Track Designation granted.
- February 9, 2004 – Acceptance into Continuous Marketing Application (CMA) Pilot 2 Program.
- July 5, 2006 – End-of-Phase 2 (EOP2) meeting with Applicant to discuss the results of the failed Phase 2 study, LBSL02, as well as design elements for the future Phase 3 trials. The following items summarize the clinical issues that were addressed and understandings reached between the Applicant and the Division at that time:
  - The Division stated that two Phase 3 studies would be required to support BLA filing
  - Agreements reached on the proposed patient population, doses to be studied (e.g., 1 mg/kg and 10 mg/kg), primary efficacy endpoint, approach to scoring and measuring proteinuria for the purposes of SELENA SLEDAI and BILAG disease activity, the structure and frequency of the Data Monitoring Committee (DMC) meetings and the statistical analysis plan for the Phase 3 primary efficacy endpoint
  - The need to control concurrent background medications in the Phase 3 trials was discussed
  - The Division agreed that the proposed size of the clinical safety database would be sufficient to support BLA filing
  - Pediatric studies could be deferred until after the Phase 3 studies in adults were completed
- July 28, 2006 – Written correspondence submitted by the Applicant providing proposals to outstanding items discussed at the EOP2 meeting:
  - Proposal for additional control of background medications
  - Proposal to include secondary endpoints to evaluate using the percentage of subjects with no new 1A or 2B BILAG domain scores compared to baseline over specified intervals
  - Proposal to stratify patients based on race/ethnicity

The Division informed the Applicant that these proposals were acceptable on August 21, 2006.

- September 6, 2006 – Applicant requested Special Protocol Assessments (SPAs) for Studies 1056 and 1057.
- October 19, 2006 – SPA agreements reached for 1056 and 1057 as follows:
  - For both Phase 3 studies, the Division and Applicant agreed to the proposed patient populations, guidelines for concomitant medications, sample size, stratification variables, the primary efficacy endpoint and statistical analysis plans
  - The SPA agreement letter also stated that positive results from both the 76-week (Study 1056) and 52-week (Study 1057) pivotal Phase 3 trials would be required to support a treatment indication for SLE
- April 10, 2009 – Conditional acceptance of Applicant’s proprietary name request (Benlysta®)
- March 8, 2010 – Meeting to discuss BLA submission format, including presentation of safety data. The following items summarize the understandings reached between the Applicant and the Division at that time.
  - The Division agreed that the nonclinical and clinical results appeared sufficient to support the filing of a BLA for belimumab treatment of patients with SLE
  - The Division reiterated the expectation that Week 76 efficacy data should be submitted in the BLA
  - Additional agreements reached regarding data cut point and content of the 120-day safety update and inclusion of datasets and listings for the Division of Scientific Investigations

## **2.6 Other Relevant Background Information**

Similar agreements regarding the pivotal Phase 3 protocols and statistical analysis plans for the primary endpoint of these trials were reached with the European Medicines Agency (EMA). According to the Applicant, no other significant regulatory actions have been instituted outside of the United States for belimumab.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

Human Genome Sciences’ submission was appropriately organized to allow information to be reviewed in an acceptable manner. The Applicant’s responses to all of FDA’s requests were timely and well organized.

### **3.2 Compliance with Good Clinical Practices**

According to statements included in the reports for the pivotal trials, 1056 and 1057, the Applicant certified that these studies were conducted in compliance with the following: good clinical practice standards as outlined in the Declaration of Helsinki or the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, with the institutional review board regulations as per 21 CFR (56), and the informed consent regulation as per 21 CFR (50).

The Division of Scientific Investigation (DSI) inspected a total of 4 foreign clinical sites in Austria (1 site), Czech Republic (1 site), and Taiwan (2 sites) that participated in the pivotal Phase 3 trials. Although they did not find any regulatory violations over the course of their audits of the 2 sites in Taiwan (TW010 and TW011), minor regulatory violations were noted for the sites in Austria (AT001) and the Czech Republic (CZ002). However, the DSI medical officer who conducted these inspections stated in his report that these violations were unlikely to have had an impact on data integrity and patient safety. The final conclusion by the inspecting DSI medical officer was that the data generated by these inspected sites appears to be reliable to support this application. Audit of the Applicant revealed no discrepancies or regulatory violations in terms of oversight and monitoring of the pivotal Phase 3 studies, test article accountability, financial disclosures, qualifications of investigators and site monitors, and adverse event reports.

### **3.3 Financial Disclosures**

The financial disclosure form signed by the Applicant certified that no financial arrangements had been made with any of the principal investigators or sub investigators involved with the clinical studies where outcomes affected compensation as defined in 21 CFR 54.2(a). Additionally, none of the principal investigators or sub investigators reportedly had a proprietary interest in this product or a significant equity in Human Genome Sciences, Inc., which is commercially developing belimumab for licensing in this country as described in 21 CFR 54.2(b).

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

According to the OBP/Division of Monoclonal Antibodies (DMA) reviewer a site inspection of the manufacturing facility was conducted in late September through early

October 2010 that did not result in the identification of any approvability issues. Product release specifications, stability protocol and data supported by 36-month expiry are acceptable. An acceptable comparability protocol is also in place for comparison of belimumab drug substance made with (b) (4). Based on the CMC data submitted in support of this application, the DMA reviewer is recommending that this application be approved with a 36-month expiry dating period based on full scale production data as well as a post marketing requirement for the Applicant to develop improved immunogenicity assays.

## 4.2 Clinical Microbiology

The Office of Compliance/DMPQ/MAPCB/BMT reviewers have stated that the CMC drug product part of the application generally appears adequate from the sterility assurance and product quality microbiology perspective and recommend approval with the following PMRs:

- Submit data supporting microbial control for the (b) (4) lifetime studies

(b) (4)

- Qualify the capper and revalidate the integrity of the drug product container closure
- Provide quantitative data to demonstrate (b) (4)

## 4.3 Preclinical Pharmacology/Toxicology

In support of belimumab's safety profile, the Applicant submitted a complete pharmacology/toxicology package for this BLA. The preclinical Pharmacology/Toxicology reviewer of this application also recommends approval of this application based on the data submitted in support of the belimumab. The belimumab preclinical program included 28-day, 3, and 6-month, repeat dose, IV toxicology studies as well as reproductive toxicology studies conducted in monkeys. The most common toxicity observed in the monkey toxicity studies was gut associated lymphoid tissue (GALT) depletion, mesenteric and mandibular lymph node hyperplasia, thyroid follicular cell degeneration and chronic splenic abscess in the 28-day repeat dose toxicity study. In the 3 and 6-month toxicity studies spleen and lymph node depletion were noted. Spleen and lymph node depletion are related pharmacodynamic effects of belimumab. No animal deaths were observed in these studies. However, fetal and infant animal deaths were observed in the monkey reproductive toxicology studies in both the control animals (3 fetal deaths) as well as in the low (6 fetal and 2 infant deaths) and high (3 fetal and 1 infant deaths) dose belimumab groups. These fetal losses and deaths could

not be explained although one dam was found to have high antibody levels to the product.

Since belimumab is a therapeutic biologic protein, special toxicology studies were also conducted that included a tissue cross reactivity study in human tissue, a rabbit hypersensitivity study, and IV and SC immunogenicity studies in monkeys. Since high levels of belimumab antibodies were noted in both mice and rats, a carcinogenicity study could not be performed which is acceptable.

#### 4.4 Clinical Pharmacology

The Applicant submitted a complete clinical pharmacology package in support of this BLA. Based on their review of the data submitted in support of belimumab, the clinical pharmacology and biopharmaceutics review teams are recommending approval of this application with the caveat that any future studies conducted by the Applicant should enroll greater numbers of black patients with varying levels of disease activity so that clinical outcomes in this racial group can be better elucidated.

##### 4.4.1 Mechanism of Action

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

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

##### 4.4.2 Pharmacodynamics

Belimumab decreases IgG, anti-dsDNA, and various B-cell populations [e.g., CD19+, CD20+, naïve CD20+/CD27-, activated CD20+/CD69+, plasmacytoid (CD19+20+138+) cells, short-lived plasma B-cells (CD20-/CD27 bright) plasma B-cells (CD20-/CD138+),

and the SLE B-cell subset (CD19+/CD27bright/CD38bright)], and increases in serum complement (C3 and C4), T-lymphocytes [helper T-cells (CD3+/CD4+) and suppressor T-cells (CD3+CD8+)] and memory B-cells (CD20+/CD27+). Higher proportions of belimumab treated subjects had normalization of these biomarkers than placebo in the pivotal Phase 3 trials. Additionally, these changes were seen as early as Week 8 of treatment and were sustained through Week 52. According to the biopharmaceutics reviewer, the changes in C3, C4 and naïve B-cells were significantly correlated with response to belimumab but did not adequately predict responses to treatment with the product.

#### 4.4.3 Pharmacokinetics

The pharmacokinetic (PK) profile of belimumab was initially assessed in study LBSL01 which was a Phase 1, single and multiple ascending-dose study that evaluated 1, 4, 10, and 20 mg/kg doses of belimumab in patients with SLE. The results from this study showed that in SLE subjects belimumab's AUC and  $C_{max}$  were dose-proportional for the dose range studied.

Based upon the population estimates of the PK model specific to 10 mg/kg dosing in the Phase 3 population (studies LBSL01, LBSL02, 1056 and 1057), belimumab's  $C_{max}$  was 313 µg/mL,  $AUC_{0-\infty}$  was 3,083 day·µg/mL, half-life was 19.4 days and systemic clearance was 3.2 mL/day/kg. Belimumab's volume of distribution at steady state was 56-80 mL/Kg. According to the clinical pharmacology reviewer, population PK analyses demonstrated that a dose adjustment is not required for age, gender, or race. Systemic clearance of the product was shown to increase with increasing weight, but the product's body-weight based dosing regimen adjusts for this effect. Studies in renal and hepatic impairment have not been conducted with the product.

No formal drug-drug interaction studies were conducted with belimumab. Since this product is a monoclonal antibody, no direct pharmacokinetic interactions with the CYP pathway or co-administered small molecular weight drugs is expected. However, results from population PK analyses showed that co-administration of drugs used to commonly treat SLE patients (e.g., NSAIDs, statins, anti-malarial medications, angiotensin pathway antihypertensives and immunosuppressants such as azathioprine, methotrexate and mycophenolate) did not affect belimumab's PK profile.

In terms of immunogenicity, the incidence of anti-belimumab antibodies was low across various clinical studies. However, the immunogenicity assay in the Phase 1 and 2 studies was not robust and the assay was also sensitive to belimumab concentrations. In the two Phase 3 trials, anti-belimumab antibodies were detected in 13% of the SLE subjects administered 1 mg/kg belimumab and 0.9% of SLE subjects administered 10mg/kg belimumab. In antibody positive subjects, the trough belimumab concentration was within the range of subjects who were antibody negative. Population analyses did not show a statistically significant effect of anti-belimumab antibodies on clearance of

the product. The clinical pharmacology reviewer concluded that the presence of antibodies to belimumab did not appear to affect the product's safety and effectiveness, however, no definitive conclusions can be made since the incidence of anti-belimumab antibodies was low.

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

As part of their clinical development program for belimumab as a treatment for SLE, the Applicant conducted a total of nine clinical trials: two Phase 1 trials (LBSL01 and HGS1006-C1058), two Phase 2 trials (LBSL02 and 1070), two Phase 3 trials (C1056 and C1057), and three ongoing open-label extension trials (LBSL99, C1066 and C1074). Key design features of these trials are summarized in Table 1, below. Studies HGS1006-C1058 and 1070, in which belimumab was administered via subcutaneous injection, are listed for completeness since this route of product administration is currently undergoing evaluation by the Applicant but is not under regulatory decision at this time. Of note, one of the two pivotal Phase 3 trials (1057) was conducted entirely outside the U.S. at 92 sites located in Asia Pacific, Latin America and Eastern Europe.

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

Study/ Objectives	Study Design; Duration; No. of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
<b>Phase 1</b>					
<b>Protocol LBSL01 Objectives:</b> 1. Assess the safety tolerability, PK/PD and immunogenicity of intravenous belimumab in patients with SLE 2. Determine the effect of belimumab on clinical disease activity, serum immunoglobulins peripheral mature B lymphocytes and plasmacytoid cells and biological markers	Multicenter, randomized, double-blind, placebo controlled, single and double dose-escalation, tolerance, safety, PK/PD and immunogenicity trial  16 sites in U.S.	Belimumab 1, 4, 10, and 20 mg/kg via intravenous (IV) infusion (single infusions administered over 2 hours or 2 infusions 21 days apart)  Placebo via IV infusion	N=70  57 subjects in Belimumab group (Cohorts 1-4 single dose: 29 subjects; Cohorts 5-8 double dose: 28 subjects )  13 subjects in placebo group	Adults age $\geq$ 18 years with SLE disease as defined by American College of Rheumatology (ACR) criteria that is active for at least 2 months prior to screening with history of measurable autoantibodies	Not Applicable
<b>Protocol HGS1006-C1058 Objectives:</b> 1. Determine the absolute bioavailability of belimumab administered via subcutaneous (SC) injection; 2. Assess the safety of SC vs IV belimumab	Multicenter, randomized, open label, parallel group, absolute bioavailability trial	Single dose of belimumab 100 mg via IV infusion over 1 hour  Single dose of belimumab 100 mg via SC injection	N=36  17 subjects in belimumab IV group  19 subjects in belimumab SC group	Healthy volunteer adults	Not Applicable

Table 2 - Key Design Features of the Belimumab SLE Clinical Development Program Trials (cont.)

Study/ Objectives	Study Design; Duration; No. of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
<b>Phase 2</b>					
<p><b>Protocol LBSL02</b>  <b>Objectives:</b>            1. Determine the safety and tolerability of belimumab in subjects with SLE; 2. Assess the efficacy of belimumab in subjects with SLE</p>	<p>Multicenter, randomized, double-blind, placebo – controlled, dose ranging, 52-week, comparative parallel group, safety, tolerability, and efficacy trial with optional 24-week extension</p> <p>57 sites in U.S. and 1 site in Canada</p>	<p>Belimumab 1, 4 and 10 mg/kg or placebo via IV infusion on Days 0, 14, 28 and every 28 days for 52 weeks of double blind portion.</p> <p>Optional 24 week extension: placebo patients switched to belimumab 10 mg/kg; others continue original dose if had satisfactory response or increased to 10 mg/kg of belimumab</p> <p>All subjects received concomitant SLE standard therapy</p>	<p>N=449</p> <p>336 subjects in belimumab group</p> <p>113 subjects in placebo group</p>	<p>Adults age <math>\geq</math> 18 years with SLE as defined by ACR criteria that is active as per SELENA SLEDAI disease activity score <math>\geq</math> 4 at screening with history of measurable autoantibodies</p>	<p>Two co-primary efficacy endpoints: 1. SELENA SLEDAI disease activity score at Week 24 and 2. Time to the 1<sup>st</sup> mild/moderate or sever flare (as defined by the SLE Flare Index) over 52 weeks</p>

**Table 2 - Key Design Features of the Belimumab SLE Clinical Development Program Trials (conti.)**

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

**Table 2 - Key Design Features of the Belimumab SLE Clinical Development Program Trials (conti.)**

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

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

## 5.2 Review Strategy

The Applicant conducted two adequate and well controlled Phase 3 trials, Studies 1056 and 1057, in support of this application which were reviewed for efficacy. Additionally, the applicant submitted the completed results from two Phase 1 trials (LBSL02 and 1058) and one completed Phase 2 trial (LBSL02), and the interim results from one ongoing open-label extension trials (LBSL99) and one ongoing Phase 2 trial (1070). This medical officer reviewed the results from the Applicant's pivotal trials (1056 and 1057) and the completed Phase 2 trial (LBSL02) for efficacy. The other trials (1058, 1070 and LBSL99) were not reviewed in support of belimumab's efficacy (b) (4)

(b) (4) in patients with active, ANA-positive SLE on standard therapy for the following reasons: LBSL99 was an open-label trial; 1058 and 1070 evaluated a different route of administration (subcutaneous injection) that is currently not under consideration for marketing; LBSL01 and 1058 evaluated doses of belimumab that were not studied in the pivotal Phase 3 trials; LBSL01, 1058, LBSL02, and LBSL99 were conducted in populations different from the patient population evaluated in the pivotal Phase 3 trials; or they (LBSL01, 1058, LBSL99 ) were designed not to evaluate the efficacy (i.e., the primary objective was safety) of the product.

The safety database included all subjects who participated in the pivotal Phase 3 trials (1056 and 1057) and the Phase 2 trial (LBSL02) as well as safety data collected from the Phase 1 and 2 studies and the open-label extension trials LBSL99, 1066, and 1076. These data will be discussed in Section 7.

### 5.3 Discussion of Individual Studies/Clinical Trials

Belimumab's efficacy as an immunomodulating agent in patients with SLE was evaluated by the Applicant in one dose-ranging, Phase 2 trial, LBSL02, and two Phase 3 clinical efficacy trials, 1056 and 1057. These trials differed in the target populations studied, primary endpoint evaluated, concomitant medication controls (as related to impacting the primary endpoint), and statistical analysis plans. Exploratory analyses of data from LBSL02 provided the basis for the design elements of the common protocol and primary endpoint utilized in 1056 and 1057 that was agreed upon by the Agency in a Special Protocol Assessment (SPA) for these trials. Although a treatment effect associated with belimumab therapy was not demonstrated for any of the primary or secondary endpoints evaluated in LBSL02, post-hoc analyses suggested that a treatment effect may have been present in the subgroup of patients who were autoantibody positive (i.e. ANA and/or anti-dsDNA), which represented 72% of the study population. Thus only autoantibody positive SLE patients were studied in the two pivotal trials 1056 and 1057.

The heterogeneity in clinical manifestations and disease severity of SLE has made it necessary to utilize extensive and somewhat complicated disease activity measurement instruments, each of which has strengths and weaknesses. The British Isles Lupus Activity Group (BILAG) index and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) were the two validated disease activity assessment tools utilized by the common protocol for Studies 1056 and 1057.

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 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.<sup>1</sup> A clinically meaningful difference has been reported to be improvement of 6 points or worsening of 8 points.<sup>2</sup> 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.

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

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

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<sup>1</sup>Abrahamowicz et al. J Rheumatol 1998; 25(2):277-284

<sup>2</sup>ACR Ad Hoc Committee on SLE Response Criteria, Arthritis & Rheum, November 2004, 50(11):3418-3426

The SELENA-SLEDAI also contains an assessment of the patient's general healthy status called the Physician Global Assessment (PGA). This is a 4-point visual analogue scale in which the scores correspond to a level of lupus disease activity (1= mild activity, 2 =moderate activity, and 3 = severe activity). A 10% increase (e.g., 0.3 points on the 3-point scale) is considered the threshold for minimum clinically meaningful worsening in disease activity.

The co-primary endpoints for the failed Phase 2 study LBSL02 were the 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. Studies 1056 and 1057 used a primary endpoint called the SLE Responder Index (SRI). This is a novel, three-component endpoint that was created based on exploratory analyses of LBSL02, with the intention of capturing clinically meaningful change, yet ensuring there would not be significant worsening in overall disease activity.<sup>3</sup> It is comprised of two disease activity scales, the SELENA-SLEDAI and BILAG, and an overall general health status instrument (PGA) that have been validated for use in SLE. Using this composite index, a patient is defined as a responder if they have the following:

- $\geq 4$ -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 organ domain scores or 2 new BILAG B organ domain scores at time of assessment (i.e. Week 52) compared to baseline.

Although minimal clinically important differences have been defined for the SELENA SLEDAI and PGA, and the BILAG was created on the principle of clinically important differences, it is not known what difference in the responder rate of the SRI would represent a clinically important difference between treatments. Although this endpoint was not validated prior to its use in Studies 1056 and 1057, its design is similar to that suggested in the 2010 FDA guidance document for the development of medical products for the treatment of SLE.

It was theorized that the unregulated use of concomitant SLE medications over the course of LBSL02 may have contributed to the lack of treatment effect associated with belimumab. Since increases in concomitant SLE medications (i.e., steroids, antimalarials, ACE inhibitors, NSAIDs and immunosuppressants/immunomodulatory agents) could potentially confound the results of the pivotal Phase 3 trials, progressive rules regarding the use of both restricted and prohibited medications were included in the common protocol for these trials and agreed upon by the Agency in the SPA. These rules permitted patients to receive the necessary treatment for their disease at any time, however, if they required an increase in background SLE medications beyond the

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<sup>3</sup> Furie et al., *Arthritis & Rheum*, 2009, 61(9):1143-1151

protocol-specified thresholds they were to be declared an SRI nonresponder and were to discontinue study treatment.

Study reports for the randomized controlled trials LBSL02, 1056 and 1057 will be presented below followed by interim reports of the ongoing open-label extension trial LBSL99.

**Study Number and Title:** LBSL02 - A Phase 2, Multicenter, Double-Blind, Placebo-Controlled, Dose-ranging Study to Evaluate the Safety, Tolerability and Efficacy of LymphoStat-B Antibody (Monoclonal Anti-BlyS Antibody) in Subjects with Systemic Lupus Erythematosus (SLE).

**Study Centers:** Multicenter (59 sites: U.S. 58 sites and Canada 1 site)

**Dates Conducted:** This trial was started on October 6, 2003 and completed on June 26, 2006 (last subject completed the 24-week follow-up).

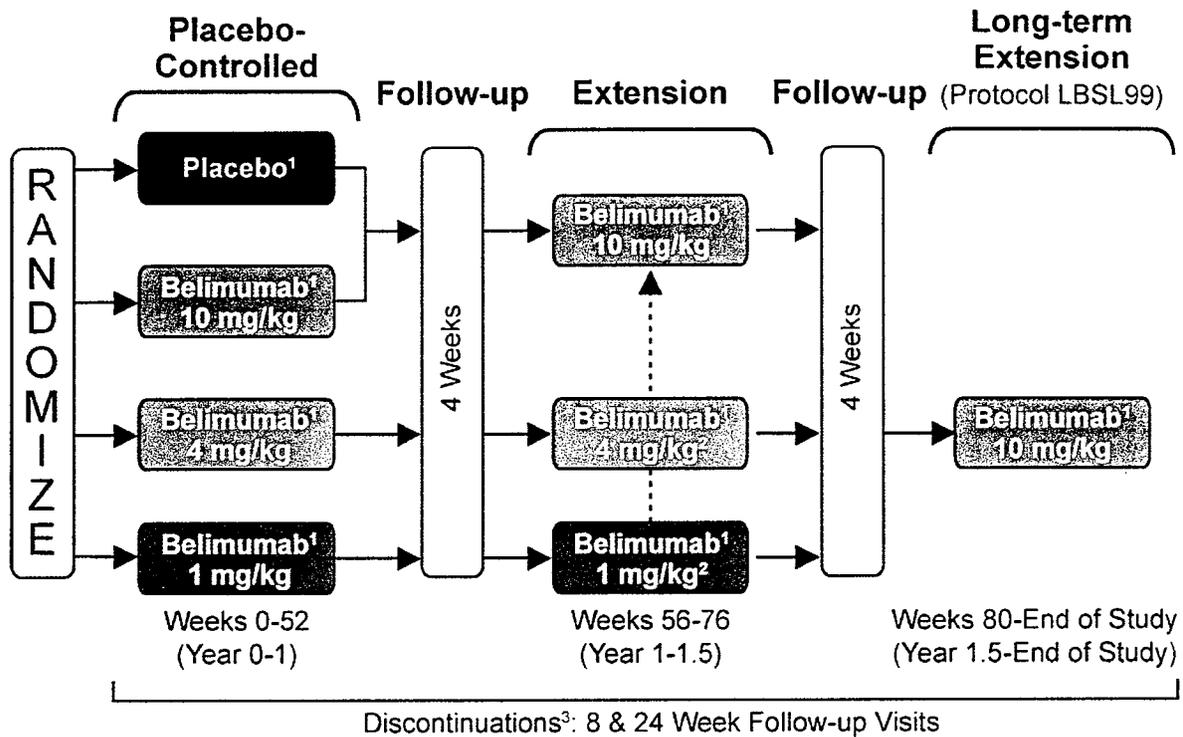
**Objectives:**

- To assess the safety and tolerability of belimumab in patients with SLE
- To assess the efficacy of belimumab in patients with SLE

**Study Design:**

Study LBSL02 was a multicenter, double-blind, placebo-controlled, randomized study in patients with active seropositive SLE on stable standard of care immunosuppressive medications for their disease. Eligible candidates were randomized via a 1:1:1 ratio to the following 3 treatment groups: 1mg/kg IV belimumab, 10 mg/kg belimumab or placebo IV. Randomization was stratified by subjects' screening SELENA SLEDAI score (6-9 vs  $\geq 10$ ), screening proteinuria level ( $< 2$  g/24 hours vs  $\geq 2$  g/24 hours equivalent) and race (African descent or indigenous-American descent vs other). All patients including those who withdrew from the trial were required to return to their respective study site for a final follow-up visit 4 weeks post-administration of last study infusion. Upon completion of the 76-week study, participants were to have the option of participating in a continuation study 1074. Those who did not wish to participate in 1074 were to have returned for an additional follow-up visit 8 weeks post-administration of their final study infusion. Figure 1 – Schema of Study LBSL02 is a schema of the proposed trial.

Figure 1 – Schema of Study LBSL02



<sup>1</sup>All treatment groups included standard of care therapy.

<sup>2</sup>Belimumab dose could be increased to 10 mg/kg at the discretion of each investigator.

<sup>3</sup>Subjects who discontinued treatment at anytime or who chose not to participate in the extension phase or continuation protocol were to return for 8 and 24 week follow-up visits.

Sponsor's Fig. 5-1; p. 28 clinical study report

### Major Inclusion Criteria:

Subjects were men and women  $\geq 18$  years of age with ANA-positive SLE who met all of the following criteria:

1. Diagnosis of SLE as per the American College of Rheumatology (ACR) criteria
2. A diagnosis of active SLE defined as a SELENA SLEDAI score  $\geq 6$  at screening
3. Unequivocally positive anti-nuclear antibody (ANA) test results from 2 independent time points as follows:
  - Positive test results from 2 independent time points within the study screening period. (A positive ANA test is defined as an ANA titer  $\geq 1:80$  and/or a positive anti-dsDNA ( $\geq 30$  IU/mL) serum antibody) or
  - One positive historical test result and 1 positive test result during the screening period
4. On a stable SLE treatment regimen consisting of any of the following medications (alone or in combination) for a period of at least 30 days prior to Day 0 (i.e., day of first dose of study agent):
  - Corticosteroids (prednisone or prednisone equivalent, up to 40 mg/day):
  - Other immunosuppressive or immunomodulatory agents: methotrexate, azathioprine, leflunomide, mycophenolate mofetil, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine or thalidomide.

- Anti-malarials (e.g. hydroxychloroquine, chloroquine, quinacrine)
- Non-steroidal anti-inflammatory drugs (NSAIDs)

**NOTE :**

- Pre-existing SLE medications were to have been stable for at least 30 days prior to Day 0
  - Corticosteroids may have been added as new medication or their doses adjusted only up to 30 days prior to Day 0
  - New SLE therapy other than corticosteroids could not be added within 60 days of Day 0
5. Individuals on angiotensin pathway antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers [ARBs]) had to be on a stable regimen for a period of at least 30 days prior to Day 0.
  6. Individuals on HMG CoA reductase inhibitors ("statins") had to be on a stable regimen for a period of at least 30 days prior to Day 0.
  7. Female candidates of childbearing potential could not be pregnant or nursing and had to have a negative serum pregnancy test at screening in addition to agreeing to practice complete abstinence from intercourse or using one of the acceptable methods of birth control listed in the protocol for the duration of the study
  8. Male candidates had to agree to use effective contraception for the duration of the study and for 3 months post-administration of last study dose

**Exclusion Criteria:** Potential study candidates were excluded from the study if any of the following criteria applied:

1. Treatment with any B-cell targeted therapy (rituximab, other anti-CD20 agents, anti-CD22, anti-CD52, BLyS-receptor fusion protein) at any time
2. Treatment within 364 days of Day 0 with abatacept or any biological investigational agent other than B-cell targeted therapy
3. Administered 3 or more courses of systemic corticosteroids for concomitant conditions such as asthma or atopic dermatitis within 364 days of Day 0 (topical and inhaled steroids are permitted)
4. Administered intravenous (IV) cyclophosphamide within 180 days of Day 0.
5. Treated with anti-TNF therapy, interleukin-1 receptor antagonist, intravenous immunoglobulin, high dose prednisone (>100 mg/d), or plasmapheresis within 90 days of Day 0
6. Treated with a non-biological investigational agent, or any new immunosuppressive/immunomodulatory agent, anti-malarial, NSAID, HMG CoA reductase inhibitor or angiotensin pathway antihypertensive within 60 Days of Day 0. (Note: New inhaled steroids or topical immunosuppressive agents were permitted. Any NSAID use for <1week was allowed.)
7. Administered a live vaccine or had a change in dose of a corticosteroid, other immunosuppressive/immunomodulatory agent, anti-malarial, NSAID, HMG CoA reductase inhibitor, or angiotensin pathway antihypertensive within 30 days of Day 0.
8. History of (H/O) severe lupus nephritis (defined by proteinuria >6 g/24 h or equivalent using spot urine protein to creatinine ration, or serum creatinine >2.5 mg/dL0, or have active nephritis, require hemodialysis or high-dose prednisone (>100 mg/day) within 90 days of Day 0
9. H/O active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident (CVA), cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 0.
10. H/O major organ transplant or hematopoietic stem cell/marrow transplant
11. H/O significant or unstable or uncontrolled acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematological, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases)
12. H/O any medical disease, lab abnormality, or condition or planning a surgical procedure during the course of the trial

13. H/O malignant neoplasm within the last 5 years with the exception of excised basal or squamous cell carcinomas of the skin or cervical carcinoma in situ
14. H/O acute or chronic infections that required hospitalization for treatment or parental antibiotic or antimicrobial agents within 60 days of Day 0 or the concurrent use of suppressive anti-infective therapy (i.e., antibacterials, antivirals, antifungals, or antiparasitic agents)
15. H/O recent alcohol or drug abuse within 364 days prior to Day 0
16. H/O a positive test for HIV-1 antibody, hepatitis B surface antigen, or hepatitis C antibody
17. H/O IgA deficiency (IgA level <10 mg/dL)
18. Have a Grade 3 or greater lab abnormality except for the following which were allowed: stable Grade 3 prothrombin time (PT) due to warfarin therapy, stable Grade 3/4 proteinuria ( $\leq 6$  g/24 h equivalent by spot urine protein to creatinine ration allowed), or stable Grade 3 neutropenia or stable Grade 3 WBC
19. H/O anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.

**Treatment:**

Study infusions were administered over 1 hour on Days 0, 14, 28 and then every 28 days through Week 72 of the study.

**Removal of Patients from Treatment or Assessment:**

Subjects were to have discontinued from this trial if they withdrew consent, developed an intercurrent illness, adverse events, treatment failure, incurred a protocol violation, for an administrative issue or other reasons.

**Concomitant Medications:**

The protocol permitted patients with a history of allergies or who had previously received IVIG to be prophylactically medicated with diphenhydramine, acetaminophen or H2-receptor antagonists which were to have been employed in cases of study-related infusion reactions.

**Efficacy and Safety Assessments:**

The following Table 3 and Table 4 are tabular flow charts of the scheduled study observations and procedures:

Table 3 - Schedule of Procedures and Evaluations for 52-Weeks of Treatment for Study LBSL02

Study day	Screening Visit	52-Week Treatment Period																		Follow-up Visit <sup>12</sup>	Follow-up Visit <sup>12</sup>	
		Day -28 to 0	Day 0	Day 14	Day 28	Day 42	Day 56	Day 70	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224	Day 252	Day 280	Day 308	Day 336	Day 364/Exit			Un-Scheduled Visit
Study week	-	-	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	-	-	-	-
Informed Consent & PHI Authorization	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History/ <sup>1</sup> Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vital Signs and Weight <sup>2</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination <sup>3</sup>	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
Hematology & Clinical Chemistry (non fasting)	X <sup>4</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X	X <sup>10</sup>	X	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>											
Urinalysis	X <sup>4</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X	X <sup>10</sup>	X	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>											
24 Hour Urine	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
Pregnancy Test <sup>5</sup>	X	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>
Pharmacokinetic Sampling <sup>6,7</sup>	-	X	X	-	-	X	-	-	-	-	X	-	-	-	-	-	-	-	X	-	X	X
Immunogenicity <sup>8</sup>	-	X <sup>10</sup>	X <sup>10</sup>	-	-	X <sup>10</sup>	-	-	-	-	X <sup>10</sup>	-	-	-	-	-	-	-	X	-	X	X
Biological Markers and Autoantibodies <sup>9, 4</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	-	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>	X <sup>10</sup>											
Total Serum Immunoglobulin G <sup>11</sup>	-	X <sup>10</sup>	-	-	-	X <sup>10</sup>	-	-	X <sup>10</sup>	-	X	X										
Disease Activity Scales <sup>12,12</sup>	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
SLE Flare Index	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
Modified HAQ	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-
Study Agent Administration	-	X	X	X	-	X	-	X	X	X	X <sup>14</sup>	X	X	X	X	X	X	X	X <sup>13,14</sup>	-	-	-
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(Footnotes listed on next page.)

<sup>1</sup>Medical history includes: SLE medical history and a history of medications and treatments within 28 days of screening.  
<sup>2</sup>Vital signs include: temperature, blood pressure, respiratory rate, and heart rate; taken prior to dosing (if applicable). Height required only at screening.  
<sup>3</sup>Full physical exam required at screening. Subsequent physical exams should be symptom driven (abbreviated).  
<sup>4</sup>Includes testing for: HIV, Hepatitis B surface antigen, Hepatitis C antibody, and urine alcohol & drug screen.  
<sup>5</sup>Pregnancy test: Screening = serum pregnancy test; all subsequent required testing = urine pregnancy test. FSH levels will be obtained at screening in addition to the pregnancy test, only for postmenopausal women with intact uteri, if FSH levels > 35 mIU/mL were not already documented.  
<sup>6</sup>Pharmacokinetic sampling: Performed at Day 0 (within 30 minutes prior to dosing), Day 14 (0-4 hours after the end of the infusion), Day 56 (within 30 minutes prior to dosing), Day 168 (within 30 minutes prior to dosing), Day 364/Exit (within 30 minutes prior to dosing for subjects continuing on the 24-week extension), 8-week follow-up visit (if applicable), and 24-week follow-up visit (if applicable).  
<sup>7</sup>A 1 time random PK sample will be drawn at any time during the study.  
<sup>8</sup>Immunogenicity testing includes screening samples for amount of LSB present in the samples using the LSB PK assay. Only samples with PK values below 1.0 µg/mL will be tested for immunogenicity.  
<sup>9</sup>Biological Markers/autoantibodies include: complement C3, C4, anti-dsDNA, ANA, CD20<sup>+</sup>, CD27<sup>+</sup>, CD27<sup>-</sup>, CD69<sup>+</sup>, CD19/CD38<sup>BRIGHT</sup>/CD27<sup>BRIGHT</sup>, CD138<sup>+</sup>, anti-Sm, anti-RNP, aCL, anti-SS-A (anti-Ro), anti-SS-B (anti-La). BlyS and APRIL will be measured at Days 0, 364/Exit and 24-week follow-up visit.  
<sup>10</sup>Total serum immunoglobulin G (IgG; and other subclasses: IgM, IgA, IgE).  
<sup>11</sup>Samples to be collected prior to dosing of study agent.  
<sup>12</sup>Disease Activity Scales include: SELINA SLEDAI, BILAG, PGA, and SF-36 Health Survey.  
<sup>13</sup>Follow-up visits for "Treatment Phase" are to occur 8 weeks and 24 weeks after completion/Exit of treatment (ie, Day 364); ONLY IF the subject does not enroll in the optional 24-week extension period.  
<sup>14</sup>Study agent should not be administered if this is the subject's Exit visit.  
<sup>15</sup>Principal investigator to assess major and active organ system involvement at Day 0, Weeks 24 and 52/Exit.

Table 4 - Schedule of Procedures and Evaluations for 24-Week Extension of Study LBSL02

Study day	Optional 24-Week Extension Period								Follow-up Visit <sup>10</sup>	Follow-up Visit <sup>10</sup>
	Day 378	Day 392	Day 420	Day 448	Day 476	Day 504	Day 532/Exit <sup>9</sup>	Un-Scheduled Visit	8 weeks post completion	24 weeks post completion
Study week	Wk 54	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	-	-	-
Vital Signs and weight	X	X	X	X	X	X	X	X	X	-
Physical Examination	-	X	X	X	X		X	X	X	-
Hematology & Clinical Chemistry	X	X <sup>6</sup>	X <sup>6</sup>	X	X <sup>6</sup>	X	X <sup>6</sup>	X	X	X
Urinalysis	X	X <sup>6</sup>	X <sup>6</sup>	X	X <sup>6</sup>	X	X <sup>6</sup>	X	X	X
24 Hour Urine	-	X	X	-	X		X	-	X	-
Pregnancy Test <sup>1</sup>	-	X <sup>6</sup>	-	-	-					
Pharmacokinetic Sampling <sup>2</sup>	-	X	-	X	-	-	X	X	X	X
Immunogenicity	-	X <sup>6</sup>	-	X <sup>6</sup>	-	-	X <sup>6</sup>	-	X	X
Biological Markers and Autoantibodies <sup>3</sup>	-	X <sup>6</sup>	X <sup>6</sup>	-	X <sup>6</sup>	-	X <sup>6</sup>	-	X	X
Total Serum Immunoglobulin G <sup>4</sup>	-	X <sup>6</sup>	X <sup>6</sup>	-	X <sup>6</sup>	-	X <sup>6</sup>	-	X	X
Disease Activity Scales <sup>5</sup>	-	X	X	-	X	-	X <sup>8</sup>	-	X	-
SLE Flare Index	-	-	-	-	-	-	-	X	-	-
Modified HAQ	-	-	-	-	-	-	X	-	-	-
Study Agent Administration	-	X	X	X	X	X	X <sup>7</sup>	-	-	-
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	-
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	-

<sup>1</sup>Pregnancy test = urine pregnancy test (Women with total hysterectomies or postmenopausal women with documented FSH level > 35mIU/mL are exempt from pregnancy testing).

<sup>2</sup>Pharmacokinetic sampling: Performed at Day 392 (0-4 hours after the end of the infusion), Day 448 (0-4 hours after the end of the infusion), Day 532 (within 30 minutes prior to dosing), and Exit.

<sup>3</sup>Biological Markers/autoantibodies include: complement C3, C4, anti-dsDNA, ANA, CD20<sup>+</sup>, CD27<sup>+</sup>, CD27<sup>-</sup>, CD69<sup>+</sup>, CD19/CD38<sup>BRIGHT</sup>/CD27<sup>BRIGHT</sup>, CD138<sup>+</sup>, anti-Sm, anti-RNP, aCL, anti-SS-A (anti-Ro), anti-SS-B (anti-La). BLYS and APRIL will be measured at the 24-week follow-up visit.

<sup>4</sup>Total serum immunoglobulin G (IgG; and other subclasses: IgM, IgA, IgE).

<sup>5</sup>Disease Activity Scales include: SELENA SLEDAI, BILAG, SLE Flare Index, PGA, SF-36 Health Survey.

<sup>6</sup>Samples to be collected prior to dosing of study agent.

<sup>7</sup>Study agent should not be administered if this is the subject's Exit visit.

<sup>8</sup>Principal Investigator to assess major and active organ system involvement at week 76/Exit.

<sup>9</sup>Assess eligibility for LBSL99, if applicable.

<sup>10</sup>8- and 24-week follow-up visits shall be completed ONLY if the subject will not participate in the optional, long-term continuation protocol, LBSL99.

Sponsor's Appendix E; p. 83.

**Outcome Measures:**

**Co-primary efficacy endpoints:**

- SELENA SLEDAI disease activity score at Week 24

- Time to the first mild/moderate or severe flare (as defined by the SLE Flare Index) over 52 weeks

**Major secondary efficacy endpoints:**

- Week 52 SELENA SLEDAI disease activity score
- Week 52 AUC of SELENA SLEDAI
- Week 52 BILAG disease activity score
- Week 52 AUC of BILAG
- Time to first SLE flare (as defined by BILAG) over 52 weeks
- Percent of subjects with average prednisone dose  $\leq$  75 mg/day and/or reduced by a minimum of 50% from baseline during Week 40 through Week 52 (in subjects whose prednisone was  $>$ 7.5 mg/day at baseline).

**Exploratory Efficacy Analyses:**

**Disease Activity:**

- Week 24 change over baseline BILAG disease activity score
- Changes from baseline of the investigator-designated SLE organ system involvement at Weeks 24, 52 and 76 as measured by BILAG disease activity scores

**Disease Flares:**

- Time to Type A BILAG flare over 24 and 52 weeks
- Time to BILAG flare with exclusion of all flares that occurred in the first 8 weeks after the first dose of study medication over 24 and 52 weeks
- Percent of subjects experiencing an SLE BILAG flare over 24 and 52 weeks
- Number of flares over 24 and 52 weeks as assessed by the BILAG
- Time to mild/moderate flare over 24 and 52 weeks as assessed by SLE Flare Index
- Time to severe flare as assessed by SLE Flare Index
- Time to flare with exclusion of all flares that occurred in the first 8 weeks after first dose of study agent as assessed by SLE Flare Index
- Percent of subjects experiencing an SLE flare as assessed by SLE Flare Index
- Number of flares over 24 and 52 weeks as assessed by SLE Flare Index

**Steroid Reduction:**

- Percentage of subjects with average prednisone dose  $\leq$  7.5 mg/day and/or reduced by a minimum of 50% from baseline during Week 16 through Week 24 (baseline prednisone  $>$ 7.5 mg)
- Percentage of subjects with average prednisone dose  $\leq$  7.5 mg/day during Week 16 through Week 24 and Week 40 through Week 52 (baseline prednisone  $>$  7.5 mg)
- Percentage of subjects with average prednisone dose reduced by a minimum of 50% from baseline during Week 16 through Week 24 and Week 40 through Week 52

- Number of days of daily prednisone dose  $\leq$  7.5 mg/day and/or reduced by a minimum of 50% from baseline during Week 16 through Week 24 and Week 40 through Week 52 (baseline prednisone > 7.5 mg/day)
- Number of days of daily prednisone dose  $\leq$  7.5 mg/day during Week 16 through Week 24 and Week 40 through Week 52 (baseline prednisone > 7.5 mg/day)
- Number of days of daily prednisone dose reduced by a minimum of 50% from baseline during Weeks 16 through Week 24 (baseline prednisone > 7.5 mg)
- Median change from baseline of prednisone does over 24 and 52 weeks (baseline > 7.5mg)

**Patient Reported Outcomes:**

- Mean change in SF-36 Health Survey PCS and MCS score at Week 52
- Mean change in modified HAQ score at Week 52

**Physician's Global Assessment (PGA)**

**Renal:**

- Change in proteinuria from baseline over time

**Biomarkers:**

- Percent change from baseline in: total serum Ig, anti-dsDNA, ANA, anti-Sm, aCL, C3, C4, interferon expression signature, and T-lymphocytes (CD3/4 and CD3/8)

**Statistical Design, Definitions of Analyzed Populations and Analyses Plan:**

Sample size calculations were based on the two primary efficacy endpoints. The proposed study had at least 80% power at a significance level of 2.5% to detect in 1 of the active groups: 1) a 25% absolute or 100% relative improvement in the percent change from baseline score in SELENA SLEDAI (assuming that an average decrease of 25% from baseline would be observed in the placebo group with a standard deviation of 50%) at Week 24 and 2) a reduction in the percent of subjects having their first flare by Week 52 from 65% in the placebo group to 43% in any one of the belimumab treated groups.

The modified intent-to-treat (mITT) population was used for the primary analysis for this trial. This was defined as the subset of all randomized patients who received at least 1 dose of study agent. The mITT analysis was performed according to the treatment that a subject was randomized to receive, regardless of actual treatment received.

The 2-sample t-test was used to analyze the primary efficacy endpoint of the SELENA SLEDAI disease activity score and the major secondary endpoints involving reduction in SELENA SLEDAI and BILAG score while the log-rank test was used to analysis the co-primary and secondary endpoints of time to first flare defined by the SLE flare index and BILAG. Reduction in prednisone was analyzed via a likelihood ratio chi-squared test. An analysis of covariance (ANCOVA) was used for the change from baseline in SF-36 PCS and MCS. Last observation carried forward (LOCF) was the imputation technique used for missing data. An adjustment for multiplicity was to be applied during the analysis of

the co-primary endpoints but no adjustments were to be made during the analyses of the secondary endpoints.

**Safety Evaluation:**

Descriptive statistics were used to summarize data describing AEs, SAEs, deaths, abnormal lab tests, vital signs, and antibodies to belimumab. Results were to have been compared across treatment groups using statistical tests for significance.

**Immunogenicity Assessments:**

Serum samples were collected for belimumab immunogenicity assays prior to initial dosing on Day 0; prior to dosing at weeks 2, 8, 24, and 52; and at follow-up visits Week 8 and 24. During the extension, samples were collected prior to dosing at weeks 56, 64 and 76; and at follow-up visits Week 8 and 24.

**Study Conduct**

**Protocol Amendments:**

Listed below are the 6 protocol amendments that were made to Study LBSL02. Approximately 10% (46 patients) of the subjects were enrolled under the original protocol and 50% (246 patients) were enrolled under Amendment 1.

1. Amendment 1 (implemented on July 21, 2003)
  - Inclusion criterion 6 and exclusion criterion 11 were revised to clarify which women were required to use a medically approved method of contraception and which women required a pregnancy testing at screening
  - 10mg/kg dose will be given during the extension period to subjects who received placebo or who received active study agent during the 52-week treatment period without a satisfactory response
  - Enhancement of section 12 regarding IRB/IEC review and ethical conduct of the study
  
2. Amendment 2 (implemented on February 2, 2004)
  - Eligibility criteria and study design were modified as follows: rituximab treatment was prohibited within 180 days of Day 0; anti-TNF treatments were prohibited within 90 days of Day 0; exclusion of subjects who had IA steroid injection within 60 days of Day 0; IgA deficiency was defined as <10mg/dL; subjects with Grade 2 and 3 proteinuria due to SLE were permitted to participate on a case by case basis; additional biological markers of interest were added; definitions of renal remission and flare were added; guidelines for scoring of proteinuria were added;
  - Sample size was increased so the study had at least 80% power to detect efficacy improvements in 1 of the active groups at a significance level of 2.5% instead of 5% to account for multiplicity adjustment for statistical testing of 2 co-primary efficacy endpoints

- Statistical methods were revised: number of major secondary endpoints was reduced; time to first flare over 52 weeks according to BILAG was added; description of sensitivity analysis of the primary endpoints was added; clarification regarding handling missing data for the analysis of time to first flare
  - DMC was made fully independent
  - Since the protocol was to be conducted at some trial sites outside the UA; US-specific language was removed
3. Amendment 3 (implemented on April 1, 2004)
- Exclusion criteria amended to prohibit subjects with a history of an anaphylactic reaction to IV contrast agents, other foreign proteins or other monoclonal antibodies be excluded from the study; washout period was extended to 60 days prior to first dose of study agent and prior administration of investigational drugs; clarified adequately treated skin cancers were those that had been completely surgically excised
  - Study protocol amended to permit subjects with history of allergic reactions to be premedicated with an antihistamine and acetaminophen prior to treatment with belimumab
4. Amendment 4 (implemented February 11, 2005)
- Subjects with a satisfactory response to therapy were given the option of entering open-label, long term extension study LBSL99 following 24-week extension of study
5. Amendment 5 (implemented June 30, 2005)
- The requirement for the use of contraception by study subjects was extended from 30 days to 60 days following the last dose of study agent due to the 10 day half life of belimumab
6. Amendment 6 (implemented February 2, 2006)
- References to the independent DMC were amended to describe the safety data monitoring after unblinding the Phase 2 studies (LBSL02 and LBRA01) for the primary analyses. After the unblinding, the safety data monitoring was to be conducted by the internal HGSRC

## **RESULTS:**

### **Disposition of Subjects:**

A total of 449 subjects were randomized to the four treatment groups as follows: 119 patients to the placebo group, 121 patients to belimumab 1 mg/kg group, 116 patients to belimumab 4 mg/kg group and 120 patients to belimumab 10 mg/kg group. As shown in Table 5 below, a higher proportion subjects discontinued from the study in the 1 mg/kg belimumab group as compared to the other belimumab treatment groups and placebo

group which were comparable. The higher rate of early discontinuation from the belimumab 1mg/kg group was due to subject request (10%) and adverse event (7%). More patients also withdrew due to an adverse event (7%) from the 10 mg/kg belimumab group as compared to the 4 mg/kg belimumab and the placebo groups which had similar rates of withdrawal except for a higher rate due to lack of compliance (5%) in the placebo group.

Table 5 –Subject Disposition for 52-Week Double Blind Treatment Period of Study LBSL02

	Placebo	Belimumab 1mg/kg	Belimumab 4mg/kg	Belimumab 10mg/kg	Total
<b>Number of Subjects Randomized</b>	119	121	116	120	<b>476</b>
<b>Number of Subjects Treated (mITT)</b>	113	114	111	111	<b>449</b>
<b>Number of Subjects Completed Wk 52</b>	93(82%)	87 (76%)	94 (85%)	90 (81%)	<b>364 (81%)</b>
<b>Number of Subjects Withdrawn Prior to Week 52:</b>	20 (18%)	27 (24%)	17 (15%)	21 (19%)	<b>85 (19%)</b>
<b>Subject Request</b>	6 (5%)	11 (10%)	7 (6%)	7 (6%)	<b>31 (7%)</b>
<b>Adverse Event</b>	5 (4%)	8 (7%)	4 (4%)	8 (7%)	<b>25 (6%)</b>
<b>Lack of Efficacy</b>	1 (1%)	2 (2%)	0	1 (1%)	<b>4 (1%)</b>
<b>Lack of Compliance</b>	6 (5%)	3 (3%)	3 (3%)	3 (3%)	<b>15 (3%)</b>
<b>Other</b>	2 (2%)	3 (3%)	3 (3%)	3 (3%)	<b>10 (2%)</b>

Modified Sponsor's Table 6-1; p. 71.

Of the 364 patients who completed the 52-week treatment period of this trial, 345 patients opted to continue treatment in the 24-week extension period. Table 6 shows that overall 93% of the subjects completed the 24-week extension period. The most common reasons for early discontinuation were due to subject request (2%) and adverse event (2%).

Table 6 – Subject Disposition for 24-Week Extension Period of Study LBSL02

	Placebo to 10mg/kg N=88	1 mg/kg to 1mg/kg N=19	1 mg/kg to 10mg/kg N=65	4 mg/kg to 4mg/kg N=24	4 mg/kg to 10mg/kg N=64	10 mg/kg to 10mg/kg N=85	Total N=345
<b>Number of Subjects Completed</b>	82 (93%)	19 (100%)	59 (91%)	23 (96%)	58 (91%)	80 (94%)	<b>321(93%)</b>
<b>Number of Subjects Withdrawn Prior to Wk 52:</b>	6 (7%)	0	6 (9%)	1 (4%)	6 (9%)	5 (6%)	<b>24 (7%)</b>
<b>Subject Request</b>	1 (1%)	0	6 (9%)	0	1 (2%)	0	<b>8 (2%)</b>
<b>Adverse Event</b>	2 (2%)	0	0	1 (4%)	1 (2%)	3 (4%)	<b>7 (2%)</b>
<b>Lack of Efficacy</b>	2 (2%)	0	0	0	0	1 (1%)	<b>3 (1%)</b>
<b>Lack of Compliance</b>	1 (1%)	0	0	0	0	1 (1%)	<b>2 (1%)</b>
<b>Other</b>	0	0	0	0	4 (6%)	0	<b>4 (1%)</b>

Adapted Sponsor's Table 6-2; p. 73.

**Protocol Deviations:**

There were a total of 92 protocol violations incurred by 84 subjects for this study as follows: 24 subjects (5.3%) did not meet study entry criteria (unstable or prohibited treatment regimens within 60 days of Day 0, did not meet screening ACR criteria for SLE or had elevated PT at screening); 42 subjects (9.4%) received the wrong treatment or an incorrect dose (used baseline weight instead of day of dosing weight or another patient's treatment for the entirety of trial), and 27 subjects (6%) had other violations (incorrect SELENA SLEDAI scores at screening or randomization prior to receipt of all lab results).

*Reviewer's Comment: The high number of protocol violations related to not meeting entry criteria or receiving an incorrect dose of study medication may have played a role in the lack of dose of response observed in this Phase 2 trial.*

**Demographics:**

As summarized in the following tables (Table 7 and Table 8), the treatment groups within LBSL02 were generally well balanced with respect to baseline demographics, disease characteristics and activity.

The subjects who participated in this trial were predominantly Caucasian (70%) and female (93%). Twenty-four (24%) of the patients were of Black/African American origin. The mean age of subjects was 42 years and mean weight of subjects was 81 kg. A higher proportion of Black/African American subjects (28%) and subjects of Hispanic origin (22%) were randomized to the 4 mg/kg belimumab group as compared to the other belimumab treatment groups and placebo but no important imbalances in demographic factors across treatment groups were noted within LBSL02.

Table 7 – Demographics Characteristics of Subjects in Study LBSL02

Demographics	Placebo N=113	Belimumab 1mg/kg N=114	Belimumab 4mg/kg N=111	Belimumab 10mg/kg N=111	Total N=449
<b>Gender:</b> Female	102 (90%)	107 (94%)	105 (95%)	105 (95%)	419 (93%)
<b>Race:</b>					
Caucasian	80 (71%)	82 (72%)	75 (68%)	78 (70%)	315 (70%)
Asian	4 (4%)	3 (3%)	1 (1%)	4 (4%)	12 (3%)
African American	23 (20%)	24 (21%)	31 (28%)	28 (25%)	106 (24%)
Alaskan Native/American Indian	2 (2%)	2 (2%)	3 (3%)	0	7 (2%)
Native Hawaiian/Pacific Islander	2 (2%)	1 (1%)	0	1 (1%)	4 (1%)
Multiracial	2 (2%)	2 (2%)	1 (1%)	0	5 (1%)
<b>Hispanic Origin:</b>	21 (19%)	17 (15%)	24 (22%)	21 (19%)	83 (19%)
<b>Age (years):</b>					
Mean (SD)	42 (11)	42 (12)	43 (11)	42 (12)	42 (11)
<b>Weight:</b>					
Mean (SD)	84 (20)	82 (24)	79 (20)	79 (23)	81 (22)
(Min, Max)	(43, 141)	(40, 157)	(45, 134)	(46, 146)	(40, 157)

Modified Sponsor's Table 6-6; p. 77.

As shown in Table 8 below, the overall mean duration of SLE disease was 9 years for patients in this trial. Overall, these subjects had a high baseline level of disease activity as manifested by a SELENA SLEDAI mean score of 9.7 with 67% of the patients having a baseline SELENA SLEDAI score of  $\geq 8$  points. The individual treatment groups were similar in their baseline disease activity with only minor differences as assessed by the mean BILAG score and SELENA SLEDAI score category 8-16 suggesting that patients with higher disease activity may have been assigned to the 1mg/kg belimumab group. A slightly higher rate of placebo subjects were also taking daily prednisone  $>7.5$  mg/day at baseline as compared to the belimumab treatment groups. The majority of patients in this trial were also seropositive for ANA (71%) or anti-dsDNA (50%). The treatment groups within this trial were also generally well balanced with respect to baseline biomarkers of disease activity with the following exceptions. A slightly lower proportion of patients in the 10 mg/kg belimumab group were seropositive for ANA (67%) as compared to the other treatment groups and placebo. Additionally, the proportions of subjects who had low C3 and C4 levels were lower in the belimumab 1mg/kg group as compared to the other treatment groups and placebo.

Table 8 – Subject’s Baseline Disease Characteristics for Study LBSL02

Characteristic	Placebo N=113	Belimumab 1mg/kg N=114	Belimumab 4mg/kg N=111	Belimumab 10mg/kg N=111	Total N=449
<b>Disease Duration (yr)</b> Mean (SD)	8 (7)	9 (7)	10 (9)	9 (8)	9 (8)
<b>SELENA SLEDAI Score Group</b>					
2	1 (1%)	1 (1%)	2 (2%)	1 (1%)	5 (1%)
4-7	42 (37%)	32 (28%)	37 (33%)	33 (30%)	144 (32%)
8-16	62 (55%)	71 (62%)	62 (56%)	69 (62%)	264 (59%)
>16	8 (7%)	10 (9%)	10 (9%)	8 (7%)	36 (8%)
<b>SELENA SLEDAI Score</b> Mean (SD)	9.5 (0.5)	9.9 (0.44)	9.4 (0.45)	9.5 (0.39)	9.6 (0.22)
<b>BILAG Score</b> Mean (SD)	9.5 (0.45)	9.8 (0.41)	10.1 (0.5)	10.0 (0.4)	9.8 (0.22)
<b>PGA</b> Mean (SD)	1.4 (0.05)	1.6 (0.05)	1.5 (0.05)	1.5 (0.05)	1.5 (0.22)
<b>Daily Prednisone Use at Baseline</b> Yes	82 (73%)	78 (68%)	73 (66%)	74 (67%)	307 (68%)
<b>Daily Prednisone Use &gt;7.5 mg at Baseline</b> Yes	48 (42%)	40 (35%)	35 (32%)	38 (34%)	161 (36%)
<b>ANA</b> Positive ( $\geq 80$ )	84 (74%)	80 (71%)	82 (75%)	74 (67%)	320 (71%)
<b>Anti-dsDNA</b> Positive ( $\geq 30$ IU/mL)	58 (51%)	59 (52%)	53 (48%)	53 (48%)	223 (50%)
<b>C3</b> Low (<90 mg/mL)	29 (26%)	40 (36%)	31 (28%)	35 (32%)	135 (30%)
<b>C4</b> Low (<16 mg/mL)	42 (38%)	53 (48%)	41 (38%)	44 (40%)	180(40%)
<b>BLyS (ng/mL)</b> Above LOD	49 (43%)	49 (43%)	49 (44%)	48 (43%)	195 (43%)

Note: LOD = Lower limit of detection  
 Modified Sponsor’s Table 6-7; p. 80.

The following table (Table 9) summarizes concomitant SLE medications used by more than 5% of subjects who participated in LBSL02. The usage of concomitant SLE medications at baseline was generally similar for the 4 treatment groups in this trial with few exceptions. A higher proportion of subjects in the placebo group were taking concomitant antimalarials as compared to the belimumab groups and the proportion of patients taking a concomitant NSIAD was higher in the 1 mg/kg belimumab group as compared to the other belimumab groups or placebo.

Table 9 – Tabular Summary of Concomitant SLE Medication ≥ 5% of Subjects in Study LBSL02

	Placebo N=113	Belimumab 1mg/kg N=114	Belimumab 4mg/kg N=111	Belimumab 10mg/kg N=111	Total N=449
<b>Antimalarials</b>	86 (76%)	80 (70%)	72 (65%)	77 (69%)	315 (70%)
<b>Immunosuppressives:</b>					
<b>Azathioprine</b>	24 (21%)	21 (18%)	24 (22%)	25 (23%)	94 (21%)
<b>Methotrexate</b>	18 (16%)	18 (16%)	23 (21%)	21 (19%)	80 (18%)
<b>Mycophenolate</b>	24 (21%)	17 (15%)	17 (15%)	21 (19%)	79 (18%)
<b>Leflunomide</b>	7 (6%)	5 (4%)	7 (6%)	3 (3%)	22 (5%)
<b>NSAIDs</b>	103 (91%)	112 (98%)	98 (88%)	101 (91%)	414 (92%)

Modified Sponsor's Table 6-10; p. 84

**Efficacy:**

**Co-Primary Endpoints:**

The SELENA SLEDAI score at Week 24 was a co-primary endpoint in this trial. As shown in Table 10, numerical improvements in the mean percent decrease in SELENA SLEDAI score was achieved by all belimumab treatment groups (range: 11 to 23%) however, these improvements were not significantly different as compared to placebo. A dose response was not demonstrated for belimumab with this parameter.

Table 10 – Co-Primary Endpoint: Percent Change from Baseline in SELENA SLEDAI Score at Week 24

SELENA SLEDAI Score	Placebo N=113	Belimumab 1mg/kg N=114	Belimumab 4mg/kg N=111	Belimumab 10mg/kg N=111
<b>Baseline (SD)</b>	9.5 (0.5)	9.9 (0.44)	9.4 (0.45)	9.5 (0.39)
<b>Percent Change at Week 24 (SD)</b>	-17.2 (5.1)	-23 (4.4)	-11.3 (5.4)	-23.7 (4.220)
<b>Mean Difference from Placebo</b>	-	-6.10	-5.94	-6.48
<b>95% CI for Mean Difference</b>	-	(-19.4, 7.2)	(-8.7, 20.6)	(-19.6, 6.6)
<b>P-value<sup>1</sup></b>	-	0.3677	0.4244	0.3296

<sup>1</sup>P-value for pairwise comparison between each active treatment and placebo group.

Modified Sponsor's Table 7-1; p. 85.

The time to first mild/moderate or severe flare over 52 weeks was the other co-primary endpoint evaluated. No significant differences in the median time to first flare over 52 weeks were observed for any of the belimumab treatment groups (range: 61-70 days) as compared to placebo (83 days) as displayed in Table 11 below. The mean number of flares was also comparable for all treatment groups ranging from 2.8 to 3.0 flares/subject. A dose response for belimumab was also not demonstrated by this endpoint. No additional analyses of data from the 24 week extension were performed for this endpoint since approximately 90% of subjects had flared by Week 52.

Table 11 – Co-Primary Endpoint: Time to SLE Flare Over 52 Weeks (mITT Population)

	Placebo N=113	Belimumab 1mg/kg N=114	Belimumab 4mg/kg N=111	Belimumab 10mg/kg N=111
Median Time to First Flare (days) P-value <sup>1</sup>	83 -	68 0.6423	61 0.8536	70 0.9705
Total Number of Flares	329	320	307	329
Mean Number of Flares/Subject	2.9	2.8	2.8	3.0

<sup>1</sup>P-value for pairwise comparison between each active treatment and placebo group.  
 Modified Sponsor's Table 7-3; p. 92.

**Secondary Endpoints:**

There were six major secondary and multiple ancillary secondary and exploratory endpoints for this trial which are presented below by corresponding assessment area.

**SELENA SLEDAI Disease Activity:**

Major secondary endpoints included the Week 52 SELENA SLEDAI score and the AUC of the SELENA SLEDAI score over 52 weeks (based on the mITT population and LOCF). The results from these analyses showed:

- Numerical improvements in the mean percent change in SELENA SLEDAI score was achieved by all belimumab treatment groups (1mg/kg: 30%, 4 mg/kg: 24%, and 10mg/kg: 28%). However, these improvements were not significantly different as compared to placebo (21%) (1mg/kg vs placebo p-value= 0.1763; 4 mg/kg vs placebo p-value= 0.7112; and 10 mg/kg vs placebo p-value 0.3320).
- Numerical improvements in the AUC percent normalized SELENA SLEDAI scores over 52 weeks were only observed in the 1 and 10 mg/kg belimumab groups (1mg/kg: 289, 4 mg/kg: 320, and 10mg/kg: 287) as compared to placebo (317). These improvements were not significantly different as compared to placebo (1mg/kg vs placebo p-value = 0.1287; 10 mg/kg vs placebo p-value = 0.1131).

In the 24-week extension, a 33% improvement in SELENA SLEDAI scores over baseline were observed at Week 76 for placebo subjects who received belimumab 10mg/kg however, this improvement was not significantly different from subjects who had received belimumab treatment at 1 to 10 mg/kg for up to 76 weeks who had a 37% mean improvement over baseline score (p-value = 0.5418).

**BILAG Disease Activity:**

The BILAG-related major secondary endpoints were the Week 52 BILAG disease activity score and the AUC of the BILAG disease activity score. (Note: The Cockcroft-Gault formula was used to calculate the creatinine clearance for the BILAG index in all analyses.) Treatment with belimumab was not associated with a significant improvement as compared to placebo for any of these assessments as follows:

- Numerical improvements in the mean percent change in the Week 52 BILAG disease activity score over baseline was achieved by all belimumab treatment groups (1mg/kg: 21%, 4 mg/kg: 27%, and 10mg/kg: 22%). However, these improvements were not significantly different as compared to placebo (19%) (1mg/kg vs placebo p-value= 0.7823; 4 mg/kg vs placebo p-value= 0.1774; and 10 mg/kg vs placebo p-value 0.6406).
- Numerical improvements in the mean AUC of BILAG disease activity score were achieved by all belimumab groups (1mg/kg: 311, 4 mg/kg: 300, and 10mg/kg: 303) as compared to placebo (315). These improvements were not significantly different as compared to placebo (1mg/kg vs placebo p-value = 0.7822; 4 mg/kg vs placebo p-value =0.3332; and 10 mg/kg vs placebo p-value = 0.4660).

Analysis of the ancillary endpoints for BILAG disease activity did not show any benefit associated with belimumab over placebo as assessed by the Week 24 BILAG disease activity scores or in changes from baseline of the investigator-designated SLE organ system involvement at Weeks 24, 52 and 76.

No BILAG disease activity analyses were performed for the 24-week extension period (through Week 76).

#### **Disease Flares:**

Belimumab's ability to decrease disease flares was assessed by both the BILAG and the SLE Flare Index. A major secondary endpoint was the time to the first SLE flare (as defined by the BILAG) over 52 weeks. The results of this analysis showed:

- Time to first A/B disease flare as assessed by the BILAG for the belimumab groups was 63 days for 1mg/kg; 84 days for 4 mg/kg; and 62 days for 10mg/kg and were not significantly different as compared to placebo (78 days) (1mg/kg vs placebo p-value= 0.5615; 4 mg/kg vs placebo p-value= 0.7593; and 10 mg/kg vs placebo p-value 0.2273).

The results from ancillary endpoints that evaluated disease flares did not demonstrate any benefit associated with belimumab treatment as compared to placebo as assessed by the following: time to Type A BILAG flare, time to BILAG flare with exclusion of all flares that occurred in the first 8 weeks after the first dose of study medication, the percent of subjects experiencing an SLE BILAG flare and the number of flares over 24 and 52 weeks as assessed by the BILAG.

Time to mild/moderate flare, time to severe flare, time to flare with exclusion of all flares that occurred in the first 8 weeks after first dose of study agent, the percent of subjects experiencing an SLE flare and the number of flares over 24 and 52 weeks as assessed by SLE Flare Index also did not demonstrated a benefit from treatment with belimumab treatment as compared to placebo.

Since approximately 90% of subjects flared by Week 52, no disease flare analyses were conducted for the 24-week extension.

### **Steroid Reduction:**

The percent of subjects with average prednisone dose  $\leq 7.5$  mg/day and/or reduced by a minimum of 50% from baseline during Week 40 through Week 52 was another major secondary endpoint.

- Numeric reductions in prednisone use were seen in all belimumab groups (1mg/kg: 20%, 4 mg/kg: 31%, and 10mg/kg: 45%). These reductions in steroid use were not significantly different compared to placebo (27%) (1mg/kg vs placebo p-value = 0.4355; 4 mg/kg vs placebo p-value = 0.6669; and 10 mg/kg vs placebo p-value = 0.0882).

Treatment with belimumab was not associated with any benefit as compared to placebo as assessed by the following exploratory steroid reduction endpoints: percentage of subjects with average prednisone dose  $\leq 7.5$  mg/day and/or reduced by a minimum of 50% from baseline during Week 16 through Week 24, percentage of subjects with average prednisone dose  $\leq 7.5$  mg/day during Week 16 through Week 24 and Week 40 through Week 52, percentage of subjects with average prednisone dose reduced by a minimum of 50% from baseline during Week 16 through Week 24 and Week 40 through Week 52, number of days of daily prednisone dose  $\leq 7.5$  mg/day and/or reduced by a minimum of 50% from baseline during Week 16 through Week 24 and Week 40 through Week 52, number of days of daily prednisone dose  $\leq 7.5$  mg/day during Week 16 through Week 24 and Week 40 through Week 52, number of days of daily prednisone dose reduced by a minimum of 50% from baseline during Weeks 16 through Week 24 and median change from baseline of prednisone does over 24 and 52 weeks (baseline  $> 7.5$ mg).

No analyses of concomitant steroid use were performed for the 24-week extension period.

### **Physician Global Assessment (PGA):**

Disease activity as assessed by the PGA was an exploratory analysis in this trial.

- Mean decreases in the PGA over baseline were seen in all belimumab groups at Week 52 (1mg/kg: 28%, 4 mg/kg: 31%, and 10mg/kg: 33%). These changes were significantly different as compared to placebo (14%) (1mg/kg vs placebo p-value = 0.0496; 4 mg/kg vs placebo p-value = 0.0238; and 10 mg/kg vs placebo p-value = 0.0075).

By Week 76 of the extension period, the mean percent decrease from baseline PGA ranged from 35-41% in subjects administered belimumab throughout the trial as

compared to 28% in subjects administered belimumab only during the 24-week extension period.

#### **Patient Reported Outcomes:**

The SF-36 PCS and MCS scores and the modified HAQ were ancillary endpoints in this trial. However, the Applicant did not provide the analyses for the modified HAQ in this report. The minimally clinically important difference (MCID) over baseline SF-36 is considered to be  $\geq 2.5$  points for the PCS and MCS scores. The results of these analyses using the mITT population and LOCF imputation for missing data are as follows:

- A significant improvement in the SF-36 PCS was achieved by subjects in the belimumab 10mg/kg group (3.4) as compared to placebo (1.4; p-value =0.0167). No significant difference was observed for the 1 mg/kg and 4mg/kg belimumab groups (2.7 and 1.7, respectively) compared to placebo (p-value=0.2256; p-value=0.6190, respectively).
- Treatment with belimumab was not associated with a MCID in the MCS (1mg/kg: 2.1, 4 mg/kg: 2.0, and 10mg/kg: 0.4; Placebo MCS: 1.3).

During the extension period, the PCS scores for subjects treated with belimumab for 76 weeks remained stable, with the increase from baseline PCS scores at Week 76 ranging from 2.2 to 3.0 across the three treatment groups, while the PCS scores for subjects in the placebo group treated with belimumab for 24 weeks increased 2.0 points from baseline.

#### **Biomarkers:**

A number of biomarkers were examined in this trial as follows:

- B cell counts (CD20, CD20/27 memory, CD20/27 naïve, CD20/69 activated, CD20/138 plasmacytoid, CD19/27/38 SLE subset and CD20/138 plasma cells) decreased in all 3 belimumab treatment groups and increased in the placebo group. Memory B cell counts increased at Week 4 and then gradually declined towards baseline levels in the belimumab groups. No dose response was observed for any of these biomarkers. These changes were sustained during the 24-week extension period.
- Treatment with belimumab resulted in decreases in IgG (10%), IgA (14%), IgM (29%), IgE (34%) and increases in C4 (23%) by Week 52. The decreases in immunoglobulins and C3 and C4 were maintained during the 24-week extension period.
- At Week 52, 15% of belimumab subjects who were anti-dsDNA positive converted to seronegative status versus 3.5% of placebo patients while 15% of belimumab treated patients who were seropositive for ANA converted to negative compared to 11% of placebo patients. No dose-response relationships were observed for any of these effects. The changes in anti-dsDNA were augmented

or maintained during the 24-week extension period for the 1mg/kg and 10mg/kg belimumab groups. (Note: Changes in ANA during the trial extension could not be assessed due to modifications to assay parameters.)

**Post Hoc Analyses:**

Exploratory analyses were performed by the sponsor in a subgroup of subjects (n=321) who were autoantibody positive (defined as having ANA titer  $\geq$  1:80 and/or anti-dsDNA  $\geq$  30 IU/mL at both screening and Day 0). The results from these analyses are as follows:

- The combined belimumab treatment groups had a greater mean decrease (29%) from baseline SELENA SLEDAI score at Week 52 as compared to placebo (14%).
- The combined belimumab treatment groups had a greater mean decrease (33%) from baseline PGA score at Week 52 as compared to placebo (11%).
- Based on a tri-component endpoint (SLE Responder Index comprised of a reduction in SELENA SLEDAI score  $\geq$  4 points, no worsening in PGA  $\geq$  0.3 points, and no new BILAG A or 2 B flare) the combined belimumab group had a greater response to treatment (46%) as compared to placebo (29%) at Week 52.

**Efficacy Conclusions:**

Treatment with 1 mg/kg, 4 mg/kg and 10 mg/kg doses of belimumab compared to placebo did not result in a significant improvement in efficacy or a dose response as assessed by the co-primary endpoints the percent change in SELENA SLEDAI score at Week 24 and time to first flare as defined by the SLENA SLEDAI SLE Flare Index. No benefit associated with belimumab treatment as assessed by the major secondary endpoints (percent change in SLENA SLEDAI score at Week 52 and AUC, percent change in BILAG disease activity score at Week 52 and AUC, time to first BILAG A or B flare, and reduction in prednisone dose  $\leq$  7.5 mg/day) was also observed in this trial. Pharmacodynamic changes associated with belimumab exposure were observed for a number of biomarkers that included decreases in immunoglobulins and anti-dsDNA, and increases in C4. These changes were not associated with a dose-response relationship. A decrease in B cell counts (CD19+, CD20+, activated, naïve, plasmacytoid, and SLE subset of plasma cells) was also observed in subjects from all 3 belimumab treatment groups. Post hoc analyses identified a subpopulation of autoantibody positive SLE subjects who were more responsive to belimumab therapy as demonstrated by greater improvements in both SELENA SLEDAI score and PGA as well as improvement measured by the composite endpoint, the SLE Responder Index.

**Study Number and Title:** HGS1006-C1056 (BLISS-76) - A Phase 3, Multicenter, Double-Blind, Placebo-Controlled, 76-Week Study to Evaluate the Efficacy and Safety of Belimumab, (HGS1006, LymphoStat-B), a Fully Human Monoclonal Anti-BlyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE) (Interim Report)

**Study Centers:** Multicenter (59 sites: U.S. 58 sites and Canada 1 site)

**Dates Conducted:** This trial was started on February 8, 2007 and 52-weeks of completed on September 22, 2009. (This interim report contains efficacy and safety data recorded through the Week 52 visit with a data cut-off of June 25, 2009.)

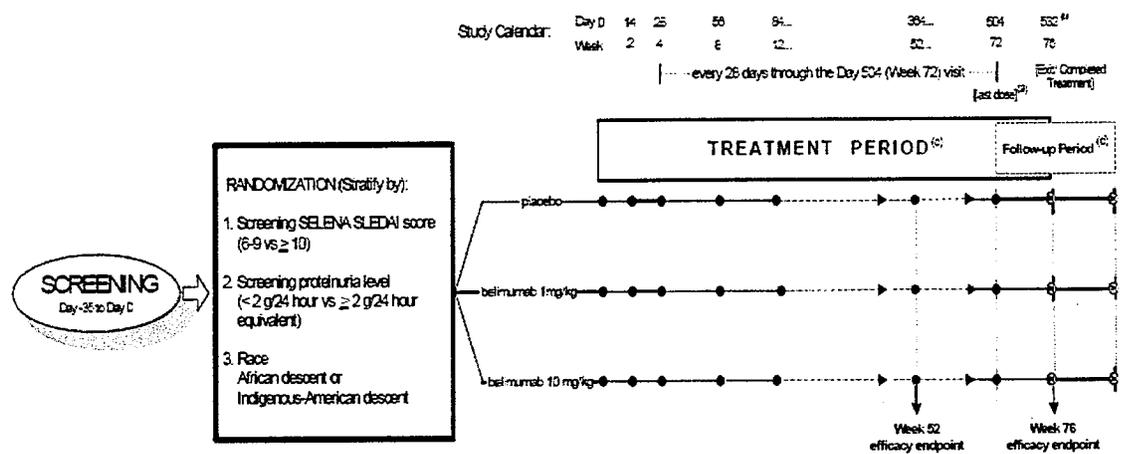
**Objectives:**

- To assess the efficacy of belimumab in patients with SLE
- To assess the safety and tolerability of belimumab in patients with SLE
- To determine the impact of belimumab on SLE patients' quality of life

**Study Design:**

Study 1056 was a multicenter, double-blind, placebo-controlled, randomized study in patients with active seropositive SLE on stable standard of care immunosuppressive medications for their disease. Eligible candidates were randomized via a 1:1:1 ratio to the following 3 treatment groups: 1mg/kg IV belimumab, 10 mg/kg belimumab or placebo IV. Randomization was stratified by subjects' screening SELENA SLEDAI score (6-9 vs  $\geq 10$ ), screening proteinuria level (<2g/24 hours vs  $\geq 2$  g/24 hours equivalent) and race (African descent or indigenous-American descent vs other). All patients including those who withdrew from the trial were required to return to their respective study site for a final follow-up visit 4 weeks post-administration of last study infusion. Upon completion of the 76-week study, participants were to have the option of participating in a continuation study 1074. Those who did not wish to participate in 1074 were to have returned for an additional follow-up visit 8 weeks post-administration of their final study infusion. Figure 2 is a schema of the proposed trial.

Figure 2 – Study schematic for 1056



- (60) The last dose of study agent is given on the Day 504 (Week 72) visit to subjects NOT participating in the continuation protocol.
- (61) Subjects continuing in the continuation protocol are dosed on the Day 532 (Week 76) visit. This Day 532 (Week 76) represents the first dose (ie, Day 0) of the continuation protocol. For subjects not participating in the continuation protocol, the Day 532 (Week 76) visit serves as the exit visit.
- (62) The treatment period includes 72 weeks of study agent administration (Day 0 to the Day 504 visit) and a follow-up visit at Week 76 which is 4 weeks after the last dose of the study agent.
- (63) The follow-up period includes 2 scheduled visits of 4 and 8 weeks after the last dose of study agent (Day 504/Week 72) for subjects not participating in the continuation protocol.

Sponsor's Fig. 5-1; p. 29 Clinical Trial Report

### Major Inclusion Criteria:

Subjects were men and women  $\geq 18$  years of age with ANA-positive SLE who met all of the following criteria:

1. Diagnosis of SLE as per the American College of Rheumatology (ACR) criteria
2. A diagnosis of active SLE defined as a SELENA SLEDAI score  $\geq 6$  at screening
3. Unequivocally positive anti-nuclear antibody (ANA) test results from 2 independent time points as follows:
  - Positive test results from 2 independent time points within the study screening period. (A positive ANA test is defined as an ANA titer  $\geq 1:80$  and/or a positive anti-dsDNA ( $\geq 30$  IU/mL) serum antibody) or
  - One positive historical test result and 1 positive test result during the screening period
4. On a stable SLE treatment regimen consisting of any of the following medications (alone or in combination) for a period of at least 30 days prior to Day 0 (i.e., day of first dose of study agent):
  - Corticosteroids (prednisone or prednisone equivalent, up to 40 mg/day):
  - Other immunosuppressive or immunomodulatory agents: methotrexate, azathioprine, leflunomide, mycophenolate mofetil, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine or thalidomide.
  - Antimalarials (e.g, hydroxychloroquine, chloroquine, quinacrine)
  - Non-steroidal anti-inflammatory drugs (NSAIDs)

### NOTE :

- Pre-existing SLE medications were to have been stable for at least 30 days prior to Day 0

- Corticosteroids may have been added as new medication or their doses adjusted only up to 30 days prior to Day 0
  - New SLE therapy other than corticosteroids could not be added within 60 days of Day 0
5. Individuals on angiotensin pathway antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers [ARBs]) had to be on a stable regimen for a period of at least 30 days prior to Day 0.
  6. Individuals on HMG CoA reductase inhibitors ("statins") had to be on a stable regimen for a period of at least 30 days prior to Day 0.
  7. Female candidates of childbearing potential could not be pregnant or nursing and had to have a negative serum pregnancy test at screening in addition to agreeing to practice complete abstinence from intercourse or using one of the acceptable methods of birth control listed in the protocol for the duration of the study
  8. Male candidates had to agree to use effective contraception for the duration of the study and for 3 months post-administration of last study dose

**Exclusion Criteria:** Potential study candidates were excluded from the study if any of the following criteria applied:

1. Treatment with any B-cell targeted therapy (rituximab, other anti-CD20 agents, anti-CD22, anti-CD52, BLyS-receptor fusion protein) at any time
2. Treatment within 364 days of Day 0 with abatacept or any biological investigational agent other than B-cell targeted therapy
3. Administered 3 or more courses of systemic corticosteroids for concomitant conditions such as asthma or atopic dermatitis within 364 days of Day 0 (topical and inhaled steroids are permitted)
4. Administered intravenous (IV) cyclophosphamide within 180 days of Day 0.
5. Treated with anti-TNF therapy, interleukin-1 receptor antagonist, intravenous immunoglobulin, high dose prednisone (>100 mg/d), or plasmapheresis within 90 days of Day 0
6. Treated with a non-biological investigational agent, or any new immunosuppressive/immunomodulatory agent, anti-malarial, NSAID, HMG CoA reductase inhibitor or angiotensin pathway antihypertensive within 60 Days of Day 0. (Note: New inhaled steroids or topical immunosuppressive agents were permitted. Any NSAID use for <1week was allowed.)
7. Administered a live vaccine or had a change in dose of a corticosteroid, other immunosuppressive/immunomodulatory agent, anti-malarial, NSAID, HMG CoA reductase inhibitor, or angiotensin pathway antihypertensive within 30 days of Day 0.
8. History of (H/O) severe lupus nephritis (defined by proteinuria >6 g/24 h or equivalent using spot urine protein to creatinine ration, or serum creatinine >2.5 mg/dL0, or have active nephritis, require hemodialysis or high-dose prednisone (>100 mg/day) within 90 days of Day 0
9. H/O active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident (CVA), cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 0.
10. H/O major organ transplant or hematopoietic stem cell/marrow transplant
11. H/O significant or unstable or uncontrolled acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematological, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases)
12. H/O any medical disease, lab abnormality, or condition or planning a surgical procedure during the course of the trial
13. H/O malignant neoplasm within the last 5 years with the exception of excised basal or squamous cell carcinomas of the skin or cervical carcinoma in situ
14. H/O acute or chronic infections that required hospitalization for treatment or parental antibiotic or antimicrobial agents within 60 days of Day 0 or the concurrent use of suppressive anti-infective therapy (i.e., antibacterials, antivirals, antifungals, or antiparasitic agents)
15. H/O recent alcohol or drug abuse within 364 days prior to Day 0

16. H/O a positive test for HIV-1 antibody, hepatitis B surface antigen, or hepatitis C antibody
17. H/O IgA deficiency (IgA level <10 mg/dL)
18. Have a Grade 3 or greater lab abnormality except for the following which were allowed: stable Grade 3 prothrombin time (PT) due to warfarin therapy, stable Grade 3/4 proteinuria ( $\leq 6$  g/24 h equivalent by spot urine protein to creatinine ration allowed), or stable Grade 3 neutropenia or stable Grade 3 WBC
19. H/O anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.

**Treatment:**

Study infusions were administered over 1 hour on Days 0, 14, 28 and then every 28 days through Week 72 of the study.

**Removal of Patients from Treatment or Assessment:**

Subjects were to have discontinued from this trial if they withdrew consent, received a prohibited concurrent medication or therapy, experienced unacceptable toxicity, became pregnant, or missed 3 or more consecutive study infusions.

**Concomitant Medications:**

The protocol permitted patients with a history of allergies or who had previously received IVIG to be prophylactically medicated with diphenhydramine, acetaminophen or H2-receptor antagonists which were to have been employed in cases of study-related infusion reactions.

The protocol required patients to be on a stable SLE treatment regimen for at least 30 days prior to Day 0 which may have consisted of any of the following medications alone or in combination: steroids ( $\leq 40$  mg/day of prednisone or equivalent), antimalarials, NSAIDs, MTX, azathioprine, leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide, 6-mercaptopurine or thalidomide. Changes in background immunosuppressive agents were permitted due to toxicity or shortages as were adjustments in concurrent medications (e.g., HMG CoA reductase inhibitors, angiotensin pathway antihypertensives, NSAIDs and aspirin) as clinically needed post-administration of the first study infusion during prespecified time periods over the course of the study. However, any changes in the following medications during restricted periods were to have resulted in the subject being considered a treatment failure and withdrawn from the study:

- Antimalarials: Initiation of treatment or changes in dose were permitted between Day 0 and Day 122 visits. After the Day 112 visit, any initiation of new therapy or increase in dose was to be considered a treatment failure
- Steroids: changes in the total dose of systemic steroids were permitted during the first 6 months of the trial (Day 168 visit) but the total systemic dose had to return to within 25% or 5 mg over baseline (Day 0) dose (whichever was higher) by the Day 168 visit, or the subject was to be considered a treatment failure. (Note: The protocol contained algorithms for both tapering and treating SLE

flares with steroids.) Intra-articular (IA) steroid injections were permitted between baseline (Day 0) and the Day 308 visit and between Day 364 (Week 52) visit and the Day 476 (Week 68) visit. Patients who receive IA steroids during the 8 weeks prior to the Week 52 or Week 76 study visit were to have been considered treatment failures.

- Other Immunosuppressive/Immunomodulatory Agents: doses were permitted to have been increased up to the Day 112 visit. Initiation of any new immunosuppressive/immunomodulatory agent after Day 0 or increase in dose over baseline or Day 112 (whichever was higher) was to be considered a treatment failure
- HMG CoA reductase inhibitors: Initiation of new treatment starting after the Day 168 visit was to be considered a treatment failure
- Angiotensin pathway antihypertensives: Initiation of new treatment starting after the Day 112 visit was to be considered a treatment failure
- NSAIDs and Aspirin: Initiation of new treatment used for  $\geq 7$  days starting after the Day 308 visit was to be considered a treatment failure

Subjects who initiated therapy with any of the following banned medications or therapies were to have been also considered treatment failures and withdrawn from the study: other investigational agents, anti-TNF therapy, other biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist), IV immunoglobulin (IVIG), IV cyclophosphamide or plasmapheresis.

**Efficacy and Safety Assessments:**

The following Table 12 and Table 13 are tabular flow charts of the scheduled study observations and procedures:

Table 12 – Schedule of Procedures and Evaluations for Study 1056

Study Visit	Treatment Period Days 0 – 504 (Weeks 0 – 72)																	Post-Treatment Follow-up Period					
	Day 0 Visit	Day 14 Visit ± 3 days	Day 28 Visit ± 3 days	Day 56 Visit ± 7 days	Day 84 Visit ± 7 days	Day 112 Visit ± 7 days	Day 140 Visit ± 7 days	Day 168 Visit ± 7 days	Day 196 Visit ± 7 days	Day 224 Visit ± 7 days	Day 252 Visit ± 7 days	Day 280 Visit ± 7 days	Day 308 Visit ± 7 days	Day 336 Visit ± 7 days	Day 364 Visit ± 7 days	Day 392 Visit ± 7 days	Day 420 Visit ± 7 days	Day 448 Visit ± 7 days	Day 476 Visit ± 7 days	Day 504 Visit ± 7 days	Day 532 or EXIT Visit (4-wks post last dose) ± 7 days <sup>a</sup>	8 wk Follow-up Visit (8-wks post last dose) ± 7 days <sup>b</sup>	Unscheduled Visit <sup>c</sup>
Study Week		Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76		
Vital Signs <sup>c,d</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight <sup>d,e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-driven Physical Exam	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology & Modified Chem 20 (non fasting) <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Spot urine (protein to creatinine ratio) <sup>g</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Pregnancy Test <sup>d,h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Sampling <sup>i</sup>	X	X		X				X							X						X	X	
Immunogenicity <sup>j</sup>	X			X				X							X						X	X	
Pharmacogenetic Sampling <sup>k</sup>	X													X							X		
Biological Markers (B cells/T cells) <sup>l</sup>	X			X				X							X							X	
C3/C4 and anti-dsDNA	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Autoantibodies (aCL, anti-Sm, anti-ribosomal P, ANA by ELISA OD & titer) <sup>m</sup>	X			X				X							X						X		

(continued)

Sponsor's Table 3; p. 52-54 of Protocol 1056.

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Table 13 - Schedule of Procedures and Evaluations for Study 1056 (cont.)

Study Visit	Treatment Period Days 0 – 504 (Weeks 0 – 72)																	Post Treatment Follow-up Period					
	Day 0 Visit	Day 14 Visit ± 3 days	Day 28 Visit ± 3 days	Day 56 Visit ± 7 days	Day 84 Visit ± 7 days	Day 112 Visit ± 7 days	Day 140 Visit ± 7 days	Day 168 Visit ± 7 days	Day 196 Visit ± 7 days	Day 224 Visit ± 7 days	Day 252 Visit ± 7 days	Day 280 Visit ± 7 days	Day 308 Visit ± 7 days	Day 336 Visit ± 7 days	Day 364 Visit ± 7 days	Day 392 Visit ± 7 days	Day 420 Visit ± 7 days	Day 448 Visit ± 7 days	Day 476 Visit ± 7 days	Day 504 Visit ± 7 days	Day 532 or EXIT Visit (4-wk post last dose) ± 7 days <sup>a</sup>	8-wk Follow-up Visit (8-wk post last dose) ± 7 days <sup>a</sup>	Unscheduled Visit <sup>s</sup>
Study Week		Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76		
BLVS Protein	X														X						X	X	
Functional Antibodies <sup>k</sup>	X														X						X	X	
Antibody Titer (Vaccine Response) See to footnote O for visit schedule.															X								
Immunoglobulins <sup>l</sup> , C-Reactive Proteins and PT/PTT	X			X		X		X		X		X			X			X			X		
Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, PGA and BILAG <sup>o</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLICC/ACR Damage Index	X														X						X		
SF-36 Health Survey, FACTT-Fatigue Scale, and EQ-5D <sup>p</sup>	X		X	X	X		X	X		X		X		X	X				X		X		
Workplace Productivity Questionnaire	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Emergency Room Visit Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Agent Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess/Record Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(continued)

<sup>a</sup> The Exit (Day 532) visit will occur approximately 4 weeks after the last dose of study agent. For subjects completing 72 weeks of treatment and continuing into the continuation protocol, this visit will also serve as their Day 0 (1<sup>st</sup> dose) visit of the continuation protocol.  
<sup>b</sup> The 8-week follow-up visit is to occur approximately 8 weeks after last dose of study agent (for subjects not continuing in the continuation protocol).  
<sup>c</sup> Vital signs includes temperature, sitting blood pressure, respiratory rate and pulse.  
<sup>d</sup> Complete prior to dosing.  
<sup>e</sup> If the subject's weight changes by more than 5% from the Day 0 weight, the weight at the current visit should be used for dose calculation.  
<sup>f</sup> Refer to Appendix 11 for a listing of laboratory assessments to be completed.  
<sup>g</sup> A 24-hour urine may be done if clinically indicated (eg, renal flare).  
<sup>h</sup> Serum pregnancy test required at screening. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See Section 6.1 (Screening Procedures) for definition of those exempted from subsequent pregnancy testing.  
<sup>i</sup> Pharmacokinetic sampling: Before the start of infusion on Days 0, 56, 364 and 532; 0-4 hours after the end of infusion on Days 14 and 168; at any time during the visit during the 8-week follow-up visit.  
<sup>j</sup> For subjects not entering the continuation study who had a positive anti-belimumab antibody response at the 8 week follow-up visit (or last study visit at which immunogenicity was assessed if 8 week follow-up visit immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or upon completion and/or unblinding of the study, whichever is later.  
<sup>k</sup> PGx sampling: Includes baseline genetics and follow-up genetic expression array analysis. PGx informed consent must be obtained prior to any blood being taken for PGx research. Refer to Section 9.0 and Appendix 12. Samples should be drawn prior to dosing.  
<sup>l</sup> Biological Markers include FACS of peripheral lymphocytes: B lymphocytes (CD20<sup>+</sup>, CD20<sup>+</sup>/27<sup>+</sup> memory, CD20<sup>+</sup>/27<sup>+</sup> naïve, CD20<sup>+</sup>/69<sup>+</sup> activated, CD20<sup>+</sup>/138<sup>+</sup> plasmacytoid, CD19<sup>+</sup>/27<sup>high</sup>/38<sup>high</sup> SLE subset and CD20<sup>+</sup>/138<sup>+</sup> plasma cells) and T lymphocytes (CD3<sup>+</sup>/4<sup>+</sup> and CD3<sup>+</sup>/8<sup>+</sup>).  
<sup>m</sup> Autoantibodies include: ANA aCL (IgM, IgG, IgA isotypes) anti-ribosomal P and anti-Sm. aCL and anti-SM autoantibodies will be measured in all subjects at Day 0 and samples will be collected at the time points specified; however, the assay will be run only on subjects with elevated titers of these autoantibodies at Day 0.  
<sup>n</sup> Functional antibodies are tested in relation to history of previously received pneumococcal, influenza or tetanus vaccines.  
<sup>o</sup> Antibody titer test will be completed on subjects that plan to receive a vaccine during the treatment period of this study. A blood sample to measure the prevaccination titer will be obtained during a study visit closest to the time prior to the planned vaccination. A postvaccine titer will be drawn on the next study visit at which other blood is drawn, provided it has been at least 21 days postimmunization. If the immunization was administered less than 21 days prior to a study visit, the postvaccination titer should be obtained at the following visit.  
<sup>p</sup> Serum immunoglobulin isotypes: IgG, IgM, IgA.  
<sup>q</sup> Refer to Section 6.8.1 for guidelines for scoring proteinuria for SELENA SLEDAI and BILAG evaluation.  
<sup>r</sup> Must be completed by the subject prior to any study-related discussion with the investigator or study coordinator. The FACTT-Fatigue Scale, EQ-5D and the Workplace Productivity Questionnaire will only be completed by subjects for whom a survey exists in the subject's language.  
<sup>s</sup> Unscheduled Visits: Other assessments as clinically indicated.

Sponsor's Table 3; p. 52-54 of Protocol 1056.

**Outcome Measures:**

**Primary efficacy endpoint:**

Primary efficacy variable is the SLE Responder Index (SRI) response rate at Week 52 which is defined as the proportion of patients with:

- ≥ 4 point reduction from baseline in SELENA SLEDAI score **AND**
- No worsening (increase of <0.30 points from baseline) in the Physician's Global Assessment (PGA) **AND**

- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52)

**Major secondary efficacy endpoints:**

- Response rate at Week 76 (as defined above for Week 52)
- Percentage of patients with  $\geq 4$  point reduction from baseline in SELENA SLEDAI score at Week 52
- Mean change in PGA at Week 24
- Mean change in SF-36 Health Survey physical component summary score (PCS) at Week 24)
- Percentage of subjects whose average prednisone dose has been reduced by  $\geq 25\%$  from baseline to  $\leq 7.5$  mg/day during Weeks 40 through 52

**Ancillary secondary variables:**

- Response rate at Weeks 12 and 24
- Time to first response
- Duration of first response
- Percent of patients with  $\geq 4$  point reduction from baseline in SELENA SLEDAI at Weeks 12, 24, and 76.
- Mean change in PGA at week 12, 52, and 76
- Percent change from baseline in SELENA SLEDAI score at Weeks 12, 24, 52, 76
- Percent of patients with no worsening (increase of  $<0.30$  points from baseline) in PGA at Weeks 12, 24, 52, and 76
- Percent of patients with not new BILAG A organ domain score or new 2 BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Weeks 12, 24, 52, and 76)
- BILAG response rates at Weeks 12, 24, 52, and 76
- Time to BILAG response
- AUC of the SLENA SLEDAI score over 52 and 76 weeks
- Change in the SLICC/ACR Damage Index at Weeks 52 and 76
- Percent of patients with no new 1A/2B organ domain scores from Week 28 through Week 52
- Percent of patients with no new 1A/2B organ domain scores from Week 52 through Week 76
- Time to SLE flares over 52 and 76 weeks
- Time to first SLE flare after 24 weeks
- Number of flares per subject and the rate of flares over 52 and 76 weeks
- Renal flare rate and time to first renal flare
- The rate and duration of renal remission and time to renal remission
- Percent change in proteinuria
- Percentage of patients with average steroid dose has been reduced by 25% from baseline to 7.5 mg/day or lower during Weeks 64 through 76
- Percent change from baseline of prednisone dose at Weeks 12, 24, 52, and 76

- Number of days of daily steroid dose  $\leq 7.5$  mg/day and/or reduced by 50% from baseline over time
- Time to reduction of daily prednisone dose  $\leq 7.5$  mg/day and/or reduced by 50% from baseline over 52 weeks and 76 weeks
- Percent of patients with daily prednisone dose reduced  $\leq 7.5$  mg/day from  $> 7.5$  mg/day at baseline over time
- Percent of patients with daily steroid dose increased to  $>7.5$  mg/day from  $\leq 7.5$  mg/day at baseline over time

**Patient Reported Outcomes:**

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

**Biomarkers:**

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

**Immune Response to Vaccines:**

- Percent change from baseline in titer of functional antibodies (total anti-pneumococcal IgG, anti-influenza IgG, anti-tetanus toxin IgG)
- Percent change in antibody levels in response to vaccines (total anti-pneumococcal IgG, anti-influenza IgG, anti-tetanus toxin IgG) following a primary or a booster vaccine
- Percent of patients vaccinated prior to the study and those receiving primary or booster vaccine during study who have antibody titer greater than or equal to those predictive of protective immunity levels for total anti-pneumococcal, anti-influenza, or anti-tetanus toxin total IgG

**Statistical Design, Definitions of Analyzed Populations and Analyses Plan:**

Sample size calculations were based on data generated from the Phase 2 SLE study conducted by the sponsor (Study LBSL02). The proposed study had approximately 90% power at a significance level of 5% to show an absolute difference in improvement of 14% in the response rate of the 10 mg/kg belimumab group (or both the 10 mg/kg and 1mg/kg belimumab groups) as compared to the placebo group at Week 52. The assumptions used in the statistical power calculations included:

- 43% placebo response rate
- A 57% belimumab response rate
- An average (population) response rate of 50% under the null hypothesis (i.e., active= placebo)

The modified intent-to-treat (mITT) population was used for the primary analysis for this trial. This was defined as the subset of all randomized patients who received at least 1 dose of study agent. The mITT analysis was performed according to the treatment that a subject was randomized to receive, regardless of actual treatment received.

Logistic regression was used to analyze the primary efficacy endpoint and the major secondary endpoints involving response rate at Week 76, reduction in SELENA SLEDAI score and prednisone reduction while an analysis of covariance (ANCOVA) was used for the change from baseline in PGA and SF-36 PCS. Subjects whose background SLE medications were changed after prespecified time points in the common protocol were imputed as treatment failures/nonresponders, as were subjects who dropped out or who had missing data for the Week 52 analysis. A step-down sequential testing procedure was used to account for multiplicity in doses in the analysis of the primary efficacy endpoint (i.e., comparison of belimumab 10 mg/kg to placebo was conducted first and only if that comparison was statistically significant was the comparison of belimumab 1 mg/kg to placebo to be conducted). However, no multiplicity correction was applied to subgroup analyses or the analyses of secondary endpoints.

**Safety Evaluation:**

Descriptive statistics were used to summarize data describing AEs, SAEs, deaths, abnormal lab tests, vital signs, and antibodies to belimumab. The likelihood ratio chi-squared test or the Fisher's exact test in cases where the number of events was less than 5 was to be used to ascertain if the occurrence of AEs was comparable across treatment groups.

**Immunogenicity Assessments:**

Serum samples were collected for belimumab immunogenicity assays prior to initial dosing on Day 0; prior to dosing at weeks 8, 24, 52 and 76/exit; and at the 8-week follow-up visit for subjects who withdrew prior to completion or choose not to enter the continuation study.

**Study Conduct**

**Protocol Amendments:**

Listed below are the 2 protocol amendments that were made to Study 1056. Each amendment was approved by the Agency's reviewing division prior to being implemented as per the SPA process.

1. Amendment 1 (implemented on May 18, 2007)

The following changes to the protocol:

- Clarification of the forms of mycophenolate available internationally and their permitted use during the study as related to Inclusion Criterion 5 and Section 5.5.1.3 Concomitant Medications

- Modification of Exclusion Criterion 16 to reflect change in HIV testing for both types 1 and 2
- Modification of Exclusion Criterion 18 to permit subjects to be randomized with stable Grade 3 hypoalbuminemia due to lupus nephritis
- Modification of the primary efficacy analysis to use the baseline (Day 0) proteinuria level instead of the screening level in the logistic regression model because a subject's proteinuria level may change over the screening period
- Revision of the timing of the initial DMC meeting for review of the data from the Phase 3 studies to occur after the first 100 subjects have been treated through Day 56 in the combined trials or within 6 months of the 1<sup>st</sup> subject, whichever is earlier. Addition clarification that the DMC would monitor these trials until the data are locked and analyzed through Week 76 for 1056 and Week 52 for 1057 after which time monitoring may be assumed by an internal HGS committee
- Modification of Table 3 "Study Calendar" to include both ELISA and a titer at every time point that an ANA specimen is tested. The Workplace Productivity Questionnaire and Emergency Room Visit Question were removed from the Unscheduled visit
- Modification of the "Guidelines for Scoring Proteinuria for SELENA SLEDAI" to require a decrease of >0.5 g/24 hour equivalent or a decrease to  $\leq 0.5$  g/24 hour equivalent from the previous visit to the current visit for improvement in proteinuria after Screening
- Modification of the analysis of safety variables which will no longer include comparative analyses across treatment groups due to multiplicity issues
- Amended the SELENA SLEDAI Disease Assessment Scales to bring text into agreement with the validated SLE Flare Index (published in 2005). Mycophenolate was also added to 1 criterion.
- Modification of the BILAG Disease Assessment Scale to include "SLE Related" check boxes that were being used in the Phase 3 eCRF in order to assist in the scoring of SLE-related lab values recorded on the BILAG
- The range for Grade 1 mild hematuria in the Adverse Event Severity Grading Tables was changed because the central lab used for the study considered the normal range for RBCs in the urine to be 0-3/hpf

2. Amendment 2 (implemented on January 31, 2008)

The following 4 changes were made to the protocol:

- Modification of the requirements and schedule for follow-up testing to maintain the study blind. Follow up testing for anti-belimumab antibodies was to be performed only on subjects who were positive for anti-belimumab antibodies at the 8-week follow-up visit (or at the last study visit at which immunogenicity was assessed if the 8-week sample was not available). This testing was to be performed at least 6 months after the last dose or after completion and/or unblinding of the study, whichever was later in order to allow the treatment blinding to remain intact until the study was completed and/or unblinded

- Modification of Exclusion Criterion 18 to allow subjects with stable Grade 3 partial thromboplastin time due to lupus anticoagulant to be randomized and to allow subjects with stable Grade 3 GGT elevation due to lupus hepatitis to be randomized
- Addition of anti-ribosomal P testing to the autoantibody panel and the analysis of changes in anti-ribosomal P autoantibody levels to the secondary efficacy analysis
- Previous IVIG administration was added as an indication for prophylaxis prior to administration of belimumab

**RESULTS:**

**Disposition of Subjects:**

A total of 826 subjects were randomized to the three treatment groups as follows: 277 patients to the placebo group, 275 patients to belimumab 1 mg/kg group and 274 patients to the belimumab 10 mg/kg group. Overall the proportions of patients who discontinued from the three treatment arms of this study were similar with a slightly higher rate of early discontinuation occurring in the placebo group than in the belimumab groups as shown in Table 14 below. A similar proportion of patients discontinued from these studies due to adverse events and lack of efficacy in the placebo and belimumab treatment groups.

**Table 14 – Subject Disposition for Study C1056**

	Placebo	Belimumab 1mg/kg	Belimumab 10 mg/kg	Total
<b>Number of Patients Randomized</b>	277	275	274	826
<b>Number of Patients Treated (mITT)</b>	275	271	273	819
<b>Number of Patients Who Completed Week 52:</b>	205 (75%)	216 (80%)	209 (77%)	630 (77%)
<b>Number of Patients Withdrawn Prior to Week 52:</b>	70 (26%)	55 (20%)	64 (23%)	189 (23%)
<b>Subject Request</b>	24 (9%)	14 (5%)	13 (5%)	51 (6%)
<b>Adverse Event</b>	16 (6%)	13 (5%)	19 (7%)	48 (6%)
<b>Lack of Efficacy</b>	15 (6%)	12 (4%)	14 (5%)	41 (5%)
<b>Non-Compliance</b>	2 (1%)	1 (0%)	2 (1%)	5 (1%)
<b>Lost to Follow-Up</b>	3 (1%)	4 (2%)	6 (2%)	13 (2%)
<b>Protocol Violation</b>	5 (2%)	2 (1%)	5 (2%)	12 (2%)
<b>Investigator Decision</b>	2 (1%)	3 (1%)	3 (1%)	8 (1%)
<b>Other</b>	3 (1%)	6 (2%)	2 (1%)	11 (1%)
<b>Pregnancy<sup>1</sup></b>	-	2 (1%)	1 (0%)	3 (0%)

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

**Protocol Deviations/Violations:**

Table 15 shows that there were a total of 138 protocol violations incurred by 119 subjects for this study as follows: 56 subjects (7%) did not meet study entry criteria (unstable or prohibited treatment regimens within 60 days of Day 0, did not meet screening ACR criteria for SLE or other entry criteria, initial lab procedures not followed); 58 subjects (7%) developed withdrawal criteria but were not withdrawn (received an increase dose of steroids or immunosuppressives), and 16 subjects (2%) received the wrong treatment or an incorrect dose. With the exception of a higher proportion of patients in the 10 mg/kg belimumab group who received the wrong treatment or incorrect dose as compared to the other treatment groups, the treatment groups are balanced with regards to occurrence of protocol violations.

**Table 15 – Summary of Protocol Violations for Study 1056**

	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)
<b>Entered Study But Did Not Meet Entry Criteria</b>	23 (8%)	15 (6%)	18 (7%)	<b>56 (7%)</b>
<b>Developed Withdrawal Criteria But Was Not Withdrawn</b>	22 (8%)	15 (6%)	21 (8%)	<b>58 (7%)</b>
<b>Received Wrong Treatment or Incorrect Dose</b>	3 (1%)	2 (1%)	10 (4%)	<b>16 (2%)</b>

Modified Sponsor's Table 17-1; Appendix 17.

*Reviewer's Comment: The high rate of protocol violations related to receiving an incorrect dose of study medication could have played a role in the robustness of the study's efficacy outcome.*

**Treatment Compliance and Drug Exposure:**

All study infusions were administered in clinic by study staff.

**Demographics:**

As summarized in the following tables (Table 16 and Table 17), the treatment groups within Study 1056 were generally well balanced with respect to baseline demographics, region, disease characteristics and activity.

The subjects who participated in this trial were predominantly Caucasian (68%) and female (92%). Fourteen percent (14%) of the patients were of Black/African American in origin. The majority (53%) of subjects were from the U.S. and Canada while the remaining subjects were from Western Europe/Israel (25%) and Eastern Europe (11%). The mean age of subjects was 40 years and mean weight of subjects was 73 kg. No important imbalances in these demographic factors across treatment groups were noted within study 1056.

Table 16 – Demographic Characteristics of Subjects Enrolled in Study C1056

Demographics	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)
<b>Gender:</b>				
Female	252 (92%)	253 (93%)	259 (95%)	764 (93%)
Male	23 (8%)			
<b>Race<sup>1</sup>:</b>				
Caucasian	188 (68%)	192 (71%)	189 (69%)	569 (70%)
Asian	11 (4%)	6 (2%)	11 (4%)	28 (3%)
African American	39 (14%)	40 (15%)	39 (14%)	118 (14%)
Alaskan Native/American Indian	36 (13%)	33 (12%)	34 (13%)	103 (13%)
Native Hawaiian/Pacific Islander	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Multiracial	2 (1%)	3 (1%)	3 (1%)	8 (1%)
<b>Hispanic Origin:</b>	55 (20%)	62 (23%)	56 (21%)	173 (21%)
<b>Age (years):</b>				
Mean (SD)	40 (12)	40 (11)	41 (11)	40 (12)
≤ 45	189 (69%)	184 (68%)	178 (65%)	551 (67%)
> 45 to <65	77 (28%)	83 (31%)	92 (34%)	252 (31%)
≥ 65 to <75	9 (3%)	4 (2%)	3 (1%)	16 (2%)
<b>Weight:</b>				
Mean (SD)	72 (18)	73 (18)	74 (21)	73 (19)
(Min, Max)	(43, 170)	(43, 136)	(45, 165)	(43, 170)
<b>Region and Country</b>				
USA/Canada	145 (53%)	155 (57%)	136 (50%)	436 (53%)
Western Europe/Israel	64 (23%)	63 (23%)	75 (28%)	202 (25%)
Eastern Europe	36 (13%)	27 (10%)	30 (11%)	93 (11%)
Americas (excluding USA/Canada)	30 (11%)	26 (10%)	32 (12%)	88 (11%)

<sup>1</sup>Subjects who checked more than one race category are counted under individual race category according to the minority rule as well as multiracial category.

As shown in Table 17 below, the overall mean duration of SLE disease was 8 years for patients in this trial. Overall, these subjects had a high baseline level of disease activity as manifested by a SELENA SLEDAI mean score of 9.7 with 50% of the patients having a baseline SELENA SLEDAI score of  $\geq 10$  points. The individual treatment groups were similar in their baseline disease activity with only minor differences as assessed by the BILAG organ domain involvement, SELENA SLEDAI score category 0 to 3, and SLE flare index suggesting that patients with lower disease activity may have been slightly more frequently assigned to the belimumab 10mg/kg treatment group as compared to the placebo group. (Note: Patients with a baseline SELENA SLEDAI score category 0 to 3 were unable to achieve a response of  $\geq 4$  points necessary for a positive response as assessed by the primary endpoint, the SRI.)

Table 17 – Tabular Summary of Subject’s Baseline Disease Characteristics for Study C1056

Characteristic	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)
<b>SLE Disease Duration (yr):</b>				
Mean (SD)	7 (7)	8 (7)	7 (8)	8 (7)
<b>BILAG Organ Domain Involvement:</b>				
At least 1A or 2B	187 (68%)	173 (64%)	160 (59%)	520 (64%)
At Least 1A	37 (14%)	38 (14%)	24 (9%)	99 (12%)
At Least 1A or 1B	258 (94%)	245 (90%)	251 (92%)	754 (92%)
No A or B	17 (6%)	26 (10%)	22 (8%)	65 (8%)
<b>SELENA SLEDAI Category:</b>				
0 to 3	3 (1%)	5 (2%)	8 (3%)	16 (2%)
4 to 9	131(48%)	122 (45%)	129 (47%)	382 (47%)
10 to 11	62(23%)	72 (27%)	65 (24%)	199 (24%)
> 12	79 (29%)	72 (27%)	71 (26%)	222(27%)
<b>SELENA SLEDAI Score:</b>				
Mean (SD)	9.8 (4.0)	9.7 (3.7)	9.5 (3.6)	9.7 (3.8)
<b>SLE Flare Index<sup>1</sup>:</b>				
At Least 1 Flare	82 (30%)	63 (23%)	59 (22%)	204 (25%)
Severe Flare	3 (1%)	1 (0%)	4 (2%)	8 (1%)
<b>PGA Category:</b>				
0 to 1	33 (12%)	39 (14%)	51 (19%)	123 (15%)
>1 to 2.5	239 (87%)	230 (85%)	219 (80%)	688 (84%)
>2.5 to 3	3 (1%)	2 (1%)	3 (1%)	8 (1%)
<b>PGA Scale:</b>				
Mean (SD)	1.48 (0.47)	1.44 (0.50)	1.40 (0.54)	1.44 (0.50)
<b>SLICC Damage Index Score</b>				
Mean (SD)	0.99 (1.45)	1.04 (1.39)	0.94 (1.38)	0.99 (1.41)
<b>Proteinuria Category (g/24 hr):</b>				
<0.5	228 (83%)	231 (85%)	230 (84%)	689 (84%)
0.5 to <1	24 (9%)	22 (8%)	13 (5%)	59 (7%)
1 to <2	12 (4%)	11 (4%)	15 (6%)	38 (5%)
≥ 2	11 (4%)	7 (3%)	15 (6%)	33 (4%)
<b>Proteinuria Level (g/24 hr)</b>				
Mean (SD)	0.39 (0.81)	0.33 (0.65)	0.4 (0.73)	0.4 (0.74)

<sup>1</sup>At baseline compared with screening assessment.  
 Adapted Sponsor’s Table 6-4; p. 80.

The majority (96%) of patients in this trial were overwhelmingly seropositive for ANA and/or anti-dsDNA as shown in Table 18 below. The treatment groups within the trial were also generally well balanced with respect to baseline biomarkers of disease activity with the following exceptions. Differences in the 3 treatment groups for were observed for the presence of CRP, anti-ribosomal P and aCL. Higher proportions of patients in the placebo group were positive for CRP (42%) and anti-ribosomal P (11%) as compared to the belimumab treatment groups (1 mg/kg group: 37% and 5%; 10 mg/kg group: 33% and 6%, respectively). Additionally, the proportions of subjects who were positive for CRP were higher in the 1 mg/kg belimumab treatment group (46%) as compared to the belimumab 10mg/kg (37%) and placebo (36%) groups.

Table 18 - Tabular Summary of Subject's Baseline Serologies, Immunoglobulins, Complement and Other Biomarkers for Study C1056

	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)
<b>Anti-dsDNA:</b>				
Positive ( $\geq 30$ IU/mL)	174 (63%)	171 (63%)	179 (66%)	524 (64%)
Mean (SD)	151 (66)	139 (63)	143 (62)	144 (62)
<b>ANA:</b>				
Positive ( $\geq 80$ Titer)	253 (92%)	256 (95%)	245 (90%)	754 (92%)
Mean (SD)	836 (493)	850 (478)	796 (488)	828 (486)
<b>ANA and/or Anti-dsDNA</b>				
Positive:	265 (96%)	262 (97%)	261 (96%)	788 (96%)
<b>aCL:</b>				
Positive	116 (42%)	101 (37%)	88 (33%)	305 (37%)
<b>Anti-ribosomal P:</b>				
Positive ( $>25$ EU/mL)	29 (11%)	14 (5%)	15 (6%)	58 (7%)
Mean (SD)	67 (41)	70 (39)	66 (42)	67 (40)
<b>Anti-Smith:</b>				
Positive ( $\geq 15$ U/mL)	72 (27%)	69 (26%)	75 (28%)	216 (27%)
Mean (SD)	937 (5128)	1042 (4275)	478 (1941)	811 (3978)
<b>IgG:</b>				
Mean (SD)	15.9 (6.1)	15.8 (6.6)	15.3 (6.0)	15.7 (6.2)
$>ULN$ (16.18 g/L)	108 (39%)	105 (39%)	94 (34%)	307 (38%)
$<LLN$ 6.94 g/L	6 (2%)	5 (2%)	6 (2%)	17 (2%)
<b>IgA:</b>				
Mean (SD)	3.0 (1.5)	2.9 (1.5)	3.0 (1.5)	3.0 (1.5)
$>ULN$ (4.63 g/L)	38 (14%)	30 (11%)	37 (14%)	105 (13%)
$<LLN$ (0.81 g/L)	6 (2%)	3 (1%)	5 (2%)	14 (2%)
<b>IgM:</b>				
Mean (SD)	1.1 (0.7)	1.1 (0.7)	1.2 (0.91)	1.1 (0.77)
$>ULN$ (2.71 g/L)	4 (1%)	10 (4%)	16 (6%)	30 (4%)
$<LLN$ (0.48 g/L)	41 (15%)	38 (14%)	37 (14%)	116 (14%)
<b>C3:</b>				
Mean (SD)	958 (303)	995 (321)	973 (325)	975 (317)
Low ( $<900$ mg/L)	116 (42%)	100 (37%)	115 (42%)	331 (40%)
<b>C4:</b>				
Mean (SD)	16 (9)	17 (10)	16 (10)	17 (10)
Low ( $<16$ mg/dL)	143 (52%)	141 (52%)	147 (54%)	431 (53%)
<b>CRP:</b>				
Positive ( $>3$ mg/L)	92 (35%)	123 (46%)	97 (37%)	312 (39%)
Mean (SD)	15.4 (20.0)	13.1 (15.5)	11.3 (11.0)	13 (15.7)
<b>BLyS:</b>				
Above LOQ	268 (99%)	267 (99%)	263 (98%)	798 (99%)
Mean (SD)	1.7 (1.5)	1.8 (1.3)	1.8 (1.5)	1.8 (1.4)

Note: aCL is positive if any of aCL-IgG, aCL-IgA, or aCL-IgM is positive  
 Adapted Sponsor's Table 6-6; p. 82-83.

The following table (Table 19) summarizes concomitant SLE medications used by more than 10% of subjects who participated in Study 1056. The usage of concomitant SLE medications at baseline was generally similar for the three treatment group in this trial.

Table 19 - Tabular Summary of Concomitant SLE medication >10% of Subjects in Study C1056

	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)
<b>Total Glucocorticoid Use:</b>				
Methylprednisolone	212 (77%)	211 (78%)	200 (73%)	<b>623 (76%)</b>
Prednisolone	37 (14%)	28 (10%)	35 (13%)	<b>100 (12%)</b>
Prednisone	33 (12%)	35 (13%)	35 (13%)	<b>103 (13%)</b>
Prednisone	141 (51%)	147 (54%)	126 (46%)	<b>414 (51%)</b>
<b>Prednisone or Equivalent Dose at Baseline:</b>				
0 mg/day	63 (23%)	60 (22%)	73 (27%)	<b>196 (24%)</b>
>0 - ≤ 7.5 mg/day	86 (31%)	81 (30%)	80 (29%)	<b>247 (30%)</b>
>7.5 mg/day	126 (46%)	130 (48%)	120 (44%)	<b>376 (46%)</b>
<b>Average Prednisone or Equivalent Dose at Baseline:</b>				
Mean (SD)	9.4 (8.9)	8.7 (7.6)	8.4 (7.9)	<b>8.8 (8.2)</b>
<b>Angiotensin Pathway Antihypertensives:</b>	68 (25%)	67 (25%)	71 (26%)	<b>206 (26%)</b>
<b>Antimalarials:</b>	180 (66%)	171 (63%)	168 (62%)	<b>519 (63%)</b>
<b>Other Immunosuppressives:</b>	154 (56%)	153 (57%)	148 (54%)	<b>455 (56%)</b>
Azathioprine	57 (21%)	52 (19%)	58 (21%)	<b>167 (20%)</b>
Methotrexate	59 (22%)	53 (20%)	38 (14%)	<b>150 (18%)</b>
Mycophenolate Mofetil	37 (14%)	44 (16%)	44 (16%)	<b>125 (15%)</b>
<b>NSAIDs</b>	119 (43%)	114 (42%)	101 (37%)	<b>334 (41%)</b>
<b>HMG CoA Reductase Inhibitors</b>	30 (11%)	25 (9%)	28 (10%)	<b>83 (10%)</b>

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

### Efficacy:

As discussed in the Background section above, the primary endpoint was the SRI response rate at Week 52 for which a positive response was defined as a:

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

As shown in Table 20, patients treated with belimumab 10 mg/kg had a statistically higher rate of response than placebo patients in Study 1056. The results from the analyses of the subcomponents of the SRI were generally consistent with those of the primary analysis. The proportions of subjects achieving success for each of the subcomponents of the SRI were numerically higher in the belimumab groups than the placebo group in the study but did not reach statistical significance.

Table 20 – Week 52 Primary Endpoint and Subcomponent Results for Study C1056

	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)
<b>Response:</b>			
<b>Observed Difference vs Placebo</b>	93 (34%)	110 (41%)	118 (43%)
<b>OR (95% CI)<sup>1</sup> vs Placebo</b>		7% 1.34 (0.94, 1.91)	9% 1.52 (1.07, 2.15)
<b>P-value</b>		<b>0.1041</b>	<b>0.0207</b>
<b>Subcomponents</b>			
<b>4-Point Reduction in SELENA SLEDAI:</b>			
<b>OR (95% CI)<sup>1</sup> vs Placebo</b>	98 (36%)	116 (43%)	128 (47%)
<b>P-value</b>		1.36 (0.96, 1.93) <b>0.0869</b>	1.63 (1.15, 2.32) <b>0.0062</b>
<b>No Worsening in PGA:</b>			
<b>OR (95% CI)<sup>2</sup> vs Placebo</b>	173 (63%)	197 (73%)	189 (69%)
<b>P-value</b>		1.60 (1.11, 2.30) <b>0.0120</b>	1.32 (0.92, 1.90) <b>0.1258</b>
<b>No New 1A/2B BILAG Domain Scores:</b>			
<b>OR (95% CI)<sup>3</sup> vs Placebo</b>	179 (65%)	203 (75%)	189 (69%)
<b>P-value</b>		1.63 (1.12, 2.37) <b>0.0108</b>	1.20 (0.84, 1.73) <b>0.3193</b>

OR=Odds Ratio; CI =Confidence Interval

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

<sup>2</sup>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

<sup>3</sup>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 21 provides the reasons subjects failed to achieve a positive SRI response in this trial. Note that the categories provided are mutually exclusive and mutually exhaustive. The proportion of subjects who dropped out is approximately 16% in study 1056 and is fairly balanced across treatment groups within the study thus the impact of imputing dropouts as failures on the treatment effect in the primary analysis should be small. However, unlike dropouts, “medication failures” are not balanced across treatment groups (17%, 9%, and 10% for placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab respectively) in this trial. Since medication failures are more frequent in the placebo group than the belimumab groups, imputing medication failures as efficacy failures could bias the treatment effect in the primary efficacy endpoint in favor of belimumab (unless these subjects would truly have been unable to achieve success on the primary endpoint had they not taken the prohibited medication).

Table 21 – Tabular Summary of Disposition of Response at Week 52 for Study 1056

	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)
<b>Response</b>	93 (34%)	110 (41%)	118 (43%)
<b>No Response:</b>	182 (66%)	161 (59%)	155 (57%)
<b>Dropout<sup>1</sup> – Not a Medication Failure</b>	43 (16%)	40 (15%)	45 (17%)
<b>Medication Failure<sup>2</sup></b>	47 (17%)	24 (9%)	27 (10%)
<b>&lt;4 Point Reduction in SELENA SLEDAI (SS)<sup>3</sup></b>	87 (32%)	91 (34%)	73 (27%)
<b>≥4 Point Reduction in SS with the following<sup>3</sup>:</b>	5 (2%)	6 (2%)	10 (4%)
<b>Worsening in PGA only<sup>3</sup></b>	4 (2%)	4 (2%)	4 (2%)
<b>New 1A/2B/BILAG only<sup>3</sup></b>	1 (0%)	2 (1%)	6 (2%)
<b>Both Worsening in PGA and New 1A/2B BILAG<sup>3</sup></b>	--	--	--

<sup>1</sup>Subjects who withdrew early and had no data in the Day 364 +/- 28 day window

<sup>2</sup>Includes subjects who withdrew early and subjects who met all 3 response criteria at week 52 but took a protocol prohibited or restricted medication or dose

<sup>3</sup>In subjects who did not dropout and were not medication failures.

Adapted Sponsor's Table 7-3; p. 88.

The sponsor provided four sensitivity analyses for the primary efficacy endpoint. These sensitivity analyses were conducted as planned in the protocol. The results of these sensitivity analyses are largely consistent with the primary efficacy analysis and are shown in Table 22. Additional sensitivity analyses that address the issue of medication failures are presented and discussed in Section 6.1.5 of this review.

Table 22 - Tabular Summary of Sensitivity Analyses for Primary Endpoint Response at Week 52 for Study 1056

	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)
<b>Unadjusted Response:</b>			
Observed Difference vs Placebo	93 (34%)	110 (41%) 7%	118 (43%) 9%
OR (95% CI) <sup>1</sup> vs Placebo		1.34 (0.94, 1.89)	1.49 (1.05, 2.11)
P-value		0.1020	0.0239
<b>LOCF Response (adjusted):</b>			
Observed Difference vs Placebo	101 (37%)	118 (44%) 7%	132 (48%) 12%
OR (95% CI) <sup>1</sup> vs Placebo		1.33 (0.94, 1.89)	1.67 (1.17, 2.36)
P-value		0.1096	0.0043
<b>Completer Response (adjusted):</b>			
Observed Difference vs Placebo	90/193 (47%)	104/205 (51%) 4%	113/200 (57%) 10%
OR (95% CI) <sup>1</sup> vs Placebo		1.19 (0.79, 1.80)	1.59 (1.04, 2.41)
P-value		0.4098	0.0308
<b>Per Protocol Response (adjusted):</b>			
Observed Difference vs Placebo	89/261 (34%)	105/258 (41%) 7%	113/263 (43%) 9%
OR (95% CI) <sup>1</sup> vs Placebo		1.35 (0.94, 1.94)	1.50 (1.04, 2.14)
P-value		0.1026	0.0281

<sup>1</sup>Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo without adjustment for any covariates

<sup>2</sup>Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDA ( $\leq 9$  vs  $\geq 10$ ), baseline proteinuria level ( $<2$  g/24 hr vs  $\geq 2$  g/24 hr equivalent) and race (African descent or indigenous-American descent vs other).

Adapted Sponsor's Table 7-4; p. 89.

A number of prespecified subgroup analyses were also conducted which are presented and discussed in Section 6.1.8 of this review. Table 23 lists the region and racial subgroup analyses. A trend is observed for the differential response rate by region for the comparison of the 10 mg/kg belimumab group versus placebo with the magnitude of treatment benefit in the Americas excluding the US and Canada (-3.5%) being much less robust than was observed in W. Europe/Israel. Statistically significant qualitative treatment-by-subgroup interactions were observed in the analyses comparing each belimumab treatment group versus placebo for race (stratification factor) in this study suggesting that there are differences in the direction of the treatment effect in the racial subgroups. This explored further in Section 6.1.8.

Table 23 – Subgroup Analyses of the Primary Endpoint by Region and Race for Study 1056

	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)
<b>Overall Response:</b>	93 (34%)	110 (41%)	118 (43%)
<b>Region:</b>			
<b>USA/Canada</b>	46/145 (32%)	59/155 (38%)	47/136 (35%)
<b>W. Europe/Israel</b>	15/64 (23%)	25/63 (40%)	38/75 (51%)
<b>E. Europe</b>	15 /36 (42%)	11/27 (41%)	16/30 (53%)
<b>Americas (excl. USA/Canada)</b>	17/30 (57%)	15/26 (58%)	17/32 (53%)
<b>Asia</b>	--	--	--
<b>Australia</b>	--	--	--
<b>Interaction P-value<sup>1</sup></b>	--	<b>0.5597</b>	<b>0.0727</b>
<b>Race (stratification factor):</b>			
<b>AIA</b>	36/74 (49%)	30/74 (41%)	29/72 (40%)
<b>Other</b>	57/201 (28%)	80/197 (41%)	89/201 (44%)
<b>Interaction P-value<sup>1</sup></b>	--	<b>0.0265</b>	<b>0.0088</b>

AIA = African descent or indigenous American descent

<sup>1</sup>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.

**Secondary Endpoints:**

There were five major and numerous ancillary secondary endpoints for this trial. The major secondary endpoints will be presented with the ancillary secondary endpoints by corresponding assessment area. As per the statistical analysis plan, no multiplicity correction was implemented for the secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate.

**SELENA SLEDAI Disease Activity:**

Two major secondary endpoints in this study were the group response to treatment by the SRI at Week 76 and the percentage of subjects with  $\geq$  4-point reduction from baseline in SELENA SELDAI score at Week 52. Table 24 lists the results from the Week 76 SRI response rate. Patients in the 1mg/kg and 10 mg/kg belimumab treatment groups had numerically higher response rates than placebo patients at Week 76, but these differences were not significant.

Table 24 – Overall Week 76 Responder Rate and Subcomponent Results for Study 1056

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

OR=Odds Ratio; CI =Confidence Interval

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

<sup>2</sup>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

<sup>3</sup>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

The other major secondary endpoint that evaluated disease activity was the percentage of subjects with  $\geq 4$  point reduction from baseline in SELENA SLEDAI score at Week 52. Since this was one of the components of the SRI, the results of this analysis are listed in Table 20 above and are generally consistent with those of the primary analysis. The proportions of subjects who achieved this endpoint were numerically higher in both belimumab treatment groups, but were not statistically significant compared to placebo.

The results of numerous ancillary secondary endpoints that also assessed disease activity in this trial are summarized as follows:

- Response rate by visit: Numeric improvements in response rates were observed in all three treatment groups starting at Week 4. A separation in the response rate curves was observed starting at Week 24 for the 10 mg/kg and at Week 36 for the 1 mg/kg belimumab treatment groups as compared to placebo that was significantly different only at the Week 52 time point for the belimumab 10 mg/kg group (43%) versus placebo (34%) (p=0.0207)
- Time to first response: A numerically shorter median time to first response was observed for both belimumab groups (range: 112-113 days) that was not significantly different from placebo (119 days)

- Duration of first response that was maintained to Week 52: Longer mean durations of first response were observed for both the 1 mg/kg (73 days) and 10mg/kg (81 days) as compared to placebo (55 days) that were significantly different on comparison of 10 mg/kg of belimumab versus placebo ( $p=0.0055$ ) and trended for the 1mg/kg belimumab versus placebo comparison ( $p=0.0614$ ).
- Percentage of subjects with  $\geq 4$  point reduction from baseline in SELENA SLEDAI score at Weeks 12, 24, and 76: The results of the Week 76 analysis (Table 24 above) demonstrated a higher percentage of subject in both the 1 mg/kg and 10 mg/kg treatment groups achieved this endpoint that reached statistical significance on comparison of the 1mg/kg belimumab group versus placebo ( $p=0.0486$ ) and trended for the 10 mg/kg belimumab versus placebo comparison ( $p=0.0660$ ). Numerically higher percentages of patients achieved this endpoint at Weeks 12 (1mg/kg 40%; 10 mg/kg: 40%) and 24 (1 mg/kg: 46%; 10 mg/kg: 46%) as compared to placebo (Wk 12: 35%; Wk 24: 41%).
- Percent change from baseline in SELENA SLEDAI: Numeric improvements were observed in all three treatment groups that were significantly different at Weeks 8, 32, 44, 48 and 52 (40%) time points for the 10 mg/kg belimumab treatment group compared to placebo (Wk 52: 30%) ( $p < 0.05$ ) and at the Week 52 time point for the 1 mg/kg belimumab group (37%) versus placebo (30%) ( $p < 0.01$ ).
- AUC of the SELENA SLEDAI score over 52 weeks: Mean AUC of SELENA SLEDAI score over 52 weeks trended lower (indicating improvement) in the 1mg/kg group (268;  $p=0.0943$ ) and 10 mg/kg group (266;  $p=0.0653$ ) compared to placebo (285).

***BILAG Disease Activity:***

- Percentage of subjects with no new BILAG 1A/2B organ domain scores at time of assessment compared with baseline: From Week 28 through Week 52 a numerically greater percentage of subjects in the 1 mg/kg belimumab group had no new BILAG 1A/2B organ domain scores from baseline compared with placebo that was significantly different at Weeks 48 (1mg/kg: 75% vs placebo: 67%;  $p=0.0226$ ) and 52 (1mg/kg: 75% vs placebo: 65%;  $p=0.0108$ ). The percentages of subjects with no new BILAG 1A/2B scores in the 10 mg/kg group were similar to that of placebo.
- Percent of subjects with no new BILAG 1A/2B organ domain scores at the time of assessment: Starting at Week 28, the percentages of subjects with no new BILAG 1A/2B organ domain scores at the time of assessment were numerically higher in both belimumab groups as compared to placebo. Significant differences for this endpoint were observed only for the 1 mg/kg belimumab group at Weeks 40 (59%), 48 (61%) and 52 (61%) as compared to placebo (51%, 50%, and 48%, respectively) ( $p < 0.05$ ).
- Percentage of subjects with no new BILAG 1A/2B organ domain scores compared with baseline after the Week 24 visit to the Week 52 visit: A numerically higher percentage of subjects in the belimumab treatment groups

had no new BILAG 1A/2B organ domain scores compared with baseline after the Week 24 visit to the Week 52 visit that was only significantly different for the 1 mg/kg group (68%) comparison to placebo (59%) (p=0.0160).

- BILAG response rates: No differences between treatment groups were observed for this endpoint as per the definition of a BILAG response which was a subject may be considered a responder if improvement is demonstrated in at least 1 organ domain score and no new BILAG 1A/2B BILAG response rates were assessed in subjects with at least 1A/2B domain score at baseline.

***Physician's Global Assessment (PGA) of Disease Activity:***

Another major secondary endpoint that assessed disease activity was the mean change and percent mean change from baseline in PGA at Week 24. Reductions in the mean percent change and mean change from baseline in PGA at Week 24 were comparable across groups and were not significantly different (see Table 52 below). Results from the ancillary secondary analyses of the PGA are as follows:

- Percentage of subjects with no worsening (increase of < 0.30 points from baseline) in PGA by visit: A greater percentage of subjects receiving 1 mg/kg (73%) and 10 mg/kg belimumab (69%) had no worsening in their PGA scores at Week 52 compared with placebo (63%) that was only significantly different on comparison of 1 mg/kg versus placebo.
- Percentage of subjects with  $\geq 0.30$  points improvement (i.e., reduction) from baseline in PGA by visit: Numerical improvements were achieved by all three treatment groups with a greater percentage of subjects with  $\geq 0.30$  points improvement from baseline PGA occurring in both belimumab groups (1 mg/kg: 54%; 10 mg/kg: 51%) versus placebo (44%) at Week 52 that was only significantly different for the 1mg/kg group versus placebo comparison.
- Mean change and mean percent change in PGA by visit: For the analysis of mean absolute change in PGA, numerical improvements were observed for both belimumab treatment groups that were significant different only for the 1 mg/kg group at Week 40 (57%; p=0.0223) and Week 52 (59%; p=0.0221) as compared to placebo (46% and 47%, respectively). For the analysis of mean percent change in PGA, numerical improvements were observed for both belimumab treatment groups that were significant different at the Week 40 time point only for the 1 mg/kg group (40%) versus placebo (20%).

***SLICC/ACR Damage Index:***

This endpoint is used to assess end organ damage in SLE patients. Baseline scores were comparable for the three treatment groups (1mg/kg: 1.04; 10mg/kg: 0.94; placebo: 0.99). The Week 52 scores were not consistent with disease progression (1mg/kg: 0.04; 10mg/kg: 0.04; placebo: 0.06) (Refer to Table 63.)

***SLE Flares:***

Results from the ancillary secondary endpoint of SLE flare conducted using the modified SLE Flare Index are as follows:

- Time to first SLE flares over 52 weeks and after Week 24 visit to the Week 52 visit: The median time to flare was similar for all three treatment groups with durations ranging from 82-85 days (see Table 54 below). Decreases in the risk for experiencing a disease flare during Weeks 24 to 52 were observed in both belimumab groups that was significantly different on comparison of only the 10 mg/kg belimumab group (28%) to placebo ( $p=0.0226$ ) and trended for the comparison of the 1 mg/kg belimumab group (19%) to placebo ( $p=0.0583$ ) (refer to Table 55 below).
- Time to first severe SLE flare over 52 weeks and after Week 24 visit to the Week 52 visit: The risk of developing a first severe flare over 52 weeks was significantly reduced in the 1 mg/kg group (36%;  $p=0.0230$ ) and numerically reduced in the 10 mg/kg group (28%) compared to placebo (see Table 54 below). Decreases in the risk for experiencing a severe disease flare during Weeks 24 to 52 were observed in both belimumab groups that was significantly different on comparison of only the 1 mg/kg belimumab group to placebo ( $p=0.0167$ ) (see Table 55 below).
- Flares per subject-year and the rate of flares over 52 weeks and after the Week 24 visit to the Week 52 visit: Flares per subject-year over 52 weeks trended lower in both belimumab groups versus placebo with rates of 3.8 per subject-years in the placebo group, 3.3 per subject-years in the 1 mg/kg group ( $p=0.0632$ ), and 3.4 per subject-years in the 10 mg/kg group ( $p=0.1276$ ) (refer to Table 54 below).
- Severe flares per subject-year and the rate of severe flares over 52 weeks and after the Week 24 visit to the Week 52 visit: The number of severe flares per subject-year over 52 weeks was comparable across groups with rates of 1.1 in the placebo group, 0.9 in the 1mg/kg group, and 1.0 in the 10 mg/kg group (see Table 54 below). Numerical decreases in severe flares were observed for both the 1 mg/kg (0.79) and 10 mg/kg (0.82) belimumab treatment groups as compared to placebo (1.09) (see Table 54).

Results from the ancillary secondary endpoints of SLE flare conducted using the BILAG are as follows:

- Time to first BILAG 1A/2B flare over 52 weeks and after the Week 24 visit to the Week 52 visit: No reduction in risk for developing a BILAG 1A/2B organ domain flare over 52 weeks was observed in either of the belimumab treatment groups (see Table 56 below). Decreases in the risk for experiencing a disease flare during Weeks 24 to 52 were observed in both belimumab groups (1mg/kg: 19%; 10 mg/kg: 20%) that were significantly different when compared to placebo (27%) for only the 1 mg/kg group ( $p=0.0394$ ) (see Table 57 below).
- BILAG flares per subject-year and the rate of flares over 52 weeks and after the Week 24 visit to the Week 52 visit: Flares per subject-years were also comparable for the three treatment groups and ranged from 1.32 to 1.45 flares/subject year over 52 weeks and 1.3 to 1.5 flares/subject-year for Week 24 to Week 52 (refer to Table 56 and Table 57).

**Steroid use:**

Another major secondary endpoint was the percentage of subjects whose average prednisone dose was reduced by  $\geq 25\%$  for baseline to  $\leq 7.5$  mg/day during Weeks 40 through 52 in subjects who were receiving  $>7.5$  mg/day prednisone at baseline. Numerically more patients in both belimumab groups (1mg/kg: 19%; 10 mg/kg: 17%) were able to reduce prednisone use by  $\geq 25\%$  as compared to placebo (13%) but these differences were not significant.

Results from the ancillary secondary endpoints of concomitant steroid use are as follows:

- Change and percent change from baseline of prednisone dose over time: A numerically higher mean percent decrease from baseline of prednisone dose was only observed in the 1mg/kg group during Weeks 24 to 52 that was not significantly different as compared to placebo at the Week 52 time point (1mg/kg: 15% vs placebo 5%;  $p=0.3298$ ). A consistent numeric decrease was not observed in the 10 mg/kg belimumab group. (Note: This analysis included subjects who took prohibited medications or a protocol restricted medication.) Comparable small decreases in daily prednisone dose over baseline were observed in all 3 treatment groups from Weeks 32 to 52.
- Number of days of daily prednisone dose  $\leq 7.5$  mg/day and/or reduced by 50% from baseline over time: The cumulative number of days of daily prednisone dose  $\leq 7.5$  mg/day and/or reduced by 50% from baseline were numerically higher for the belimumab groups (range: 79 days for the 1mg/kg group and 63 days for the 10 mg/kg group) as compared to the placebo group (60 days).
- Time to first daily prednisone reduction  $\leq 7.5$  mg/day and/or reduction by 50% from baseline over 52 Weeks: The likelihood of a prednisone reduction over the 52 weeks of study treatment was similar for the three treatment groups (hazard ratio of 1.14 ( $p=0.5066$ ) for 1 mg/kg vs placebo; hazard ratio of 0.86 ( $p=0.4814$ ) for 10mg/kg vs placebo).
- Percentage of subjects with daily prednisone dose reduced to  $\leq 7.5$  mg/day from  $> 7.5$  mg/day at baseline over time: A numerically higher percentage of subjects achieved a reduction in prednisone to  $\leq 7.5$  mg/day in each belimumab group versus placebo by Week 16 in the 1 mg/kg (14% vs placebo: 8%) group and by Week 36 in the 10 mg/kg (15% vs placebo: 13%) which was maintained for the remainder of the 52-week treatment period (Week 52: 1mg/kg; 22%; 10 mg/kg: 23%; placebo: 16%).
- Percentage of subjects with daily prednisone dose increased to  $> 7.5$  mg/day from  $\leq 7.5$  mg/day at baseline over time: A numerically lower percentage of subjects in the 1 mg/kg group had their daily prednisone dose increased to  $>7.5$  mg/day at all time points as compared to placebo group while the percentage of subjects in the 10mg/kg group with daily prednisone increase to  $>7.5$  mg/day was similar to that of placebo.
- Percentage of subjects with durable prednisone reduction over 24 and 52 weeks: The percentage of subjects with a durable prednisone reduction over 24 to 52

weeks was similar for the 3 treatment groups (1mg/kg: 26%; 10 mg/kg: 20%; placebo: 20%).

- Time to and duration of sustained prednisone reduction over 52 weeks: Time to sustained prednisone reduction was similar for the three treatment groups. The mean duration of sustained prednisone reduction was numerically longer in the 1 mg/kg belimumab group (66 days) compared to placebo (49 days) which was similar to that of the 10mg/kg belimumab group (50 days).

**Renal Measures:**

Due to the small numbers of subjects who developed renal flares while participating in this trial (placebo: 3 subjects; 1mg/kg: 2 subjects; 10mg/kg: 4 subjects) the median time to renal flare could not be observed. Although the protocol prohibited entry of subjects with active lupus nephritis, it did permit the entry of patients with proteinuria. A subgroup of patients (n=33) with renal disorder (defined as proteinuria  $\geq 2\text{g}/24\text{ hrs}$ ) who participated in this trial were assessed for potential renal disease remission (defined as urine RBC count  $<10\text{ cells}/\text{hpf}$ , the absence of cellular casts, and proteinuria  $<1\text{g}/24\text{ h}$  without doubling of serum creatinine level). The rates of renal remission in this subgroup were 36% (4/11) in the placebo group, 29% (2/7) in 1mg/kg belimumab group, and 27% (4/15) in the 10mg/kg belimumab group. Again, the small numbers of patients resulted in the median time to remission from being observed. No apparent differences among the three treatment groups were observed for the other prespecified renal remission endpoints. A numerical trend for mean percent decrease from baseline proteinuria was observed during Weeks 16 to 48 for the 1mg/kg belimumab group which was not sustained at the Week 52 endpoint (1mg/kg: 48% vs placebo: 48%) in patients with proteinuria at baseline (defined as proteinuria  $\geq 0.5\text{ g}/24\text{ h}$ ). At Week 52, the mean decrease from baseline proteinuria for the 10mg/kg group (45%) was similar to placebo (48%).

**Patient Reported Outcomes (PROs):**

Another major secondary endpoint was the change from baseline to Week 24 in the SF-36 physical component score (PCS) for the belimumab groups as compared to placebo. The change from baseline to Week 24 in the SF-36 PCS was comparable for all three treatment groups (1mg/kg: 6.2; 10mg/kg: 5.4; placebo: 5.6). (See Table 51 below.)

Results from the ancillary secondary PRO endpoints are as follows:

- Mean change in SF-36 Health Survey Scores (8 Domains and MCS) at Week 52: Significant improvements for the SF-36 domain scores for role physical, bodily pain, general health, vitality, and MCS for the belimumab 1 mg/kg group versus placebo at Week 52. Numerical improvements for the SF-36 domain scores for mental health, social functioning, role emotional, and physical functioning for the 1 mg/kg group versus placebo were also observed. For the belimumab 10mg/kg group, numerical improvements in bodily pain, physical functioning, vitality, social functioning, and MCS score compared to placebo were observed at the Week 52 time point.

- Mean change in FACIT-Fatigue Scale score: At Week 52, numerical improvements in the mean change in FACIT-Fatigue score were observed in the 1mg/kg (6.4) and 10 mg/kg (4.6) belimumab groups as compared to placebo (3.8) that were significantly different for only the 1mg/kg comparison ( $p=0.0023$ ).
- EQ-5D, Workplace Productivity, and ER Visits: Significant improvement was observed for the EQ-5D<sub>vas</sub> score at Week 52 for the 1mg/kg belimumab group (12) versus placebo (8.7) ( $p=0.0492$ ). No difference in the EQ-5D<sub>vas</sub> score at Week 52 for the belimumab 10 mg/kg group (7.4) versus placebo (8.7) or for the EQ-5D utility index scores between the belimumab treatment groups compared to placebo. No differences were observed in workplace productivity or ER visits in the belimumab groups compared to placebo.

**Biomarkers:**

Results from the ancillary secondary biomarker endpoints are as follows:

- Significant reductions in median percent change and mean absolute change from baseline in IgG, IgA, and IgM was observed at Week 52 in both belimumab groups versus placebo ( $p<0.0001$ ).
- Significant reductions in anti-dsDNA antibody levels in subjects with measurable anti-dsDNA at baseline was observed in the 1 mg/kg (27%;  $p<0.0001$ ) and 10 mg/kg (25%;  $p<0.0001$ ) at Week 52 compared to placebo (0%). At Week 52, more belimumab treated subjects had converted to seronegative status (15-17%) compared to placebo (8%). Fewer patients in the 1mg/kg (4.0%) and 10mg/kg (1.4%) belimumab groups who were seronegative at baseline converted to seropositive at Week 52 as compared to placebo (9.1%).
- More belimumab treated patients who were seropositive for ANA at baseline converted to seronegative status at Week 52 (1mg/kg: 5.6%; 10 mg/kg: 4.5%) compared to placebo (3.9%). Fewer patients in the 1mg/kg belimumab group converted from seronegative to seropositive ANA status at Week 52 compared to placebo.
- More patients who were seropositive for anti-Sm, aCL, and anti-ribosomal P at baseline converted to seronegative status at week 52 in the belimumab treatment groups compared to placebo.
- More patients who were seropositive for anti-Sm, aCL, and anti-ribosomal P at baseline converted to seronegative status at week 52 in the belimumab treatment groups compared to placebo. Significant differences versus placebo were observed for both belimumab groups versus placebo for anti-ribosomal P and aCL IgG and for the 10mg/kg group versus placebo for anti-Sm ( $p=0.0252$ ).
- More belimumab treated patients with low C3 at baseline converted to normal/high C3 at Week 52 compared to placebo (1mg/kg: 32%; 10 mg/kg: 44%; placebo: 21%) that was significantly different on comparison of the 10 mg/kg belimumab group versus placebo ( $p=0.0018$ ). Fewer belimumab treated patients with normal/high C3 at baseline converted to low C3 at Week 52 compared to

- placebo (1mg/kg: 1%; 10 mg/kg: 7%; placebo: 19%) that was significantly different on comparison of the 10 mg/kg group versus placebo (p=0.0097).
- More belimumab treated patients with low C4 at baseline converted to normal/high C4 at Week 52 compared to placebo (1mg/kg: 33%; 10 mg/kg: 46%; placebo: 17%) that was significantly different on comparison of both the 1 mg/kg (p=0.0076) and 10 mg/kg (p<0.0001) belimumab groups versus placebo. Fewer belimumab treated patients with normal/high C4 at baseline converted to low C4 at Week 52 compared to placebo (1mg/kg: 5%; 10 mg/kg: 6%; placebo: 17%) that was significantly different on comparison of both the 1mg/kg (p=0.0062) and 10 mg/kg (p=0.0259) groups versus placebo.
  - Belimumab significantly reduced various B cell subsets including CD19+, CD20+, naïve, activated, plasma, and the SLE subset at Week 52. Memory cells increased initially and slowly declined to near baseline levels. At Week 52, there was no decrease in T cells in subjects treated with belimumab.

#### **Efficacy Conclusions:**

A significantly higher response rate as assessed by the primary endpoint, the SRI, was demonstrated for the belimumab 10 mg/kg plus standard of care group compared to placebo plus standard of care. The SRI response rate for the belimumab 1 mg/kg plus standard of care group was less robust with demonstration of a numerically higher response rate compared to placebo plus standard of care. The response rates for the study's treatment groups were generally consistent with the results from the individual component analyses of the SRI and the prespecified sensitivity analyses. Durability of treatment effect was not demonstrated at the Week 76 time point as assessed by the SRI response rate in both the 1mg/kg and 10 mg/kg belimumab treatment groups which had numerically higher response rates that were not significantly different compared to placebo. The results from the analyses of the remaining major secondary endpoints (e.g., percentage of subjects with  $\geq 4$  point reduction from baseline in SLENA SLEDAI score at Week 52, mean change in SF-36 PCS score at Week 24, mean change in PGA at Week 24 and percentage of subjects with a  $\geq 25\%$  reduction in steroids from Weeks 40 through 52) were generally less robust with numerical improvements observed in the belimumab treatment groups compared to placebo without demonstration of a consistent dose-response. The results from remaining secondary endpoints of clinical interest (e.g., SLE disease flares and improvement or worsening in organ systems as assessed by the BILAG or SLENA SLEDAI) were suggestive of improvements with belimumab but declaring statistical significance of the multiple secondary endpoints evaluated in this trial using unadjusted p-values would be inappropriate since no multiplicity correction was planned in the protocol or implemented during the analyses of the secondary endpoints. Higher proportions of belimumab treated subjects had normalization of biomarkers such as C3, C4 and naive B-cells than placebo which significantly correlated with response to belimumab but did not adequately predict responses to treatment with the product.

**Study Number and Title:** HGS1006-C1057 (BLISS-52) - A Phase 3, Multicenter, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab, (HGS1006, LymphoStat-B), a Fully Human Monoclonal Anti-BlyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE).

**Dates Conducted:** This trial was started on May 25, 2007 and completed on May 19, 2009.

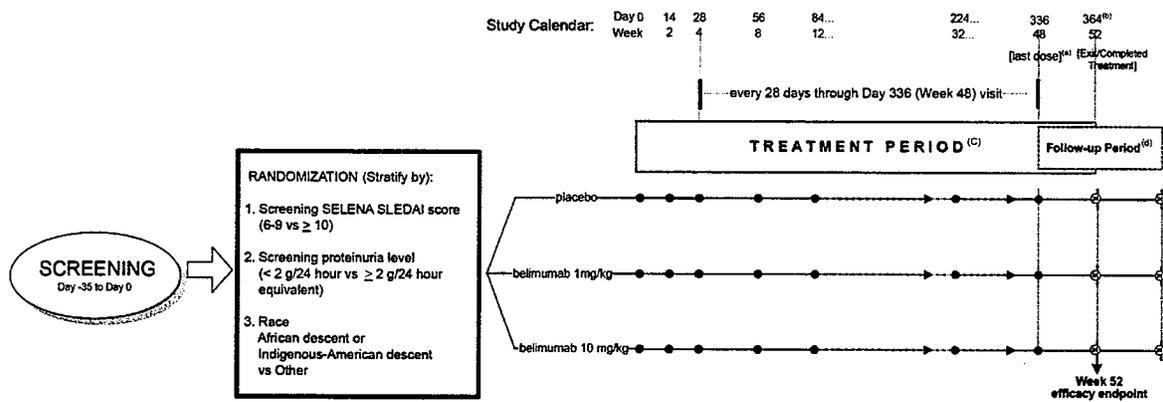
**Objectives:**

- To assess the efficacy of belimumab in patients with SLE
- To assess the safety and tolerability of belimumab in patients with SLE
- To determine the impact of belimumab on SLE patients' quality of life

**Study Design:**

Study 1057 was a multicenter, double-blind, placebo-controlled, randomized study in patients with active seropositive SLE on stable standard of care immunosuppressive medications for their disease. Eligible candidates were randomized via a 1:1:1 ratio to the following 3 treatment groups: 1mg/kg IV belimumab, 10 mg/kg belimumab or placebo IV. Randomization was stratified by subjects' screening SELENA SLEDAI score (6-9 vs  $\geq 10$ ), screening proteinuria level ( $<2\text{g}/24$  hours vs  $\geq 2$  g/24 hours equivalent) and race (African descent or indigenous-American descent vs other). All patients including those who withdrew from the trial were required to return to their respective study site for a final follow-up visit 4 weeks post-administration of last study infusion. Upon completion of the 48-week study, participants were to have the option of participating in a continuation study 1074. Those who did not wish to participate in 1074 were to have returned for an additional follow-up visit 8 weeks post-administration of their final study infusion. Figure 3 is a schema of the proposed trial.

Figure 3 – Schema of Study 1057



<sup>(A)</sup> The last dose of study agent is given on the Day 336 (Week 48) visit to subjects NOT participating in the continuation protocol.  
<sup>(B)</sup> Subjects continuing in the continuation protocol are dosed on the Day 364 (Week 52) visit. This Day 364 (Week 52) represents the first dose (i.e., Day 0) of the continuation protocol. For subjects not participating in the continuation protocol, the Day 364 (Week 52) visit serves as the exit visit.  
<sup>(C)</sup> The treatment period includes 48 weeks of study agent administration [Day 0 to the Day 336 (Week 48 visit)] and a follow-up visit at Day 364 (Week 52).  
<sup>(D)</sup> The follow-up period includes 2 scheduled visits of 4 and 8 weeks after the last dose of study agent (Day 336/Week 48) for subjects not participating in the continuation protocol.

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Sponsor's Fig. 5-1; p. 28 Clinical Trial Report

**Major Inclusion Criteria:**

Subjects were men and women  $\geq 18$  years of age with ANA-positive SLE who met all of the following criteria:

1. Diagnosis of SLE as per the American College of Rheumatology (ACR) criteria
2. A diagnosis of active SLE defined as a SELENA SLEDAI score  $\geq 6$  at screening
3. Unequivocally positive anti-nuclear antibody (ANA) test results from 2 independent time points as follows:
  - Positive test results from 2 independent time points within the study screening period. (A positive ANA test is defined as an ANA titer  $\geq 1:80$  and/or a positive anti-dsDNA ( $\geq 30$  IU/mL) serum antibody) or
  - One positive historical test result and 1 positive test result during the screening period
4. On a stable SLE treatment regimen consisting of any of the following medications (alone or in combination) for a period of at least 30 days prior to Day 0 (i.e., day of first dose of study agent):
  - Corticosteroids (prednisone or prednisone equivalent, up to 40 mg/day):
  - Other immunosuppressive or immunomodulatory agents: methotrexate, azathioprine, leflunomide, mycophenolate mofetil, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine or thalidomide.
  - Antimalarials (e.g, hydroxychloroquine, chloroquine, quinacrine)
  - Non-steroidal anti-inflammatory drugs (NSAIDs)

**NOTE :**

- Pre-existing SLE medications were to have been stable for at least 30 days prior to Day 0
- Corticosteroids may have been added as new medication or their doses adjusted only up to 30 days prior to Day 0
- New SLE therapy other than corticosteroids could not be added within 60 days of Day 0

5. Individuals on angiotensin pathway antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers [ARBs]) had to be on a stable regimen for a period of at least 30 days prior to Day 0.
6. Individuals on HMG CoA reductase inhibitors ("statins") had to be on a stable regimen for a period of at least 30 days prior to Day 0.
7. Female candidates of childbearing potential could not be pregnant or nursing and had to have a negative serum pregnancy test at screening in addition to agreeing to practice complete abstinence from intercourse or using one of the acceptable methods of birth control listed in the protocol for the duration of the study
8. Male candidates had to agree to use effective contraception for the duration of the study and for 3 months post-administration of last study dose

**Exclusion Criteria:** Potential study candidates were excluded from the study if any of the following criteria applied:

1. Treatment with any B-cell targeted therapy (rituximab, other anti-CD20 agents, anti-CD22, anti-CD52, BLYS-receptor fusion protein) at any time
2. Treatment within 364 days of Day 0 with abatacept or any biological investigational agent other than B-cell targeted therapy
3. Administered 3 or more courses of systemic corticosteroids for concomitant conditions such as asthma or atopic dermatitis within 364 days of Day 0 (topical and inhaled steroids are permitted)
4. Administered intravenous (IV) cyclophosphamide within 180 days of Day 0.
5. Treated with anti-TNF therapy, interleukin-1 receptor antagonist, intravenous immunoglobulin, high dose prednisone (>100 mg/d), or plasmapheresis within 90 days of Day 0
6. Treated with a non-biological investigational agent, or any new immunosuppressive/immunomodulatory agent, anti-malarial, NSAID, HMG CoA reductase inhibitor or angiotensin pathway antihypertensive within 60 Days of Day 0. (Note: New inhaled steroids or topical immunosuppressive agents were permitted. Any NSAID use for <1week was allowed.)
7. Administered a live vaccine or had a change in dose of a corticosteroid, other immunosuppressive/immunomodulatory agent, anti-malarial, NSAID, HMG CoA reductase inhibitor, or angiotensin pathway antihypertensive within 30 days of Day 0.
8. History of (H/O) severe lupus nephritis (defined by proteinuria >6 g/24 h or equivalent using spot urine protein to creatinine ration, or serum creatinine >2.5 mg/dL), or have active nephritis, require hemodialysis or high-dose prednisone (>100 mg/day) within 90 days of Day 0
9. H/O active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident (CVA), cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 0.
10. H/O major organ transplant or hematopoietic stem cell/marrow transplant
11. H/O significant or unstable or uncontrolled acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematological, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases)
12. H/O any medical disease, lab abnormality, or condition or planning a surgical procedure during the course of the trial
13. H/O malignant neoplasm within the last 5 years with the exception of excised basal or squamous cell carcinomas of the skin or cervical carcinoma in situ
14. H/O acute or chronic infections that required hospitalization for treatment or parental antibiotic or antimicrobial agents within 60 days of Day 0 or the concurrent use of suppressive anti-infective therapy (i.e., antibacterials, antivirals, antifungals, or antiparasitic agents)
15. H/O recent alcohol or drug abuse within 364 days prior to Day 0
16. H/O a positive test for HIV-1 antibody, hepatitis B surface antigen, or hepatitis C antibody
17. H/O IgA deficiency (IgA level <10 mg/dL)
18. Have a Grade 3 or greater lab abnormality except for the following which were allowed: stable Grade 3 prothrombin time (PT) due to warfarin therapy, stable Grade 3/4 proteinuria ( $\leq 6$  g/24 h

equivalent by spot urine protein to creatinine ration allowed), or stable Grade 3 neutropenia or stable Grade 3 WBC

19. H/O anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.

**Treatment:**

Study infusions were administered over 1 hour on Days 0, 14, 28 and then every 28 days through Week 48 of the study.

**Removal of Patients from Treatment or Assessment:**

Subjects were to have discontinued from this trial if they withdrew consent, received a prohibited concurrent medication or therapy, experienced unacceptable toxicity, became pregnant, or missed 3 or more consecutive study infusions.

**Concomitant Medications:**

The protocol permitted patients with a history of allergies or who had previously received IVIG to be prophylactically medicated with diphenhydramine, acetaminophen or H2-receptor antagonists which were to have been employed in cases of study-related infusion reactions.

The protocol required patients to be on a stable SLE treatment regimen for at least 30 days prior to Day 0 which may have consisted of any of the following medications alone or in combination: steroids ( $\leq 40$  mg/day of prednisone or equivalent), antimalarials, NSAIDs, MTX, azathioprine, leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide, 6-mercaptopurine or thalidomide. Changes in background immunosuppressive agents were permitted due to toxicity or shortages as were adjustments in concurrent medications (e.g., HMG CoA reductase inhibitors, angiotensin pathway antihypertensives, NSAIDs and aspirin) as clinically needed post-administration of the first study infusion during prespecified time periods over the course of the study. However, any changes in the following medications during restricted periods were to have resulted in the subject being considered a treatment failure and withdrawn from the study:

- Antimalarials: Initiation of treatment or changes in dose were permitted between Day 0 and Day 122 visits. After the Day 112 visit, any initiation of new therapy or increase in dose was to be considered a treatment failure
- Steroids: changes in the total dose of systemic steroids were permitted during the first 6 months of the trial (Day 168 visit) but the total systemic dose had to return to within 25% or 5 mg over baseline (Day 0) dose (whichever was higher) by the Day 168 visit, or the subject was to be considered a treatment failure. (Note: The protocol contained algorithms for both tapering and treating SLE flares with steroids.) Intra-articular (IA) steroid injections were permitted between baseline (Day 0) and the Day 308 visit and between Day 364 (Week 52) visit and the Day 476 (Week 68) visit. Patients who receive IA steroids during the 8 weeks

prior to the Week 52 or Week 76 study visit were to have been considered treatment failures.

- Other Immunosuppressive/Immunomodulatory Agents: doses were permitted to have been increased up to the Day 112 visit. Initiation of any new immunosuppressive/immunomodulatory agent after Day 0 or increase in dose over baseline or Day 112 (whichever was higher) was to be considered a treatment failure
- HMG CoA reductase inhibitors: Initiation of new treatment starting after the Day 168 visit was to be considered a treatment failure
- Angiotensin pathway antihypertensives: Initiation of new treatment starting after the Day 112 visit was to be considered a treatment failure
- NSAIDs and Aspirin: Initiation of new treatment used for  $\geq 7$  days starting after the Day 308 visit was to be considered a treatment failure

Subjects who initiated therapy with any of the following banned medications or therapies were to have been also considered treatment failures and withdrawn from the study: other investigational agents, anti-TNF therapy, other biologics (e.g., rituximab, abatacept, and interleukin-1 receptor antagonist), IV immunoglobulin (IVIG), IV cyclophosphamide or plasmapheresis.

### Efficacy and Safety Assessments:

The following Table 25 and Table 26 are tabular flow charts of the scheduled study observations and procedures:

**Table 25 - Schedule of Procedures and Evaluations for Study 1057**

Study Day	52-Week Treatment Period Days 0 – 364 (Weeks 0 – 52)														Post-Treatment Follow-up Period		
	Day 0 visit	Day 14 visit ± 3 days	Day 28 visit ± 3 days	Day 56 visit ± 7 days	Day 84 visit ± 7 days	Day 112 visit ± 7 days	Day 140 visit ± 7 days	Day 168 visit ± 7 days	Day 196 visit ± 7 days	Day 224 visit ± 7 days	Day 252 visit ± 7 days	Day 280 visit ± 7 days	Day 308 visit ± 7 days	Day 336 visit ± 7 days	Day 364 OR EXIT (4-wks post dose) ± 7 days	8-week Follow-up <sup>n</sup> + 7 Days	Unscheduled Visit <sup>o</sup>
Study Week	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52			
Vital Signs <sup>c,d</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight <sup>d,e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-driven Physical Exam	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Labs: Hematology & Modified Chem 20 (non fasting) <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spot urine (protein to creatinine ratio) <sup>g</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test <sup>h,i</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Sampling <sup>j</sup>	X	X		X													X
Immunogenicity <sup>k</sup>	X			X				X									X
Pharmacogenetic Sampling <sup>l</sup>	X																X
BLyS Protein	X														X		X
C3/C4, anti-dsDNA	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Autoantibodies (aCL, anti-Sm, anti-ribosomal P, ANA by titer, ANA by ELISA OD) <sup>j</sup>	X														X		

(continued)

Sponsor's Table 3; p. 51-53 of Protocol 1057.

Table 26 - Schedule of Procedures and Evaluations for Study 1056 (cont.)

Study Day	52-Week Treatment Period Days 0 – 364 (Weeks 0 – 52)														Post Treatment Follow-up Period		
	Day 0 visit	Day 14 visit ± 3 days	Day 28 visit ± 3 days	Day 56 visit ± 7 days	Day 84 visit ± 7 days	Day 112 visit ± 7 days	Day 140 visit ± 7 days	Day 168 visit ± 7 days	Day 196 visit ± 7 days	Day 224 visit ± 7 days	Day 252 visit ± 7 days	Day 280 visit ± 7 days	Day 308 visit ± 7 days	Day 336 visit ± 7 days	Day 364 OR EXIT (4-wks post dose) <sup>A, M</sup> ± 7 days	8-week Follow-up <sup>B</sup> ± 7 Days	Unscheduled Visit <sup>O</sup>
Study Week		Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52		
IgG <sup>K</sup> & CRP	X			X				X				X			X		
IgA & IgM <sup>K</sup>	X														X		
PT/PTT	X			X				X				X			X		
Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, PGA and BILAG <sup>N</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
SLICC/ACR Damage Index	X														X		
SF-36 Health Survey <sup>C</sup>	X		X	X	X			X				X			X		
FACIT-Fatigue Scale <sup>L</sup> , and EQ-5D <sup>R</sup>	X		X	X	X			X				X			X		
Workplace Productivity Questionnaire <sup>R</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Emergency Room Visit Question	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Agent Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Record Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess/Record Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(concluded)

- <sup>A</sup> The Exit (Day 364) visit will occur approximately 4 weeks after the last dose of study agent. For subjects completing all 48 weeks of treatment and continuing into the long-term continuation protocol, this visit will also serve as their 1<sup>st</sup> (ie, Day 0) visit of the continuation protocol.
- <sup>B</sup> The 8-week follow-up visit is to occur approximately 8 weeks after last dose of study agent, only if the subject does not enroll in the long term continuation protocol.
- <sup>C</sup> Vital signs includes temperature, sitting blood pressure, respiratory rate and pulse.
- <sup>D</sup> Complete prior to dosing.
- <sup>E</sup> If the subject's weight changes by more than 5% from the Day 0 weight, the weight at the current visit should be used for calculating the dose to be administered.
- <sup>F</sup> Refer to Appendix 11 for a listing of laboratory assessments to be completed.
- <sup>G</sup> A 24-hour urine may be done if clinically indicated (eg, renal flare).
- <sup>H</sup> Serum pregnancy test required at screening. Results of urine pregnancy test at subsequent visits, if required, must be available prior to dose. See Section 6.1 (Screening Procedures) for definition of those exempted from subsequent pregnancy testing.
- <sup>I</sup> Pharmacokinetic sampling: Before the start of infusion on Days 0, 56, and 364 (only if enrolled in continuation study); 0-4 hours after the end of infusion on Days 14 and 168; at any time during the visit during the 8-week follow-up visit.
- <sup>J</sup> Autoantibodies include: ANA, aCL (IgM, IgG, IgA isotypes), anti-ribosomal P and anti-Sm. aCL and anti-Sm autoantibodies will be measured in all subjects at Day 0 and samples will be collected at the time points specified; however, the assay will be run only on subjects with elevated titers of these autoantibodies at Day 0.
- <sup>K</sup> Serum immunoglobulin isotypes: IgG, IgM, IgA.
- <sup>L</sup> Must be completed by the subject prior to any study-related discussion with the investigator or study coordinator.
- <sup>M</sup> Study agent is to be administered only if the subject is enrolling in the open-label, long term continuation protocol, and this dose will be the 1<sup>st</sup> dose in the continuation study. Dosing information will be recorded in the Day 0 CRF of the continuation protocol.
- <sup>N</sup> Refer to Section 6.8.1 for guidelines for scoring proteinuria for SELENA SLEDAI and BILAG evaluation.
- <sup>O</sup> Unscheduled Visits: Other assessments as clinically indicated.
- <sup>P</sup> For subjects not entering the continuation study who had a positive anti-belimumab antibody response at the 8 week follow-up visit (or last study visit at which immunogenicity was assessed if 8 week follow-up visit immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-belimumab antibodies at least 6 months after the last dose of study agent or upon completion and/or unblinding of the study, whichever is later.
- <sup>Q</sup> PGx sampling: Includes baseline genetics and follow-up genetic expression array analysis. PGx informed consent must be obtained prior to any blood being taken for PGx research. Refer to Section 9.0 and Appendix 12. Samples should be drawn prior to dosing.
- <sup>R</sup> Must be completed by the subject prior to any study-related discussion with the investigator or study coordinator. The FACIT-Fatigue Scale, EQ-5D and the Workplace Productivity Scale Questionnaire will only be completed by subjects for whom a survey exists in the subject's language.

Sponsor's Table 3; p. 51-53 of Protocol 1057.

**Outcome Measures:**

**Primary efficacy endpoint:**

Primary efficacy variable is the SLE Responder Index (SRI) response rate at Week 52 which is defined as the proportion of patients with:

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

**Major secondary efficacy endpoints:**

- Percentage of patients with  $\geq 4$  point reduction from baseline in SELENA SLEDAI score at Week 52
- Mean change in PGA at Week 24
- Mean change in SF-36 Health Survey physical component summary score (PCS) at Week 24)
- Percentage of subjects whose average prednisone dose has been reduced by  $\geq 25\%$  from baseline to  $\leq 7.5$  mg/day during Weeks 40 through 52

**Ancillary secondary variables:**

- Response rate at Weeks 12 and 24
- Time to first response
- Duration of first response
- Percent of patients with  $\geq 4$  point reduction from baseline in SELENA SLEDAI at Weeks 12, 24, and 76.
- Mean change in PGA at week 12, 52, and 76
- Percent change from baseline in SELENA SLEDAI score at Weeks 12, 24, 52, 76
- Percent of patients with no worsening (increase of  $<0.30$  points from baseline) in PGA at Weeks 12, 24, 52, and 76
- Percent of patients with not new BILAG A organ domain score or new 2 BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Weeks 12, 24, 52, and 76)
- BILAG response rates at Weeks 12, 24, 52, and 76
- Time to BILAG response
- AUC of the SLENA SLEDAI score over 52 and 76 weeks
- Change in the SLICC/ACR Damage Index at Weeks 52 and 76
- Percent of patients with no new 1A/2B organ domain scores from Week 28 through Week 52
- Percent of patients with no new 1A/2B organ domain scores from Week 52 through Week 76
- Time to SLE flares over 52 and 76 weeks
- Time to first SLE flare after 24 weeks
- Number of flares per subject and the rate of flares over 52 and 76 weeks

- Renal flare rate and time to first renal flare
- The rate and duration of renal remission and time to renal remission
- Percent change in proteinuria
- Percentage of patients with average steroid dose has been reduced by 25% from baseline to 7.5 mg/day or lower during Weeks 64 through 76
- Percent change from baseline of prednisone dose at Weeks 12, 24, 52, and 76
- Number of days of daily steroid dose  $\leq$  7.5 mg/day and/or reduced by 50% from baseline over time
- Time to reduction of daily prednisone dose  $\leq$  7.5 mg/day and/or reduced by 50% from baseline over 52 weeks and 76 weeks
- Percent of patients with daily prednisone dose reduced  $\leq$  7.5 mg/day from  $>$  7.5 mg/day at baseline over time
- Percent of patients with daily steroid dose increased to  $>$ 7.5 mg/day from  $\leq$  7.5 mg/day at baseline over time

**Patient Reported Outcomes:**

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

**Biomarkers:**

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

**Statistical Design, Definitions of Analyzed Populations and Analyses Plan:**

Sample size calculations were based on data generated from the Phase 2 SLE study conducted by the sponsor (Study LBSL02). The proposed study had approximately 90% power at a significance level of 5% to show an absolute difference in improvement of 14% in the response rate of the 10 mg/kg belimumab group (or both the 10 mg/kg and 1mg/kg belimumab groups) as compared to the placebo group at Week 52. The assumptions used in the statistical power calculations included:

- 43% placebo response rate
- A 57% belimumab response rate
- An average (population) response rate of 50% under the null hypothesis (i.e., active= placebo)

The modified intent-to-treat (mITT) population was used for the primary analysis for each trial. This was defined as the subset of all randomized patients who received at least 1 dose of study agent. The mITT analysis was performed according to the

treatment that a subject was randomized to receive, regardless of actual treatment received.

Logistic regression was used to analyze the primary efficacy endpoint and the major secondary endpoints involving response rate at Week 76, reduction in SELENA SLEDAI score and prednisone reduction while an analysis of covariance (ANCOVA) was used for the change from baseline in PGA and SF-36 PCS. Subjects whose background SLE medications were changed after prespecified time points in the common protocol were imputed as treatment failures/nonresponders, as were subjects who dropped out or who had missing data for the Week 52 analysis. A step-down sequential testing procedure was used to account for multiplicity in doses in the analysis of the primary efficacy endpoint (i.e., comparison of belimumab 10 mg/kg to placebo was conducted first and only if that comparison was statistically significant was the comparison of belimumab 1 mg/kg to placebo to be conducted). However, no multiplicity correction was applied to subgroup analyses or the analyses of secondary endpoints.

**Safety Evaluation:**

Descriptive statistics were used to summarize data describing AEs, SAEs, deaths, abnormal lab tests, vital signs, and antibodies to belimumab. The likelihood ratio chi-squared test or the Fisher's exact test in cases where the number of events was less than 5 was to be used to ascertain if the occurrence of AEs was comparable across treatment groups.

**Immunogenicity Assessments:**

Serum samples were collected for belimumab immunogenicity assays prior to initial dosing on Day 0; prior to dosing at weeks 8, 24, and 52/exit; and at the 8-week follow-up visit for subjects who withdrew prior to completion or choose not to enter the continuation study.

**Study Conduct:**

**Protocol Amendments:**

Listed below are the 2 protocol amendments that were made to Study 1057. Each amendment was approved by the Agency's reviewing division prior to being implemented as per the SPA process.

1. Amendment 1 (implemented on June 5, 2007)

The following changes were made to the protocol:

- Clarification of the forms of mycophenolate available internationally and their permitted use during the study as related to Inclusion Criterion 5 and Section 5.5.1.3 Concomitant Medications
- Modification of Exclusion Criterion 16 to reflect change in HIV testing for both types 1 and 2

- Modification of Exclusion Criterion 18 to permit subjects to be randomized with stable Grade 3 hypoalbuminemia due to lupus nephritis
- Modification of the primary efficacy analysis to use the baseline (Day 0) proteinuria level instead of the screening level in the logistic regression model because a subject's proteinuria level may change over the screening period
- Revision of the timing of the initial DMC meeting for review of the data from the Phase 3 studies to occur after the first 100 subjects have been treated through Day 56 in the combined trials or within 6 months of the 1<sup>st</sup> subject, whichever is earlier. Addition clarification that the DMC would monitor these trials until the data are locked and analyzed through Week 76 for 1056 and Week 52 for 1057 after which time monitoring may be assumed by an internal HGS committee
- Modification of Table 3 "Study Calendar" to include both ELISA and a titer at every time point that an ANA specimen is tested. The Workplace Productivity Questionnaire and Emergency Room Visit Question were removed from the Unscheduled visit
- Modification of the "Guidelines for Scoring Proteinuria for SELENA SLEDAI" to require a decrease of  $>0.5$  g/24 hour equivalent or a decrease to  $\leq 0.5$  g/24 hour equivalent from the previous visit to the current visit for improvement in proteinuria after Screening
- Modification of the analysis of safety variables which will no longer include comparative analyses across treatment groups due to multiplicity issues
- Amended the SELENA SLEDAI Disease Assessment Scales to bring text into agreement with the validated SLE Flare Index (published in 2005). Mycophenolate was also added to 1 criterion.
- Modification of the BILAG Disease Assessment Scale to include "SLE Related" check boxes that were being used in the Phase 3 eCRF in order to assist in the scoring of SLE-related lab values recorded on the BILAG
- The range for Grade 1 mild hematuria in the Adverse Event Severity Grading Tables was changed because the central lab used for the study considered the normal range for RBCs in the urine to be 0-3/hpf

## 2. Amendment 2 (implemented on February 6, 2008)

The following 4 changes were made to the protocol:

- Modification of the requirements and schedule for follow-up testing to maintain the study blind. Follow up testing for anti-belimumab antibodies was to be performed only on subjects who were positive for anti-belimumab antibodies at the 8-week follow-up visit (or at the last study visit at which immunogenicity was assessed if the 8-week sample was not available). This testing was to be performed at least 6 months after the last dose or after completion and/or unblinding of the study, whichever was later in order to allow the treatment blinding to remain intact until the study was completed and/or unblinded
- Modification of Exclusion Criterion 18 to allow subjects with stable Grade 3 partial thromboplastin time due to lupus anticoagulant to be randomized and to allow

subjects with stable Grade 3 GGT elevation due to lupus hepatitis to be randomized

- Addition of anti-ribosomal P testing to the autoantibody panel and the analysis of changes in anti-ribosomal P autoantibody levels to the secondary efficacy analysis
- Previous IVIG administration was added as an indication for prophylaxis prior to administration of belimumab

**Disposition:**

As shown in Table 27 below, overall, the proportions of patients who discontinued from the three treatment arms of this study were similar with just a slightly higher rate of early discontinuation occurring in the placebo group than belimumab groups. A similar proportion of patients discontinued from this study due to adverse events and lack of efficacy in the placebo and belimumab treatment groups. More patients withdrew from the 10mg/kg belimumab group due to pregnancy than in the other treatment groups.

**Table 27 – Subject Disposition for Study C1057**

	Placebo	Belimumab 1mg/kg	Belimumab 10 mg/kg	Total
<b>Number of Patients Randomized</b>	288	289	290	<b>867</b>
<b>Number of Patients Treated</b>	287	288	290	<b>865</b>
<b>Number of Patients Who Completed Wk 52:</b>	226 (79%)	240 (83%)	241 (83%)	<b>707 (82%)</b>
<b>Number of Patients Withdrawn Prior to Wk 52:</b>	61 (21%)	48 (17%)	49 (17%)	<b>158 (18%)</b>
<b>Subject Request</b>	7 (2%)	6 (2%)	3 (1%)	<b>16 (2%)</b>
<b>Adverse Event</b>	19 (7%)	16 (6%)	15 (5%)	<b>50 (6%)</b>
<b>Lack of Efficacy</b>	16 (6%)	12 (4%)	12 (4%)	<b>40 (5%)</b>
<b>Non-Compliance</b>	1 (0%)	1 (0%)	1 (0%)	<b>3 (0%)</b>
<b>Lost to Follow-Up</b>	4 (1%)	6 (2%)	3 (1%)	<b>13 (2%)</b>
<b>Protocol Violation</b>	7 (2%)	2 (1%)	3 (1%)	<b>12 (1%)</b>
<b>Investigator Decision</b>	3 (1%)	2 (1%)	3 (1%)	<b>8 (1%)</b>
<b>Other:</b>	4 (1%)	3 (1%)	9 (3%)	<b>16 (2%)</b>
<b>Pregnancy<sup>1</sup></b>	4 (1%)	3 (1%)	8 (3%)	<b>15 (2%)</b>

<sup>1</sup>Subject BR001-005 in the placebo group discontinued treatment due to an AE of spontaneous abortion and Subject RO005-001 in the 10 mg/kg group discontinued treatment due to investigator decision (pregnancy).

Adapted Sponsor's table 6-1; p. 69.

**Protocol Deviations/Violations:**

Table 28 shows there were a total of 84 protocol violations incurred by 76 subjects for this study as follows: 34 subjects (4%) did not meet study entry criteria (unstable or prohibited treatment regimens within 60 days of Day 0, did not meet screening ACR criteria for SLE or other entry criteria, initial lab procedures not followed); 25 subjects (3%) developed withdrawal criteria but were not withdrawn (received an increase dose of steroids or immunosuppressives), and 14 subjects (2%) received the wrong treatment or an incorrect dose. Overall, the three treatment groups were balanced with regards to occurrence of protocol violations.

Table 28 – Summary of Protocol Violations for Study 1057

	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
<b>Entered Study But Did Not Meet Entry Criteria</b>	11 (4%)	13 (5%)	10 (3%)	<b>34 (4%)</b>
<b>Developed Withdrawal Criteria But Was Not Withdrawn</b>	12 (4%)	5 (2%)	8 (3%)	<b>25 (3%)</b>
<b>Received Wrong Treatment or Incorrect Dose</b>	6 (2%)	3 (1%)	5 (2%)	<b>14 (2%)</b>
<b>Received an Excluded Concomitant Medication</b>	1 (0.3%)	1 (0.3%)	1 (0.3%)	<b>3 (0.3%)</b>

Modified Sponsor's Table 17-1; Appendix 17.

**Treatment Compliance and Drug Exposure:**

All study infusions were administered in clinic by study staff.

**Demographics:**

As summarized in the following tables (Table 29 and Table 30), the treatment groups within this trial were generally well balanced with respect to baseline demographics, region, disease characteristics and activity.

The population of this study, which was conducted outside the U.S., was predominantly female (94%) and was comprised of 38% Asians 32% Native or American Indians, 27% Caucasians, and 4% Black/African American subjects. The mean age of subjects was 36 years and mean weight of subjects was 61 kg. The majority (50%) of subjects were from Latin America while the remaining subjects were from Asia (38%) and Eastern Europe (11%). No important imbalances in these demographic factors across treatment groups were noted within this study.

Table 29 – Demographic Characteristics of Subjects Enrolled in Study C1057

Demographics	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
<b>Gender:</b>				
Female	270 (94%)	271 (94%)	280 (97%)	821 (95%)
Male	5 (6%)	17 (6%)	10 (3%)	44 (5%)
<b>Race:</b>				
Caucasian	82 (29%)	76 (26%)	71 (25%)	229 (27%)
Asian	105 (37%)	106 (37%)	116 (40%)	327 (38%)
African American	11 (4%)	8 (3%)	11 (4%)	30 (4%)
Alaskan Native/American Indian	89 (31%)	98 (34%)	92 (32%)	279 (32%)
Multiracial	1 (0%)	3 (1%)	1 (0%)	5 (1%)
<b>Hispanic Origin</b>	143 (50%)	141 (49%)	136 (47%)	420 (49%)
<b>Age (years)</b>				
Mean (SD)	36 (12)	35 (11)	35 (11)	36 (11)
≤ 45	225 (78%)	236 (82%)	236 (81%)	697 (81%)
> 45 to <65	57 (20%)	48 (17%)	52 (18%)	157 (18%)
≥ 65 to <75	5 (2%)	4 (1%)	2 (1%)	11 (1%)
<b>Weight</b>				
Mean (SD)	62 (12)	61 (13)	62 (13)	61 (13)
(Min, Max)	(35, 128)	(36, 120)	(36, 129)	(35, 129)

Adapted Sponsor's Table 6-3; p. 74

As shown in Table 30, subjects in Study 1057 had an overall mean duration of SLE disease of 5.9 years. Overall, these patients had a high baseline level of disease activity as manifested by a SELENA SLEDAI mean score of 10 with 53% of the patients having a baseline SELENA SLEDAI score of  $\geq 10$  points. No imbalances in baseline disease activity were observed for the three treatment groups in this trial.

Table 30 – Tabular Summary of Subject’s Baseline Disease Characteristics for Study C1057

Characteristic	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
<b>SLE Disease Duration (yr):</b> Mean (SD)	6 (6)	5 (5)	5 (5)	5 (5)
<b>BILAG Organ Domain Involvement:</b>				
At least 1A or 2B	166 (58%)	166 (58%)	172 (59%)	504 (58%)
At Least 1A	52 (18%)	58 (20%)	54 (19%)	164 (19%)
At Least 1A or 1B	259 (90%)	255 (89%)	258 (89%)	772 (89%)
No A or B	28 (10%)	33 (12%)	32 (11%)	93 (11%)
<b>SELENA SLEDAI Category:</b>				
0 to 3	1 (05)	4 (1%)	3 (1%)	8 (1%)
4 to 9	128 (45%)	145 (50%)	127 (44%)	400 (46%)
10 to 11	75 (26%)	53 (18%)	72 (25%)	200 (23%)
> 12	83 (29%)	86 (30%)	88 (30%)	257 (30%)
<b>SELENA SLEDAI Score</b> Mean (SD)	9.7 (3.6)	9.6 (3.8)	10 (3.9)	9.8 (3.8)
<b>SLE Flare Index</b>				
At Least 1 Flare	57 (20%)	53 (18%)	56 (19%)	166 (19%)
Severe Flare	1 (0.3%)	5 (2%)	4 (1%)	10 (1%)
<b>PGA Scale:</b> Mean (SD)	1.4 (0.48)	1.4 (0.47)	1.4 (0.45)	1.4 (0.47)
<b>SLICC Damage Index Score</b> Mean (SD)	0.55 (0.93)	0.60 (1.1)	0.55 (1.0)	0.57 (1.0)
<b>Proteinuria Category (g/24 hr)</b>				
<0.5	215 (75%)	216 (75%)	220 (76%)	651 (75%)
0.5 to <1	20 (7%)	23 (8%)	22 (8%)	65 (8%)
1 to <2	31 (11%)	23 (8%)	29 (10%)	83 (10%)
≥ 2	21 (7%)	26 (9%)	19 (7%)	66 (8%)
<b>Proteinuria Level (g/24 hr)</b> Mean (SD)	0.62 (1.2)	0.63 (1.1)	0.54 (0.9)	0.6 (1.1)

Adapted Sponsor’s table 6-4; p. 75.

The majority (98%) of patients in this trial were overwhelmingly seropositive for ANA and/or anti-dsDNA as shown in Table 31 below. The treatment groups were also generally well balanced with respect to baseline biomarkers of disease activity with a slightly lower proportion of patients seropositive for anti-ribosomal P in the 10 mg/kg belimumab group as compared to the other treatment groups.

Table 31 - Tabular Summary of Subject's Baseline Serologies, Immunoglobulins, Complement and Other Biomarkers for Study C1057

	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
<b>Anti-dsDNA:</b>				
Positive ( $\geq 30$ IU/mL)	205 (71%)	221 (77%)	218 (75%)	644 (75%)
Mean (SD)	144 (64)	146 (62)	144 (62)	145 (62)
<b>ANA<sup>1</sup>:</b>				
Positive ( $\geq 80$ Titer)	264 (92%)	272 (94%)	276 (95%)	812 (94%)
Mean (SD)	881 (466)	851 (483)	903 (476)	878 (475)
<b>ANA and/or Anti-dsDNA</b>				
Positive:	280 (98%)	281 (98%)	284 (98%)	845 (98%)
<b>aCL<sup>2</sup>:</b>				
Positive	88 (31%)	106 (37%)	111 (39%)	305 (35%)
<b>Anti-ribosomal P:</b>				
Positive ( $>25$ EU/mL)	80 (29%)	79 (28%)	62 (22%)	221 (26%)
Mean (SD)	73 (36)	66 (36)	67 (37)	69 (36)
<b>Anti-Smith:</b>				
Positive ( $\geq 15$ U/mL)	101 (35%)	102 (35%)	105 (37%)	308 (36%)
Mean (SD)	1152 (4547)	438 (1276)	505 (1471)	695 (2847)
<b>IgG:</b>				
Mean (SD)	17.2 (6.0)	17.4 (6.2)	17.2 (5.6)	17.3 (5.9)
>ULN (16.18 g/L)	146 (51%)	140 (49%)	151 (52%)	437 (51%)
<LLN (6.94 g/L)	1 (0%)	0 (0%)	3 (1%)	4 (0%)
<b>IgA:</b>				
Mean (SD)	3.1 (1.3)	3.3 (1.4)	3.2 (1.4)	3.2 (1.4)
>ULN (4.63 g/L)	33 (12%)	40 (14%)	36 (12%)	109 (13%)
<LLN (0.81 g/L)	2 (1%)	3 (1%)	7 (2%)	12 (1)
<b>IgM:</b>				
Mean (SD)	1.2 (0.8)	1.1 (0.7)	1.2 (0.7)	1.2 (0.7)
>ULN (2.71 g/L)	12 (4%)	10 (4%)	9 (3%)	31 (4%)
<LLN (0.48 g/L)	37 (13%)	32 (11%)	33 (11%)	102 (12%)
<b>C3:</b>				
Mean (SD)	938 (313)	898 (303)	917 (321)	918 (313)
Low ( $<900$ mg/L)	132 (46%)	148 (51%)	147 (51%)	427 (49%)
<b>C4:</b>				
Mean (SD)	16 (10)	15 (9.4)	15 (10)	16 (9.7)
Low ( $<16$ mg/dL)	160 (56%)	173 (60%)	180 (62%)	513 (59%)
<b>CRP:</b>				
Positive ( $>3$ mg/L)	114(41%)	119 (42%)	119 (42%)	352 (41%)
Mean (SD)	13.0 (17.7)	12.1 (12.5)	12.1 (11.9)	12.4 (14.2)
<b>BLyS:</b>				
Above LOQ	272 (97%)	272 (96%)	281 (99%)	827 (97%)
Mean (SD)	1.8 (1.5)	1.8 (1.6)	1.8 (2.8)	1.8 (2.0)

<sup>1</sup>ANA titer equals to the maximum titer of the individual patterns

<sup>2</sup>aCL is positive if any of aCL-IgG, aCL-IgA, or aC

Modified Sponsor's Table 6-6; p. 78 Clinical Study C1057 Report.

The following Table 32 summarizes concomitant SLE medications used by more than 10% of subjects who participated in this trial. The usage of concomitant SLE medications at baseline was generally similar for the three treatment groups in this trial, however, with a higher proportion of patients in the 10mg/kg belimumab group (25%)

taking concomitant angiotensin pathway inhibitors as compared to the other treatment groups.

Table 32 - Tabular Summary of Concomitant SLE medication >10% of Subjects in Study C1057

SLE Medications	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
<b>Total Glucocorticoid Use:</b>	276 (96%)	276 (96%)	278 (96%)	<b>830 (96%)</b>
Methylprednisolone	46 (16%)	55 (19%)	52 (18%)	<b>153 (18%)</b>
Prednisolone	132 (46%)	123 (43%)	127 (44%)	<b>382 (44%)</b>
Prednisone	86 (30%)	88 (31%)	91 (31%)	<b>265 (31%)</b>
<b>Prednisone or Equivalent Dose at Baseline:</b>				
0 mg/day	11 (4%)	12 (4%)	12 (4%)	<b>35 (4%)</b>
>0 - < 7.5 mg/day	84 (29%)	72 (25%)	74 (26%)	<b>230 (27%)</b>
>7.5 mg/day	192 (67%)	204 (71%)	204 (70%)	<b>600 (69%)</b>
<b>Average Prednisone or Equivalent Dose at Baseline:</b>				
Mean (SD)	12 (8)	13 (9)	13 (10)	<b>13 (9)</b>
<b>Angiotensin Pathway Antihypertensives:</b>	61 (21%)	49 (17%)	72 (25%)	<b>182 (21%)</b>
<b>Antimalarials:</b>	201 (70%)	195 (68%)	185 (64%)	<b>581(67%)</b>
<b>Other Immunosuppressives:</b>	122 (43%)	120 (42%)	123 (42%)	<b>365 (42%)</b>
Azathioprine	67 (23%)	71 (25%)	84 (29%)	<b>222 (26%)</b>
Methotrexate	35 (12%)	24 (8%)	20 (7%)	<b>79 (9%)</b>
Mycophenolate Mofetil	19 (7%)	15 (5%)	17 (6%)	<b>52 (6%)</b>
<b>NSAIDs</b>	59 (21%)	56 (19%)	58 (20%)	<b>173 (20%)</b>
<b>HMG CoA Reductase Inhibitors</b>	16 (6%)	13 (5%)	16 (6%)	<b>45 (5%)</b>

Adapted Sponsor's Table T19; p. 474.

### Efficacy:

As discussed in the Background section above, the primary endpoint was the SRI response rate at Week 52 for which a positive response was defined as a:

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

Subjects whose background SLE medications were changed after prespecified time points in the common protocol were imputed as treatment failures/nonresponders, as were subjects who dropped out or who had missing data for the Week 52 analysis. A sequential step-down procedure to adjust for multiple comparisons was utilized in the analysis of the primary endpoint of the modified intent-to-treat (mITT) population. As shown in Table 33, patients treated with belimumab 10 mg/kg and 1 mg/kg had a statistically higher rate of response than placebo patients in Study 1057. The results from the analyses of the subcomponents of the SRI were generally consistent with those of the primary analysis for both belimumab treatment groups. The proportions of subjects achieving success for each of the subcomponents of the SRI were numerically

higher in the belimumab groups than the placebo group, although these differences only reached statistical significance for the belimumab 10 mg/kg to placebo.

Table 33 – Tabular Summary of Primary Endpoint Response at Week 52 (adjusted) for Study 1057

	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
<b>Response:</b>	125 (44%)	148 (51%)	167 (58%)
<b>Observed Difference vs Placebo</b>		8%	14%
<b>OR (95% CI)<sup>1</sup> vs Placebo</b>		1.55 (1.10, 2.19)	1.83 (1.3, 2.59)
<b>P-value</b>		0.0129	0.0006
<b>Subcomponents</b>			
<b>4-Point Reduction in SELENA SLEDAI:</b>	132 (46%)	153 (53%)	169 (58%)
<b>OR (95% CI)<sup>2</sup> vs Placebo</b>		1.51 (1.07, 2.14)	1.71 (1.21, 2.41)
<b>P-value</b>		0.0189	0.0024
<b>No Worsening in PGA:</b>	199 (69%)	277 (79%)	231 (80%)
<b>OR (95% CI)<sup>3</sup> vs Placebo</b>		1.68 (1.15, 2.47)	1.74 (1.18, 2.55)
<b>P-value</b>		0.0078	0.0048
<b>No New 1A/2B BILAG Domain Scores:</b>	210 (73%)	226 (79%)	236 (81%)
<b>OR (95% CI)<sup>4</sup> vs Placebo</b>		1.38 (0.93, 2.04)	1.62 (1.09, 2.42)
<b>P-value</b>		0.1064	0.0181

OR=Odds Ratio; CI =Confidence Interval

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

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

<sup>3</sup>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

<sup>4</sup>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)

Adapted Sponsor's tables 7-1 and 7-2; p. 80-81.

Table 34 provides the reasons subjects failed to achieve a positive SRI response in these trials. Note that the categories provided are mutually exclusive and mutually exhaustive. The proportions of subjects who dropped out are approximately 12% in study 1057 and are fairly balanced across treatment groups within the study thus the impact of imputing dropouts as failures on the treatment effect in the primary analysis should be small. However, unlike dropouts, "medication failures" are not balanced across treatment groups (11%, 7%, and 6% for placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab, respectively). Since medication failures are more frequent in the placebo group than the belimumab groups, imputing medication failures as efficacy failures could bias the treatment effect in the primary efficacy endpoint in favor of belimumab (unless these subjects would truly have been unable to achieve success on the primary endpoint had they not taken the prohibited medication).

Table 34 – Tabular Summary of Disposition of Response at Week 52 for Study 1057

	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
<b>Response</b>	125 (44%)	148 (51%)	167 (58%)
<b>No Response:</b>	162 (56%)	140 (49%)	123 (42%)
<b>Dropout<sup>1</sup> – Not a Medication Failure</b>	38 (13%)	34 (12%)	31 (11%)
<b>Medication Failure<sup>2</sup></b>	30 (11%)	21 (7%)	18 (6%)
<b>&lt;4 Point Reduction in SELENA SLEDAI (SS)<sup>3</sup></b>	87 (30%)	80 (28%)	72 (25%)
<b>≥4 Point Reduction in SS with the following<sup>3</sup>:</b>	7 (2%)	5 (2%)	2 (1%)
<b>Worsening in PGA only<sup>3</sup></b>	5 (2%)	3 (1%)	1 (0%)
<b>New 1A/2B/BILAG only<sup>3</sup></b>	2 (1%)	2 (1%)	1 (0%)
<b>Both Worsening in PGA and New 1A/2B BILAG<sup>3</sup></b>	--	--	--

<sup>1</sup>Subjects who withdrew early and had no data in the Day 364 +/- 28 day window

<sup>2</sup>Includes subjects who withdrew early and subjects who met all 3 response criteria at week 52 but took a protocol prohibited or restricted medication or dose

<sup>3</sup>In subjects who did not dropout and were not medication failures.

Adapted Sponsor's Table 7-3; p. 82

The sponsor provided four sensitivity analyses for the primary efficacy endpoint. These sensitivity analyses were conducted as planned in the protocol. The results of these sensitivity analyses are largely consistent with the primary efficacy analysis and are shown in Table 35. Additional sensitivity analyses that address the issue of medication failures are presented and discussed in Section 6.1.5 of this review.

Table 35 – Tabular Summary of Sensitivity Analyses for Primary Endpoint Response at Week 52 for Study 1057

	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
<b>Unadjusted Response:</b>			
Observed Difference vs Placebo	125 (44%)	148 (51%)	167 (58%)
OR (95% CI) <sup>1</sup> vs Placebo		8 1.37 (0.99, 1.90)	14 1.76 (1.27, 2.45)
P-value		0.0602	0.0008
<b>LOCF Response (adjusted):</b>			
Observed Difference vs Placebo	137 (48%)	155 (54%)	182 (63%)
OR (95% CI) <sup>1</sup> vs Placebo		6 1.44 (1.02, 2.03)	15 1.94 (1.37, 2.76)
P-value		0.0402	0.0002
<b>Completer Response (adjusted):</b>			
Observed Difference vs Placebo	125/225 (56%)	144/236 (61%)	165/240 (69%)
OR (95% CI) <sup>1</sup> vs Placebo		5 1.46 (0.98, 2.18)	13 1.87 (1.24, 2.81)
P-value		0.0639	0.0027
<b>Per Protocol Response (adjusted):</b>			
Observed Difference vs Placebo	122/278 (44%)	145/278 (52%)	164/281 (58%)
OR (95% CI) <sup>1</sup> vs Placebo		8 1.56 (1.10, 2.22)	14 1.86 (1.31, 2.65)
P-value		0.0123	0.0005

<sup>1</sup>Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo without adjustment for any covariates

<sup>2</sup>Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDA ( $\leq 9$  vs  $\geq 10$ ), baseline proteinuria level ( $< 2$  g/24 hr vs  $\geq 2$  g/24 hr equivalent) and race (African descent or indigenous-American descent vs other).

Adapted Sponsor's Table 7-4; 83.

A number of prespecified subgroup analyses were also conducted which are presented and discussed in Section 6.1.8 of this review.

### **Secondary Endpoints:**

There were four major and numerous ancillary secondary endpoints for this trial. The major secondary endpoints will be presented with the ancillary secondary endpoints by corresponding assessment area. As per the statistical analysis plan, no multiplicity correction was implemented for the secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate.

### **SELENA SLEDAI Disease Activity:**

A major secondary endpoints in this study was the percentage of subjects with  $\geq 4$ -point reduction from baseline in SELENA SELDAI score at Week 52. Since this was one of the components of the SRI, the results of this analysis are listed in Table 33 above and are generally consistent with those of the primary analysis. The proportions of subjects who achieved this endpoint were numerically higher in both belimumab treatment groups and were statistically significant on comparison to placebo.

The results of numerous ancillary secondary endpoints that also assessed disease activity in this trial are summarized as follows:

- Response rate by visit: Numeric improvements in response rates were observed in all three treatment groups starting at Week 4. A separation in the response rate curves was observed starting at Week 12 with significantly higher response rates for both belimumab treatment groups observed at Week 28 compared to placebo that was sustained to Week 52.
- Time to first response: A numerically shorter median time to first response was observed for both belimumab groups (range: 84-85 days) that was not significantly different from placebo (112 days)
- Duration of first response that was maintained to Week 52: Longer mean durations of first response were observed for both the 1 mg/kg (103 days) and 10mg/kg (123 days) as compared to placebo (95 days) that were significantly different on comparison of only the 10 mg/kg of group versus placebo (p=0.0080).
- Percentage of subjects with  $\geq 4$  point reduction from baseline in SELENA SLEDAI score at Weeks 12, 24, and 52: The results of the Week 52 analysis (Table 24 above) for this endpoint demonstrated a significantly higher proportion of subjects in the belimumab treatment groups were able to achieve this reduction compared to placebo. A numerically higher percentage of subjects in the 10mg/kg group (50%) achieved this reduction compared to placebo (46%) which was similar to that in the 1mg/kg group (44%) at Week 12. A significantly higher percentage of subjects in the 10mg/kg group (60%) achieved compared to placebo (52%) at Week 24 (p=0.0434) that was maintained through Week 52. Significant improvement in the 1mg/kg group (53%) compared to placebo (47%) occurred at Week 40 (p=0.0446) and was maintained through Week 52.
- Percent change from baseline in SELENA SLEDAI: Numeric improvements were observed in all three treatment groups that were significantly different at Weeks 24, 28, 36 through 52 (40%) time points for the 10 mg/kg belimumab treatment group compared to placebo (Wk 52: 30%) (p=0.0018) and at the Week 44 time point for the 1 mg/kg belimumab group (34%) versus placebo (26%) (p=0.0328).
- AUC of the SELENA SLEDAI score over 52 weeks: Mean AUC of SELENA SLEDAI score over 52 weeks was significantly lower (indicating improvement) in the 10 mg/kg group (242; p=0.0142) compared to placebo (226) while the 1mg/kg group (262) was similar to placebo.

***BILAG Disease Activity:***

- Percentage of subjects with no new BILAG 1A/2B organ domain scores at time of assessment compared with baseline: From Week 4 through Week 52 a numerically greater percentage of subjects in the 10 mg/kg belimumab group had no new BILAG 1A/2B organ domain scores from baseline compared with placebo that was significantly different at Weeks 28 through 52 (10mg/kg: 81% vs placebo: 73%; p=0.0181). The percentages of subjects with no new BILAG

1A/2B scores in the 1 mg/kg group were numerically higher than placebo starting at Week 20 that were significantly different at Weeks 28 (1mg/kg: 89%; placebo: 83%;  $p=0.0211$ ) and 44 (1mg/kg: 82%; placebo: 75%;  $p=0.0488$ ).

- Percent of subjects with no new BILAG 1A/2B organ domain scores at the time of assessment: Starting at Week 4, the percentages of subjects with no new BILAG 1A/2B organ domain scores at the time of assessment were numerically higher in the both belimumab group as compared to placebo. Significant differences for this endpoint were observed for the 10 mg/kg belimumab group at Week 8 (77%) and Weeks 28 through 52 (71%) as compared to placebo (60%, and 62%, respectively) ( $p<0.05$ ) and for the 1mg/kg group at Weeks 8 (69%), 28 (74%), and 36-44 (70%) compared to placebo (60%, 66% and 62%) ( $p<0.05$ ).
- Percentage of subjects with no new BILAG 1A/2B organ domain scores compared with baseline after the Week 24 visit to the Week 52 visit: A significantly higher percentage of subjects in the belimumab 1mg/kg (74%) and 10 mg/kg (79%) treatment groups had no new BILAG 1A/2B organ domain scores compared with baseline after the Week 28 visit to the Week 52 on comparison to placebo (57%) ( $p=0.0383$ ;  $p=0.0012$ , respectively).
- BILAG response rates: As per the definition of a BILAG response which was a subject may be considered a responder if improvement is demonstrated in at least 1 organ domain score and no new BILAG 1A/2B BILAG response rates were assessed in subjects with at least 1A/2B domain score at baseline, responses were significantly higher in the 10 mg/kg group at Weeks 8 (83%), 12 (70%,) and 20 (84%) that was maintained through Week 52 (72%) versus placebo (66%, 71%, 72% and 60%, respectively) ( $p<0.05$ ). The BILAG response was significantly higher in the 1mg/kg group at Week 28 (77%) to the end of study treatment (71%) as compared to placebo (68% and 62%, respectively) ( $p<0.05$ ).

***Physician's Global Assessment (PGA) of Disease Activity:***

Another major secondary endpoint that assessed disease activity was the mean change and percent mean change from baseline in PGA at Week 24. Reductions in the mean percent change and mean change from baseline in PGA at Week 24 were comparable across groups and were not significantly different (see Table 52 below). Results from the ancillary secondary PGA endpoints are as follows:

- Percentage of subjects with no worsening (increase of  $< 0.30$  points from baseline) in PGA by visit: A significantly higher percentage of subjects the belimumab groups had no worsening in their PGA scores at Week 28 which was maintained through Week 52 as compared with placebo (1mg/kg: 79%, 10 mg/kg: 80%; placebo: 69%) ( $p=0.0078$ ;  $p=0.0048$ ).
- Percentage of subjects with  $\geq 0.30$  points improvement (i.e., reduction) from baseline in PGA by visit: A significantly higher percentage of subjects the belimumab groups had no worsening in their PGA scores at Week 12 which was maintained through Week 52 as compared with placebo (1mg/kg: 59%, 10 mg/kg: 65%; placebo: 49%) ( $p=0.0147$ ;  $p=0.0002$ ).

- Mean change and mean percent change in PGA by visit: For the analysis of mean absolute change in PGA, numerical improvements were observed for both belimumab treatment groups that were significant different for the 1 mg/kg group starting at Week 40 through Week 52 (49%;  $p=0.0307$ ) and for the 10mg/kg group starting at Week 8 through Week 52 (57%;  $p=0.0001$ ) as compared to placebo (38%). For the analysis of mean percent change in PGA, significant improvements were observed for both belimumab treatment groups that starting at the Week 8 and maintained to Week 52 (1mg/kg: 34%; 10mg/kg: 40%; placebo: 22%) ( $p=0.0039$ ) ( $p<0.001$ ).

***SLICC/ACR Damage Index:***

This endpoint is used to assess end organ damage in SLE patients. Baseline scores were comparable for the three treatment groups (1mg/kg: 0.60; 10mg/kg: 0.55; placebo: 0.55). The Week 52 scores were not consistent with disease progression (1mg/kg: 0.07; 10mg/kg: 0.03; placebo: 0.05) (Refer to Table 63.)

***SLE Flares:***

Results from the ancillary secondary endpoints of SLE flare conducted using the modified SLE Flare Index are as follows:

- Time to first SLE flares over 52 weeks and after Week 24 visit to the Week 52 visit: The median time to flare for both the 1 mg/kg (126 days) and 10 mg/kg (119 days) belimumab groups was longer as compared to placebo (84 days) (see Table 54 below). Decreases in the risk for experiencing a disease flare during Weeks 24 to 52 were observed in both belimumab groups that were significantly different on comparison of both belimumab groups (1mg/kg: 42%; 10 mg/kg: 29%) to placebo ( $p<0.0001$ ;  $p=0.0027$ , respectively) (refer to Table 55 below).
- Time to first severe SLE flare over 52 weeks and after Week 24 visit to the Week 52 visit: The risk of developing a first severe flare over 52 weeks was significantly reduced in the 10 mg/kg group (43%;  $p=0.0055$ ) and numerically reduced in the 1 mg/kg group (24%) compared to placebo (see Table 54 below). Numerical decreases in the risk for experiencing a severe disease flare during Weeks 24 to 52 were observed in both belimumab groups (1mg/kg: 28%; 10 mg/kg: 30%) as compared to placebo (see Table 55 below).
- Flares per subject-year and the rate of flares over 52 weeks and after the Week 24 visit to the Week 52 visit: Flares per subject-year over 52 weeks were significantly lower in both belimumab groups versus placebo with rates of 3.2 per subject-years in the placebo group, 2.5 per subject-years in the 1 mg/kg group ( $p=0.0012$ ), and 2.4 per subject-years in the 10 mg/kg group ( $p=0.0002$ ) (refer to Table 54 below).
- Severe flares per subject-year and the rate of severe flares over 52 weeks and after the Week 24 visit to the Week 52 visit: The number of severe flares per subject-year was lower in the 10 mg/kg belimumab group (0.6) as compared to placebo (0.9) and 1mg/kg belimumab (0.8) (see Table 54 below). Numerical decreases in the rates of severe flares were seen after the Week 24 to the Week

52 visit in both the 1mg/kg (0.58) and 10 mg/kg (0.45) belimumab groups as compared to placebo (0.82) (refer to Table 54 below).

Results from the ancillary secondary endpoints of SLE flare conducted using the BILAG are as follows:

- Time to first BILAG 1A/2B flare over 52 weeks and after the Week 24 visit to the Week 52 visit: A reduction in flares was observed in the 10 mg/kg belimumab group that was significantly different from placebo ( $p=0.0016$ ) while no reduction in risk was observed in the 1mg/kg belimumab group (see Table 56 below). Decreases in the risk for experiencing a disease flare during Weeks 24 to 52 were observed in both belimumab groups (1mg/kg: 26%; 10 mg/kg: 42%) that were significantly different when compared to placebo for only the 10 mg/kg group ( $p=0.0185$ ) (see Table 57 below).
- BILAG flares per subject-year and the rate of flares over 52 weeks and after the Week 24 visit to the Week 52 visit: Flares per subject-years were also reduced over 52 weeks in the 1 mg/kg group (1.04) and 10 mg/kg (0.75) belimumab groups as compared to placebo (1.21) that was only significantly different on comparison of the 10 mg/kg belimumab group versus placebo ( $p=0.0104$ ) (refer to Table 56). Reductions in flares per subject-years were also observed during Weeks 24 to Week 52 for both belimumab groups (1mg/kg: 0.88; 10 mg/kg: 0.64) that was significantly different on comparison of the 10mg/kg group versus placebo ( $p=0.0041$ ) and trended on comparison of the 1mg/kg group versus placebo ( $p=0.0611$ ) (see Table 57).

***Steroid use:***

Another major secondary endpoint was the percentage of subjects whose average prednisone dose was reduced by  $\geq 25\%$  for baseline to  $\leq 7.5$  mg/day during Weeks 40 through 52 in subjects who were receiving  $>7.5$  mg/day prednisone at baseline. Numerically more patients in both belimumab groups (1mg/kg: 21%; 10 mg/kg: 19%) were able to reduce prednisone use by  $\geq 25\%$  as compared to placebo (12%) which was significantly different for the 1mg/kg versus placebo comparison ( $p=0.0252$ ) and trended on comparison of the 10 mg/kg group versus placebo ( $p=0.0526$ ).

Results from the ancillary secondary endpoints of concomitant steroid use are as follows:

- Change and percent change from baseline of prednisone dose over time: A numerically higher mean percent decrease from baseline of prednisone dose was only observed in the 10mg/kg group starting at Week 12 that was sustained through Week 52 that was significantly different as compared to placebo at the Week 52 time point (10mg/kg: 19% vs placebo: 9.7%;  $p=0.0009$ ). A consistent numeric decrease was observed in the 1 mg/kg belimumab group starting at Week 44 through Week 52. (Note: This analysis included subjects who took prohibited medications or a protocol restricted medication.)

- Number of days of daily prednisone dose  $\leq 7.5$  mg/day and/or reduced by 50% from baseline over time: The cumulative number of days of daily prednisone dose  $\leq 7.5$  mg/day and/or reduced by 50% from baseline were significantly higher for the 10 mg/kg group (70 days) versus placebo (45 days) by Week 40 through Week 52 was numerically greater in the 1mg/kg group compared to placebo by Week 36 through Week 52.
- Time to first daily prednisone reduction  $\leq 7.5$  mg/day and/or reduction by 50% from baseline over 52 Weeks: The likelihood of a prednisone reduction over the 52 weeks of study treatment was similar for the three treatment groups (hazard ratio of 1.12 ( $p=0.5211$ ) for 1 mg/kg vs placebo; hazard ratio of 1.47 ( $p=0.0285$ ) for 10mg/kg vs placebo).
- Percentage of subjects with daily prednisone dose reduced to  $\leq 7.5$  mg/day from  $> 7.5$  mg/day at baseline over time: A significantly higher percentage of subjects achieved a reduction in prednisone to  $\leq 7.5$  mg/day in each belimumab group versus placebo by Week 32 in the 1 mg/kg (18% vs placebo: 10%) group and by Week 36 in the 10 mg/kg (18% vs placebo: 10%) which was maintained for the remainder of the 52-week treatment period (Week 52: 1mg/kg; 22%; 10 mg/kg: 22%; placebo: 14%) ( $p<0.05$ ).
- Percentage of subjects with daily prednisone dose increased to  $> 7.5$  mg/day from  $\leq 7.5$  mg/day at baseline over time: At Week 52, 30% of subjects in the 1mg/kg group ( $p=0.5576$ ) and 20% of subjects in the 10mg/kg group ( $p=0.0196$ ) required increases in steroids compared with 36% in the placebo group.
- Percentage of subjects with durable prednisone reduction over 24 and 52 weeks: The percentage of subjects with a durable prednisone reduction over 24 to 52 weeks was higher in the belimumab treatment groups as compared to placebo (1mg/kg: 26%; 10 mg/kg: 28%; placebo: 17%) that was significantly different on comparison between the 10 mg/kg group and placebo ( $p=0.0177$ ).
- Time to and duration of sustained prednisone reduction over 52 weeks: The mean duration of sustained prednisone reduction was numerically longer in the 1 mg/kg (54 days) and 10mg/kg belimumab group (60 days) as compared to placebo (33 days) and was significantly different on comparison of the 10 mg/kg group versus placebo ( $p=0.0159$ ). The likelihood of a sustained prednisone reduction over the 52 weeks of study treatment was greater for both the 1mg/kg group (hazard ratio of 1.60;  $p=0.0465$ ) and for the 10 mg/kg group (hazard ratio of 1.96  $p=0.0032$ ) as compared to placebo (15%).

### ***Renal Measures:***

Due to the small numbers of subjects who developed renal flares while participating in this trial (placebo: 13 subjects; 1mg/kg: 12 subjects; 10mg/kg: 4 subjects) the median time to renal flare could not be observed. Although the protocol prohibited entry of subjects with active lupus nephritis, it did permit the entry of patients with proteinuria. A subgroup of patients ( $n=66$ ) with renal disorder (defined as proteinuria  $\geq 2g/24$  hrs) who participated in this trial were assessed for potential renal disease remission (defined as

urine RBC count <10 cells/hpf, the absence of cellular casts, and proteinuria <1g/24 h without doubling of serum creatinine level). The rates of renal remission in this subgroup were 19% (4/21) in the placebo group, 31% (8/26) in 1mg/kg belimumab group, and 42% (8/19) in the 10mg/kg belimumab group. Again, the small numbers of patients resulted in the median time to remission from being observed. No apparent differences among the three treatment groups were observed for the other prespecified renal remission endpoints. In patients with proteinuria at baseline (defined as proteinuria .0.5 g/24 h), the mean percent decrease from baseline in proteinuria was numerically greater in both belimumab groups versus placebo at all time points after Week 8 and were significantly different by Week 24. At Week 52, the mean decrease from baseline proteinuria was 18% in the placebo group, 19% in the 1 mg/kg group, and 42% in the 10 mg/kg belimumab group.

***Patient Reported Outcomes (PROs):***

Another major secondary endpoint was the change from baseline to Week 24 in the SF-36 physical component score (PCS) for the belimumab groups as compared to placebo. The change from baseline to Week 24 in the SF-36 PCS was comparable for all three treatment groups (1mg/kg: 3.4; 10mg/kg: 3.3; placebo: 3.3) (see Table 51 below.)

Results from the ancillary secondary PRO endpoints are as follows:

- Mean change in SF-36 Health Survey Scores (8 Domains and MCS) at Week 52: Significant improvements for the SF-36 domain scores for physical functioning, bodily pain, vitality, and role emotional for the belimumab 10 mg/kg group versus placebo at Week 52. The 10 mg/kg group was numerically better than placebo for the domains of mental health, social functioning, general health and MCS. Significant improvements for the SF-36 domain scores for physical functioning, bodily pain, social functioning, role emotional and general health for the belimumab 1 mg/kg group versus placebo at Week 52 were observed. Numeric improvements for the 1mg/kg group in the domains of vitality and mental health compared to placebo were observed. No treatment benefit was observed for both belimumab groups for the role physical domain and for the 1mg/kg group for MCS score compared to placebo.
- Mean change in FACIT-Fatigue Scale score: At Week 52, numerical improvements in the mean change in FACIT-Fatigue score were observed in the 1mg/kg (3.6) and 10 mg/kg (4.3) belimumab groups as compared to placebo (1.7) that were significantly different for both belimumab groups compared to placebo ((p<0.05).
- EQ-5D, Workplace Productivity, and ER Visits: No differences were observed in the EQ-5D utility index, the EQ-5D<sub>vas</sub> scores, the workplace productivity or ER visits in the belimumab groups compared to placebo.

***Biomarkers:***

Results from the ancillary secondary biomarker endpoints are as follows:

- Significant reductions in median percent change and mean absolute change from baseline in IgG, IgA, and IgM was observed at Week 52 in both belimumab groups versus placebo ( $p < 0.0001$ ).
- Significant reductions in anti-dsDNA antibody levels in subjects with measurable anti-dsDNA at baseline was observed in the 1 mg/kg (13%;  $p = 0.0145$ ) and 10 mg/kg (17%;  $p = 0.0008$ ) at Week 52 compared to placebo (6%). At Week 52, more belimumab treated subjects had converted to seronegative status (15-17%) compared to placebo (8%). Fewer patients in the 1mg/kg (10%) and 10mg/kg (5%) belimumab groups who were seronegative at baseline converted to seropositive at Week 52 as compared to placebo (11%).
- More belimumab treated patients who were seropositive for ANA at baseline converted to seronegative status at Week 52 (1mg/kg: 4.4%; 10 mg/kg: 4.8%) compared to placebo (2.4%). Fewer patients in the 10mg/kg group (36%) converted from seronegative to seropositive ANA status at Week 52 compared to placebo (53%) and the 1mg/kg group (54%).
- More patients who were seropositive for anti-Sm, aCL, and anti-ribosomal P at baseline converted to seronegative status at week 52 in the belimumab treatment groups compared to placebo. Significant differences versus placebo were observed for both belimumab groups versus placebo for anti-ribosomal P and aCL IgG and for the 10mg/kg group versus placebo for anti-Sm ( $p = 0.0252$ ).
- More belimumab treated patients with low C3 at baseline converted to normal/high C3 at Week 52 compared to placebo (1mg/kg: 23%; 10 mg/kg: 34%; placebo: 14%) that was significantly different on comparison of the 10 mg/kg belimumab group versus placebo ( $p = 0.0005$ ). Fewer belimumab treated patients with normal/high C3 at baseline converted to low C3 at Week 52 compared to placebo (1mg/kg: 21%; 10 mg/kg: 7%; placebo: 19%) that was significantly different on comparison of the 10 mg/kg group versus placebo ( $p = 0.0055$ ).
- More belimumab treated patients with low C4 at baseline converted to normal/high C4 at Week 52 compared to placebo (1mg/kg: 36%; 10 mg/kg: 45%; placebo: 19%) that was significantly different on comparison of both the 1 mg/kg ( $p = 0.0024$ ) and 10 mg/kg ( $p < 0.0001$ ) belimumab groups versus placebo. Fewer belimumab treated patients with normal/high C4 at baseline converted to low C4 at Week 52 compared to placebo (1mg/kg: 5%; 10 mg/kg: 6%; placebo: 16%) that was significantly different on comparison of both the 1mg/kg ( $p = 0.0119$ ) and 10 mg/kg ( $p = 0.0307$ ) groups versus placebo.

### **Efficacy Conclusions:**

A significantly higher response rate as assessed by the primary endpoint, the SRI, was demonstrated for belimumab 10 mg/kg plus standard of care group compared to placebo plus standard of care. The belimumab 1 mg/kg plus standard of care group also demonstrated a higher response rate compared to placebo plus standard of care although the magnitude of response was smaller than that observed for the 10 mg/kg dose. The response rates for the study's treatment groups were generally consistent

with the results from the individual component analyses of the SRI and the prespecified sensitivity analyses. These results were supported by similarly significant outcomes from the analyses of three out of the four major secondary endpoints (e.g., percentage of subjects with  $\geq 4$  point reduction from baseline in SLENA SLEDAI score at Week 52, mean change in PGA at Week 24 and percentage of subjects with a  $\geq 25\%$  reduction in steroids from Weeks 40 through 52) which were also suggestive of a dose-response. The results from remaining secondary endpoints of clinical interest (e.g., SLE disease flares and improvement or worsening in organ systems as assessed by the BILAG or SLENA SLEDAI) demonstrated dose-related improvements with belimumab particularly in decreasing the risk of disease flares and time to flare but declaring statistical significance of the multiple secondary endpoints evaluated in this trial using unadjusted p-values would be inappropriate since no multiplicity correction was planned in the protocol or implemented during the analyses of the secondary endpoints. Higher proportions of belimumab treated subjects had normalization of biomarkers such as C3, and C4 than placebo which significantly correlated with response to belimumab but did not adequately predict responses to treatment with the product.

**Study Number and Title:** LBSL99 - A Multicenter, Open-Label, Continuation Trial for LymphoStat-B Antibody (Monoclonal Anti-BLyS Antibody) in Subjects with Systemic Lupus Erythematosus (SLE) Who Completed the Phase 2 Protocol LBSL02

**Study Centers:** Multicenter (58 sites: U.S. 57 sites and Canada 1 site)

**Dates Conducted:** This trial was started on May 9, 2005 to March 6, 2009 (cut-off date for interim clinical study report)

**Objectives:**

- To provide continuing treatment to patients with SLE who achieved satisfactory response to LBSL02
- To assess the long-term safety of belimumab in patients with SLE

**Study Design:**

Study LBSL99 was a multicenter, open label extension Phase 2 study to evaluate the long term safety of belimumab in SLE patients who had achieved a satisfactory response in the Phase 2 study LBSL02. Patients who opted to enroll this trial received their first infusion of 10 mg/kg of belimumab 4 weeks after receiving their last dose of the product in the 24-week extension period of LBSL02. Subjects who decided not to continue treatment with belimumab were to return at 8 and 24 weeks for follow-up safety visits. A total of 298 patients from LBSL02 enrolled in this trial.

**Major Inclusion Criteria:**

In order to be eligible for this trial, potential study subjects were to have

- Completed LBSL02 through Day 532 **and**
- Improvement in the PGA score at the Day 532 or Day 476 visit of the 24-week extension period of LBSL02 as compared to PGA score at Day 364 (Week 52) or Day 0 (baseline) of LBSL02

**Exclusion Criteria:**

Potential trial candidates were to have been prohibited from participating in this trial if the following criteria applied:

- Had a mild/moderate or severe SLE flare s defined by the SLE Flare Index during the last 30 days of LBSL02 and through the first dose of LBSL99

(Note: Based on the opinion of study investigators, the protocol permitted patients with mild/moderate disease flares during the above period to enroll if their overall response on Day 532 or Day 476 compared to Day 364 or Day 0 of LBSL02 outweighed the effect of the flare.)

**Treatment:**

Study infusions were administered intravenously over 1 hour every 28 days.

**Removal of Patients from Treatment or Assessment:**

Subjects were to have discontinued from this trial if they withdrew consent, received a prohibited concurrent medication or therapy, experienced unacceptable toxicity, became pregnant, or missed 3 or more consecutive study infusions.

**Concomitant Medications:**

The protocol permitted subjects to continue the medication regimens they used during LBSL02.

Subjects who initiated therapy with any of the following banned medications or therapies were to have been also considered treatment failures and withdrawn from the study: other investigational agents, anti-TNF therapy, other biologics (e.g., rituximab, abatacept, and interleukin-1 receptor antagonist), IV immunoglobulin (IVIG), IV cyclophosphamide or plasmapheresis.

**Efficacy and Safety Assessments:**

The following are tabular flow charts of the scheduled study observations and procedures:

**Outcome Measures:**

**Safety parameters**

Included the following

- Adverse events
- Laboratory parameters
- Immunogenicity
- Vital signs

**Efficacy parameters**

Included the following:

- Time to flare (defined by the SLE Flare Index and BILAG)
- SELENA SLEDAI
- PGA
- BILAG
- Reduction in steroid use

**Biomarker parameters**

Included the following:

- ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-SSA, anti-SSB, and anti-cardiolipin
- IgG, IgA, IGM, IgE
- C3 and C4

**Statistical Design, Definitions of Analyzed Populations and Analyses Plan:**

Since LBSL99 was an open-label continuation of study LBSL02, no statistical sample size calculations were performed. This trial also did not have a prespecified analytical plan since all analyses were to be exploratory in nature using descriptive statistics and summarized accordingly. All analyses were to be performed on the population of subjects who received at least 1 dose of belimumab in this study.

**Immunogenicity Assessments:**

Serum samples were collected for belimumab immunogenicity assays prior to initial dosing on Day 0, every 24 weeks, at the exit visit, and at the 24-week post-Exit follow-up visit for subjects who withdrew prior to completion.

**Study Conduct**

**Protocol Amendments:**

Listed below are the 3 protocol amendments that were made to LBSL99.

1. Amendment 1 (implemented on June 30, 2005)

In addition to editorial changes to provide clarification, the following changes were made to the protocol:

- The requirement for the use of contraception by study subjects was extended from 30 days to 60 days following the last dose of study medication

2. Amendment 2 (implemented on August 5, 2005)

The following changes were made to the protocol:

- Modifications to reflect the original intent that subjects who presented with mild/moderate flare during the eligibility period could be enrolled if they had experienced a documented benefit while on LBSL02 study that clearly outweighed the effect of the flare

3. Amendment 3 (implemented on March 13, 2006)

The following changes were made to the protocol:

- References to the DMC were amended to indicate that the HGSRC was to assume the responsibility of safety data monitoring after unblinding of the Phase 2 studies LBSL02 and LBRA01.

**Disposition:**

Of the 321 patients who completed the extension period of LBSL02, 298 enrolled and 296 were treated in the ongoing study LBSL99 (Table 36). Over the four years that this study has been ongoing, rates of discontinuation ranged from 2-11%. The most common reason for discontinuation was subject request followed by AE.

Table 36 – Completion Status by Protocol Study Year in LBSL99

	Year 1	Year 2	Year 3	Year 4
<b>Number of Subjects Starting Interval</b>	296	264	246	227
<b>Number of Subjects Who Discontinued</b>	34 (11%)	18 (7%)	19 (8%)	4 (2%)
<b>Subject Request</b>	15 (5%)	6 (2%)	7 (3%)	1 (0%)
<b>AE</b>	7 (2%)	5 (2%)	4 (2%)	1 (0%)
<b>Disease Progression/Lack of Efficacy</b>	5 (2%)	4 (2%)	2 (1%)	0
<b>Entered But Not Dosed<sup>1</sup></b>	2 (1%)	0	0	0
<b>Lack of Compliance</b>	2 (1%)	2 (1%)	0	1 (0%)
<b>Other</b>	2 (1%)	0	3 (1%)	1 (0%)
<b>Lost to Follow-Up</b>	1 (0%)	1 (0%)	0	0
<b>Investigator Decision</b>	0	0	3 (1%)	0
<b>Ongoing</b>	264 (89%)	246 (93%)	227 (92%)	223 (98%)

Each study year =48 weeks in LBSL99

Subject US016-005 discontinued due to AE. Subject US037-001 discontinued due to Subject request.

Adapted Sponsor's Table 6-1; p. 48.

### **Demographics:**

The demographic characteristics and baseline disease activity in this trial were similar to that observed in the overall population of LBSL02. The subjects were predominantly female (93%), Caucasian (72%), and had a mean age of 43 years. In this study, the baseline mean SLENA SLEDAI score was 9.2 and the baseline mean PGA score was 1.4.

### **Efficacy:**

Sustained improvements in SLE disease activity were observed over 4.5 to 5 years of open-label treatment with belimumab plus standard of care particularly in subjects who were autoantibody positive as assessed by a gradual decrease in SLE disease flares assessed by the SLE flare index, and improvements in mean SLENA SLEDAI and PGA scores. No treatment-dependent change in percentage of subjects with no new BILAG 1A/2B scores over time was observed for the total study population. However, a higher percentage of autoantibody positive subjects who had received belimumab during LBSL02 had no new BILAG 1A/2B scores over the 4.5 to 5 years of this uncontrolled trial. The frequency of C3 and C4 normalization increased to 60-70% of subjects on belimumab therapy over 4.5 to 5 years. The frequency of subjects who were anti-dsDNA positive at baseline that seroconverted to negative status increased gradually to about 30% after about 3 years of continuous belimumab therapy.

The results from the safety analyses for this trial will be discussed in Section 7.

## 6 Review of Efficacy

### Efficacy Summary

The clinical data submitted in support of belimumab as a treatment [REDACTED] (b) (4) [REDACTED] adult patients with active, autoantibody-positive SLE on standard therapy was generated from two Phase 3 trials, 1056 and 1057. These were multiregional, randomized, double-blind, placebo-controlled, parallel group studies in 1,684 patients with active SLE on stable immunosuppressive medications that evaluated the efficacy of two dosing regimens of belimumab when administered as 1mg/kg or 10 mg/kg IV infusions on Days 0, 14, and 28 and then every 28 days compared to placebo. To minimize potential confounding, the common protocol utilized by these studies contained specifications regarding the use of concomitant SLE medications to treat patients' disease flares. The primary objective of these trials was to demonstrate the efficacy of belimumab compared to placebo as assessed by a novel, unvalidated, composite endpoint, the SLE Responder Index (SRI), which had been agreed upon by the Agency in SPA agreements reached with the Applicant. Although a positive response for the SRI represents a statistically rigorous achievement given that it requires demonstration of both improvement and no worsening in overall disease activity as assessed by three different indices, a clinically meaningful difference has not been established for this endpoint.

In both of these studies, patients treated with belimumab 10m/kg had a statistically higher rate of response than placebo patients (1056: p=0.0207; 1057: p=0.0006). A statistically higher rate of response for the belimumab 1mg/kg group was demonstrated for only 1057 (p=0.0129) after controlling for multiple comparisons. Notably the more robust of these studies, 1057, was conducted outside the United States. A basis for the modest degree of efficacy associated with belimumab observed in these trials was sought from a variety of sources. Since these studies were designed to assess belimumab as add-on therapy to standard of care in patients with active disease, the magnitude of efficacy demonstrated by belimumab may have been tempered by the concomitant use of immunosuppressive agents particularly in 1056 where the use of background immunosuppressive agents was higher (56%) than in 1057 (42%). Explorations for other potential causes of belimumab's modest treatment effect were also conducted involving the three subcomponents of the SRI and reasons for failure to respond to study treatment.

Although numerically higher proportions of subjects in the belimumab treatment groups in each study achieved success for each of the SRI's subcomponents as compared to placebo, these differences were only significantly different on comparison of the 10 mg/kg belimumab group to placebo in Study 1057 (see Table 44). In Study 1056, the response rates for two out of the three subcomponents appear to be in favor of the 1 mg/kg belimumab group rather than the 10 mg/kg group. This lack of a dose-response effect may be the result of a small imbalance in patients with lower disease activity as

assessed by BILAG organ domain 1A/2B involvement, SELENA SLEDAI category 0 to 3, and SLE flare index randomized to the 10 mg/kg belimumab group as compared to the 1mg/kg belimumab and placebo groups in 1056 (refer to). However, the positive results observed for the primary endpoint analysis were shown not to be attributable to the differential use of concomitant medications in the different treatment arms as demonstrated by the higher rates of medication failures in the placebo groups in both studies compared to belimumab (1056: 17%, 9%, and 10%; and 1057:11%, 7%, and 6% for placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab, respectively in each study) (see Table 46 and Table 47). The higher need for prohibited medication in addition to their standard of care immunosuppressive medications by subjects in the placebo groups may be interpreted as evidence supportive of belimumab's efficacy as add-on therapy in patients with active SLE despite standard of care. Additional support for the findings of the primary efficacy analysis was provided by the results from the four prespecified sensitivity analyses that looked at response unadjusted for stratification variables, imputation of missing data with last observation carried forward (LOCF), as well as completer and per protocol responses (refer to Table 47). Overall, the results of the sensitivity analyses were consistent with those of the primary efficacy analysis attesting to the robustness of these findings. The consistently positive results from other post hoc analyses that employed higher reductions in SELENA SLEDAI thresholds (e.g., SELENA SLEDAI  $\geq 5$  through  $\geq 10$ ) for the SRI responder analysis were also supportive of the primary efficacy analysis and suggestive that a higher magnitude of treatment effect may have been observed if patients with higher levels of SLE disease activity at baseline had been enrolled in these two pivotal trials.

However, the results of numerous major and ancillary secondary endpoints were less robust, and at times, discordant to those of the primary analysis. Since no multiplicity correction was planned in the protocols or implemented during the analyses of the secondary endpoints, declaring statistical significance of the secondary endpoints evaluated in these trials using unadjusted p-values would be inappropriate. Although numerically higher SRI response rates were observed in the 1 mg/kg and 10 mg/kg belimumab groups compared to placebo at Week 76 in 1056, these differences were not significant (see Table 49). The results from the analyses of the three subcomponents of the Week 76 response rate for the 10 mg/kg group were also less robust than those of the 1mg/kg group. Review of the reasons for failure to respond to treatment did not identify a basis for these findings, thus again raising the question if the small imbalance in baseline disease activity observed in the three treatment group could have impacted again on the lack of dose-response for the belimumab treatment groups at this time point. In spite of this, a higher percentage of placebo patients (19%) were medication failures at this time point as compared to the belimumab groups which had similar rates of medication failures (11-12%) that is suggestive of some benefit from treatment with belimumab. Higher proportions of patients in the belimumab treatment groups were also able to reduce their baseline corticosteroids by at least 25% to  $\leq 7.5$  mg/day during Weeks 40 through 52 that was significantly different for the 1 mg/kg comparison to placebo ( $p=0.0252$ ) and trended for the 10 mg/kg comparison to placebo

( $p=0.0526$ ) in 1057. The results of this clinically relevant endpoint were not as robust for 1056 which only had numerically higher proportions of patients in both belimumab treatment groups that also favored the 1 mg/kg group who were able to reduce their prednisone use by  $\geq 25\%$  as compared to placebo (refer to Table 50). Although belimumab treatment appeared to be associated with a lower proportion of patients requiring an increase in daily prednisone dose  $> 7.5\text{mg/day}$  in both studies that was only significantly different for the 10 mg/kg belimumab versus placebo comparison in 1057, an inconsistency that again favored the 1mg/kg group was observed in 1056. The inability to demonstrate steroid sparing in 1056 may have been influenced by the overall lower use of concomitant corticosteroids by subjects (76%) in this trial as compared to 1057 (96%).

Inconsistencies in dose-response effect were also observed in the analyses for SLE flares assessed by both the SELENA SLEDAI Flare Index (SFI) and the BILAG (Table 54 through Table 57). A significant prolongation in the risk for both flare ( $p=0.0036$ ) and severe flare ( $p=0.0055$ ), as well a reduction in the number of disease flares ( $p=0.0002$ ) and severe flares ( $p=0.0381$ ) over 52 weeks and during Week 24 through Week 52 ( $p<0.0001$ ) of study treatment was observed for the 10 mg/kg belimumab treatment group in 1056 as assessed by the SFI. Similarly significant results for these same outcomes for the 10 mg/kg belimumab group as assessed by the BILAG were also observed in this study ( $p<0.05$ ). Analyses of the data for the same outcomes for the 1mg/kg belimumab group in 1057 were not as robust with only a significant reduction in risk for disease flares ( $p=0.0026$ ) and number of flares ( $p=0.0012$ ) over 52 weeks as well as during Weeks 24 through 52 ( $p<0.0001$ ;  $p<0.0001$ ) as assessed by the SFI compared to placebo. In study 1056, treatment with belimumab 10 mg/kg was only associated with a significant reduction in risk for flare ( $p=0.0226$ ) and number of flares ( $p=0.0045$ ) during Weeks 24 through 52 while treatment with belimumab 1 mg/kg in this trial was associated with a reduction in the risk for a severe flare over 52 weeks ( $p=0.0230$ ) as well as during Weeks 24 through 52 ( $p=0.0167$ ) and a reduction in number of flares during Weeks 24 through 52 ( $p=0.0091$ ) as assessed by the SFI, and a reduction in risk for flares during Weeks 24 through 52 ( $p=0.0394$ ) as assessed by the BILAG.

Additional evidence in support of the primary endpoint results comes from the analyses of the data for the percent change and absolute change in PGA from baseline to Week 24 which showed significantly greater improvements in both of these parameters for the 10 mg/kg ( $p<0.0001$ ;  $p=0.003$ , respectively) and for the percent change for the 1mg/kg ( $p=0.0342$ ) belimumab groups compared to placebo in 1057 (Table 52). However, these results were not replicated in 1056 where the improvements from baseline as assessed by the PGA were comparable for all three treatment groups. No additional support for the primary endpoint results was observed for the analysis of the physical component score (PCS) for the SF-36 for either study (see Table 51).

Exploratory post hoc analyses of the belimumab's effect on various organ system manifestations are also suggestive of a treatment benefit associated with belimumab (see Table 59 through Table 61). However, the numbers of patients with certain organ manifestations are too low to make definitive conclusions particularly regarding renal and CNS disease as a result of the trials' exclusion criteria.

Results from subgroup analyses involving patients of African American or African heritage suggest an unfavorable response to belimumab (see Table 64 and Table 65). Although the results of this subgroup analyses should be interpreted cautiously given the small number of subjects involved, they suggest the need for additional studies in this population who is at risk for more aggressive disease and worse disease outcomes.

The heterogeneity in clinical manifestations and disease severity of SLE in addition to the risk for morbidity associated with untreated disease has made it difficult to evaluate the efficacy of potential treatments for this disease. Although a clinically meaningful difference has yet to be determined for the SRI, it represents both a statistically and clinically rigorous endpoint to achieve. In spite of this, there is adequate statistical evidence to support the efficacy of the 10 mg/kg dose of belimumab as add-on treatment for patients with active, sero-positive SLE despite standard of care based on the totality of data generated from the well-controlled studies 1056 and 1057.

## 6.1 Indication

(b) (4) adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) on standard therapy

### 6.1.1 Methods

The review of efficacy relies primarily on the findings of two pivotal, randomized, placebo-controlled efficacy and safety trials, 1056 and 1057. The design and conduct of these trials is presented in further detail in Section 5.3.

### 6.1.2 Demographics

As summarized in the following tables (Table 37 and), the treatment groups within the Phase 3 trials were generally well balanced with respect to baseline demographics, region, disease characteristics and activity.

The subjects who participated in Study 1056 were predominantly Caucasian (68%) and female (92%). Fourteen percent (14%) of the patients were of Black/African American in origin. The majority (53%) of subjects in Study 1056 were from the U.S. and Canada while the remaining subjects were from Western Europe/Israel (25%) and Eastern

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

Table 37 - Baseline Demographics for Subjects in Studies 1056 and 1057

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

<sup>1</sup>Subjects who checked more than one race category are counted under individual race category according to the minority rule as well as multiracial category.

Adapted Sponsor's Table 6-3; p. 78 and Sponsor's Table T3; p. 449 of the study reports for Trials 1056 and 1057.

As shown in Table 38 below, the overall mean duration of SLE disease was 8 years for patients in Study 1056. Overall, these subjects had a high baseline level of disease activity as manifested by a SELENA SLEDAI mean score of 9.7 with 50% of the patients having a baseline SELENA SLEDAI score of ≥ 10 points. The individual treatment

groups were similar in their baseline disease activity with only minor differences as assessed by the BILAG organ domain involvement, SELENA SLEDAI score category 0 to 3, and SLE flare index suggesting that patients with lower disease activity may have been slightly more frequently assigned to the belimumab 10mg/kg treatment group as compared to the placebo group. (Note: Patients with a baseline SELENA SLEDAI score category 0 to 3 were unable to achieve a response of  $\geq 4$  points necessary for a positive response as assessed by the primary endpoint, the SRI.)

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

Table 38 - Baseline Disease Characteristics of Subjects in Studies 1056 and 1057

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

<sup>1</sup>At baseline compared with screening assessment.

Adapted Sponsor's Table 6-4; p. . Adapted Sponsor's Table A81; p. 479.

As shown in Table 39 below, the majority of patients who participated in Study 1056 had musculoskeletal and/or mucocutaneous manifestations of SLE disease at baseline as assessed by the SELENA SLEDAI disease activity index. Baseline disease involvement was generally well balanced between the three treatment groups with the exception of rash. Higher proportions of placebo patients (68%) and patients in the 1 mg/kg

belimumab group (66%) had rash at study entry as compare to patients in the 10 mg/kg (56%). A similar pattern of SLE disease involvement at baseline was observed for subjects in Study 1057, however, a lower rate of arthritis (59%) was reported by subjects in this study as compared to Study 1056 (72%). Baseline disease involvement was also similar for all three treatment groups in this trial.

**Table 39 - Selected Baseline SELENA SLEDAI Scores for Subjects in Studies 1056 and 1057**

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

Modified Sponsor's Table T20

A summary of moderate to severe BILAG organ system involvement (A or B score) at baseline for both pivotal trials is displayed in Table 40 below. The most common organ systems involved in subjects participating in Study 1056 were musculoskeletal (67%), mucocutaneous (58%) and hematology (14%). The three treatment groups in this trial were generally well balanced for baseline organ involvement with the exception of slight differences in the rate of musculoskeletal involvement. A similar pattern for moderate to severe organ involvement that was generally balanced across the three treatment groups was observed for subjects participating in Study 1057, however, a lower rate of musculoskeletal involvement (42%) and a higher rate of renal involvement (13%) were reported by patients in this trial as compared to patients in Study 1056 (67% and 7%, respectively).

Table 40 - Summary of Baseline BILAG Category by Organ Domain for Subjects in Studies 1056 and 1057

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

Modified Sponsor's Summary Table T12

The vast majority (96-98%) of patients in these trials were seropositive for ANA and/or anti-dsDNA as shown in Table 41 below. The treatment groups within each of the Phase 3 trials were generally well balanced with respect to baseline biomarkers of disease activity with the following exceptions. Differences in the 3 treatment groups for Study 1056 were observed for the presence of CRP, anti-ribosomal P and aCL. Higher proportions of patients in the placebo group of Study 1056 were positive for CRP (42%) and anti-ribosomal P (11%) as compared to the belimumab treatment groups (1 mg/kg group: 37% and 5%; 10 mg/kg group: 33% and 6%, respectively). Additionally, the proportions of subjects who were positive for CRP were higher in the 1 mg/kg belimumab treatment group (46%) as compared to the belimumab 10 mg/kg (37%) and placebo (36%) groups. Overall, higher proportions of patients in Study 1057 were seropositive for anti-ribosomal P (26%) and anti-Smith (36%) as compared to Study 1056 (7% and 27%, respectively).

Table 41 - Tabular Summary of Subjects' Baseline Serologies, Immunoglobulins, Complement, and Other Biomarkers for Trials 1056 and 1057

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

<sup>1</sup>ANA titer equals to the maximum titer of the individual patterns

<sup>2</sup>aCL is positive if any of aCL-IgG, aCL-IgA, or aCL-IgM is positive

Adapted Sponsor's Table 6-6; p. 82-83 Clinical Study C1056 Report and Sponsor's Table 6-6; p. 78 Clinical Study C1057 Report.

The following table (Table 42) summarizes concomitant SLE medications used by more than 10% of subjects who participated in the Phase 3 trials. The usage of concomitant SLE medications at baseline was generally similar for the three treatment groups in each of these studies; however, there were major differences in the overall use of concomitant glucocorticosteroids, immunosuppressives and NSAIDs observed between trials. The overall concomitant use of glucocorticosteroids was considerably higher in Study 1057 (96%) as compared to Study 1056 (76%) with 24% of the patients in Study

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

**Table 42 - Concomitant SLE Medication Usage by >10% of Subjects at Baseline in Studies 1056 and 1057**

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

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

### 6.1.3 Subject Disposition

As shown in Table 43 below, overall, the proportions of patients who discontinued from the three treatment arms of these studies were similar with just a slightly higher rate of early discontinuation occurring in the placebo groups than belimumab groups in each trial. A similar proportion of patients discontinued from these studies due to adverse events and lack of efficacy in the placebo and belimumab treatment groups. Of note, a higher number of patients were withdrawn from Study 1057 due to pregnancy.

Table 43 - Subject Disposition in Trials 1056 and 1057

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

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

#### 6.1.4 Analysis of Primary Endpoint

##### **Primary Endpoint Selection and Validation: The SLE Responder Index (SRI)**

Studies 1056 and 1057 were adequate and well controlled trials by virtue of their double blind, randomized controlled design. These two trials shared a common protocol whose design was based on post hoc analyses of the Applicant's failed Phase 2 study, LBSL02. The results from the exploratory analyses of LBSL02 gave rise to the primary endpoint used in studies 1056 and 1057, the SRI. The latter is a novel, tri-component endpoint comprised of 3 different validated disease assessment tools (SELENA SLEDAI, PGA and BILAG) for SLE that are individually discussed in detail in Section 5.3. The design of the SRI is similar to that suggested in the 2010 FDA guidance document for the development of medical products for the treatment of SLE. The PGA, is a 4-point VAS that evaluates overall general health status. Both the SELENA SLEDAI and BILAG are complex disease activity instruments that evaluate a number of organ systems or domains affected in SLE. Although there is some overlap in terms of the clinical evaluations provided by these components, they were selected with the intent of capturing clinically meaningful disease change (e.g. a reduction in SELENA SLEDAI score) while ensuring there would not be significant worsening in overall disease activity (e.g., no worsening in PGA and no new BILAG 1A or 2B flares) in view of the spectrum of clinical manifestations and disease severity observed in SLE patients. Despite the establishment of minimally clinically important differences for both the SELENA SLEDAI and PGA, and the BILAG's premise of clinically important differences, it was not known what difference in the responder rate of the SRI would represent a clinically important

difference between treatments. In addition, this composite endpoint had not been validated at the time the SPA agreements were reached on the protocols for Studies 1056 and 1057.

The pivotal Phase 3 trials in support of this application both used the SRI response rate at Week 52 for which a positive response was defined as:

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

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

As shown in Table 44, patients treated with belimumab 10 mg/kg had a statistically higher rate of response than placebo patients in both Studies 1056 and 1057. A statistically higher rate of response for the belimumab 1 mg/kg group as compared to placebo was demonstrated for only study 1057. The results from the analyses of the subcomponents of the SRI were generally consistent with those of the primary analysis. The proportions of subjects achieving success for each of the subcomponents of the SRI were numerically higher in the belimumab groups than the placebo group in each study, although these differences only reached statistical significance for the belimumab 10 mg/kg to placebo comparison in Study 1057.

Table 44 - Primary Efficacy Analyses (Adjusted, Week 52) for Trials 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
<b>Response:</b>						
<b>Observed Difference vs PLO</b>	93 (34%)	110 (41%)	118 (43%)	125 (44%)	148 (51%)	167 (58%)
<b>OR (95% CI)<sup>1</sup> vs PLO</b>		7%	9%		8%	14%
<b>P-value</b>		1.34 (0.94, 1.91) <b>0.1041</b>	1.52 (1.07, 2.15) <b>0.0207</b>		1.55 (1.10, 2.19) <b>0.0129</b>	1.83 (1.3, 2.59) <b>0.0006</b>
<b>Subcomponents</b>						
<b>4-Point Reduction in SELENA SLEDAI:</b>						
<b>OR (95% CI)<sup>1</sup> vs PLO</b>	98 (36%)	116 (43%)	128 (47%)	132 (46%)	153 (53%)	169 (58%)
<b>P-value</b>		1.36 (0.96, 1.93) <b>0.0869</b>	1.63 (1.15, 2.32) <b>0.0062</b>		1.51 (1.07, 2.14) <b>0.0189</b>	1.71 (1.21, 2.41) <b>0.0024</b>
<b>No Worsening in PGA:</b>						
<b>OR (95% CI)<sup>2</sup> vs PLO</b>	173(63%)	197 (73%)	189 (69%)	199 (69%)	227 (79%)	231 (80%)
<b>P-value</b>		1.60 (1.11, 2.30) <b>0.0120</b>	1.32 (0.92, 1.90) <b>0.1258</b>		1.68 (1.15, 2.47) <b>0.0078</b>	1.74 (1.18, 2.55) <b>0.0048</b>
<b>No New 1A/2B BILAG Domain Scores:</b>						
<b>OR (95% CI)<sup>3</sup> vs PLO</b>	179(65%)	203 (75%)	189 (69%)	210 (73%)	226 (79%)	236 (81%)
<b>P-value</b>		1.63 (1.12, 2.37) <b>0.0108</b>	1.20 (0.84, 1.73) <b>0.3193</b>		1.38 (0.93, 2.04) <b>0.1064</b>	1.62 (1.09, 2.42) <b>0.0181</b>

PLO= Placebo; OR=Odds Ratio; CI =Confidence Interval

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

<sup>2</sup>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

<sup>3</sup>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 45 provides the reasons subjects failed to achieve a positive SRI response in these trials. Note that the categories provided are mutually exclusive and mutually exhaustive. The proportions of subjects who dropped out are approximately 16% in study 1056 and 12% in study 1057 and are fairly balanced across treatment groups within each study thus the impact of imputing dropouts as failures on the treatment effect in the primary analysis should be small. However, unlike dropouts, "medication failures" are not balanced across treatment groups (17%, 9%, and 10% for placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab respectively in study 1056 and 11%, 7%, and 6% for the same in study 1057). Since medication failures are more frequent in the placebo groups than the belimumab groups, imputing medication failures as efficacy failures could bias the treatment effect in the primary efficacy endpoint in favor of belimumab (unless these subjects would truly have been unable to achieve success on the primary endpoint had they not taken the prohibited medication).

Table 45 - Disposition of Patients in the Primary Efficacy Analyses for Trials 1056 and 1057

Response:	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)
<b>No Response:</b>	93 (34%)	110 (41%)	118 (43%)	125 (44%)	148 (51%)	167 (58%)
<b>Dropout<sup>1</sup> – Not a Medication Failure</b>	182(66%)	161 (59%)	155 (57%)	162 (56%)	140 (49%)	123 (42%)
<b>Medication Failure<sup>2</sup></b>	43 (16%)	40 (15%)	45 (17%)	38 (13%)	34 (12%)	31 (11%)
<b>&lt;4 Point Reduction in SELENA SLEDAI (SS)<sup>3</sup></b>	47 (17%)	24 (9%)	27 (10%)	30 (11%)	21 (7%)	18 (6%)
<b>≥4 Point Reduction in SS with the following<sup>3</sup>:</b>	87 (32%)	91 (34%)	73 (27%)	87 (30%)	80 (28%)	72 (25%)
<b>Worsening in PGA only<sup>3</sup></b>	5 (2%)	6 (2%)	10 (4%)	7 (2%)	5 (2%)	2 (1%)
<b>New 1A/2B/BILAG only<sup>3</sup></b>	4 (2%)	4 (2%)	4 (2%)	5 (2%)	3 (1%)	1 (0%)
<b>Both Worsening in PGA and New 1A/2B BILAG<sup>3</sup></b>	1 (0%)	2 (1%)	6 (2%)	2 (1%)	2 (1%)	1 (0%)
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<sup>1</sup>Subjects who withdrew early and had no data in the Day 364 +/- 28 day window

<sup>2</sup>Includes subjects who withdrew early and subjects who met all 3 response criteria at week 52 but took a protocol prohibited or restricted medication or dose

<sup>3</sup>In subjects who did not dropout and were not medication failures.

Table 46 provides sensitivity analyses designed to aid in addressing the issue of the medication failures. The first set of rows in Table 46 includes the protocol-specified primary efficacy analysis as conducted by the statistical reviewer for this application. (After careful review, the reasons for the small numerical differences in the results of the protocol-specified primary efficacy analyses conducted by the sponsor [Table 44] and the agency's statistician [Table 46] remain unclear.) The second set of results show the primary efficacy analysis ignoring the fact that prohibited medications were taken by some subjects, that is the data is used as it was observed or otherwise imputed (e.g., dropouts continue to be imputed as failures). The final analysis in Table 46 assigns the primary efficacy outcome for subjects who are medication failures post-hoc according to the judgment of the Agency's medical team. The primary endpoint for subjects using prohibited medication other than HMG CoA reductase inhibitors or angiotensin pathway antihypertensives were assigned as per-protocol (i.e., failures). The primary endpoint for subjects using HMG CoA reductase inhibitors or angiotensin pathway antihypertensives was assigned as a success for the placebo subjects and a failure for the Belimumab subjects. Motivation for this imputation scheme was to take a very conservative approach for medication failure subjects who the clinical team did not feel would have unquestionably proceeded to be an efficacy failure had they not received the prohibited medication.

As expected since the frequency of medication failures is lower in study 1057 than study 1056 and since the primary efficacy result is stronger in study 1057 than study 1056, the sensitivity analyses of study 1057 are generally consistent with and supportive of the primary efficacy analysis for that study while they are slightly less definitive for study 1056. However, the apparently higher need for prohibited medication in the placebo group may be taken as a signal of efficacy for belimumab.

Table 46 - Medication Failure Sensitivity Analyses of the Primary Efficacy Endpoint (Adjusted, Week 52) for Trials 1056 and 1057

	Trial 1056			Trial 1057		
	Protocol-Specified Primary Efficacy Analysis <sup>1</sup> (FDA Analysis)					
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
<b>Response:</b>	93(34%)	110 (41%)	118 (43%)	125(44%)	148 (51%)	167 (58%)
<b>Observed Difference vs PLO</b>		7%	9%		8%	14%
<b>OR (95% CI)<sup>1</sup> vs PLO</b>		1.34 (0.95, 1.92)	1.51 (1.06, 2.15)		1.52 (1.08, 2.14)	1.82 (1.29,2.56)
<b>P-value</b>		<b>0.0996</b>	<b>0.0215</b>		<b>0.0170</b>	<b>0.0006</b>
	Subjects with Medication Failure Analyzed as Observed <sup>2</sup> (FDA Analysis)					
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
<b>Response:</b>	103(37%)	117 (43%)	124 (45%)	130(45%)	149 (52%)	171 (59%)
<b>Observed Difference vs PLO</b>		6%	8%		7%	14%
<b>OR (95% CI)<sup>1</sup> vs PLO</b>		1.28 (0.90, 7.81)	1.41 (1.00, 1.99)		1.44 (1.02, 2.03)	1.80 (1.28, 2.55)
<b>P-value</b>		<b>0.1691</b>	<b>0.0530</b>		<b>0.0379</b>	<b>0.0008</b>
	Subjects with Medication Failure Analyzed using Post-hoc Assignment by FDA Medical Team <sup>3</sup> (FDA Analysis)					
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
<b>Response:</b>	95(35%)	110 (41%)	118 (43%)	128(45%)	148 (51%)	167 (58%)
<b>Observed Difference vs PLO</b>		6%	9%		7%	13%
<b>OR (95% CI)<sup>1</sup> vs PLO</b>		1.30 (0.91, 1.84)	1.47 (1.03, 2.08)		1.48 (1.05, 2.09)	1.75 (1.24, 2.47)
<b>P-value</b>		<b>0.1489</b>	<b>0.0329</b>		<b>0.0257</b>	<b>0.0014</b>

PLO= Placebo; OR=Odds Ratio; CI =Confidence Interval

<sup>1</sup>OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates including baseline SELENA SLEDAI ( $\leq 9$  vs  $\geq 10$ ), baseline proteinuria level ( $<2$  g/24 hour equivalent) and race (AIA vs other). Subjects who received prohibited medication are imputed as failures.

<sup>2</sup>Use of prohibited medication ignored (i.e., treatment failure subjects were included in the analysis as their data was observed)

<sup>3</sup>Primary endpoint for subjects using prohibited medication other than HMG CoA Reductase Inhibitors or Angiotensin Pathway Antihypertensives were assigned as per-protocol (i.e., failures). The primary endpoint for subjects using HMG CoA Reductase Inhibitors or Angiotensin Pathway Antihypertensives was assigned as a success for the placebo subjects and a failure for the Belimumab subjects. Selection of the medication categories, HMG CoA Reductase Inhibitors and Angiotensin Pathway Antihypertensives, for this analysis was made post-hoc by the FDA medical team.

Table courtesy Dr. Ruthanna Davi

The sponsor provided four sensitivity analyses for the primary efficacy endpoint. These sensitivity analyses were conducted as planned in the protocol. The results of these sensitivity analyses are largely consistent with the primary efficacy analysis and are shown in Table 47. The first analysis, referred to as “unadjusted response” uses identical methods to the primary efficacy analysis with the exception that the logistic regression model does not include the stratification factors for randomization as independent variables. The results of this analysis are very similar to the primary efficacy results indicating that the estimated treatment effect was not overly influenced by the stratification factors. The second sensitivity analysis, the “LOCF response” differed from the primary efficacy analysis in the handling of subjects who were

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

Table 47 - Sensitivity Analyses of the Primary Efficacy Endpoint for Studies 1056 and 1057

Analyses	Trial 1056			Trial 1057		
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
Unadjusted Response: Obs. Diff. vs PLO: OR (95% CI) <sup>1</sup> vs PLO P-value	93 (34%)	110 (41%) 7%	118 (43%) 9%	125 (44%)	148 (51%) 8%	167 (58%) 14%
		1.34 (0.94, 1.89) <b>0.1020</b>	1.49 (1.05, 2.11) <b>0.0239</b>		1.37 (0.99, 1.90) <b>0.0602</b>	1.76 (1.27, 2.4) <b>0.0008</b>
LOCF Response (adj.): Obs. Diff. vs PLO OR (95% CI) <sup>1</sup> vs PLO P-value	101 (37%)	118 (44%) 7%	132 (48%) 12%	137 (48%)	155 (54%) 6%	182 (63%) 15%
		1.33 (0.94, 1.89) <b>0.1096</b>	1.67 (1.17, 2.36) <b>0.0043</b>		1.44 (1.02, 2.03) <b>0.0402</b>	1.94 (1.37, 2.76) <b>0.0002</b>
Completer Response (adj.): Obs. Diff. vs PLO OR (95% CI) <sup>1</sup> vs PLO P-value	90/193 (47%)	104/205 (51%) 4%	113/200 (57%) 10%	125/225 (56%)	144/236 (61%) 5%	165/240 (69%) 13%
		1.19 (0.79, 1.80) <b>0.4098</b>	1.59 (1.04, 2.41) <b>0.0308</b>		1.46 (0.98, 2.18) <b>0.0639</b>	1.87 (1.24, 2.81) <b>0.0027</b>
Per Protocol Response (adj.): Obs. Diff. vs PLO OR (95% CI) <sup>1</sup> vs PLO P-value	89/261 (34%)	105/258 (41%) 7%	113/263 (43%) 9%	122/278 (44%)	145/278 (52%) 8%	164/281 (58%) 14%
		1.35 (0.94, 1.94) <b>0.1026</b>	1.50 (1.04, 2.14) <b>0.0281</b>		1.56 (1.10, 2.22) <b>0.0123</b>	1.86 (1.31, 2.65) <b>0.0005</b>

Obs. Diff. = Observed Difference; PLO = Placebo; adj. = adjusted

<sup>1</sup>Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo without adjustment for any covariates

<sup>2</sup>Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDA ( $\leq 9$  vs  $\geq 10$ ), baseline proteinuria level ( $<2$  g/24 hr vs  $\geq 2$  g/24 hr equivalent) and race (African descent or indigenous-American descent vs other).

Adapted Sponsor's Table 7-4; p. 89.

### 6.1.5 Analysis of Secondary Endpoints(s)

A number of secondary variables were evaluated in Trials 1056 and 1057 as shown in Table 48 below. No multiplicity correction was planned for the protocols for these studies or implemented here for the secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate. The results from a number of the secondary endpoints evaluated in these trials were numerically supportive of the primary analysis. The remaining discussion will highlight major and selected secondary endpoints of interest.

**Table 48 - Secondary Endpoints Evaluated in Trials 1056 and 1057**

<p><b>Major Secondary Endpoints:</b></p> <ol style="list-style-type: none"> <li>1. Response Rate at Week 76 (Trial C1056 only)</li> <li>2. Percentage of Subjects with <math>\geq 4</math> Point Reduction from Baseline in SELENA SLEDAI Score at Week 52</li> <li>3. Mean Change in SF-36 Health Survey PCS Score at Week 24</li> <li>4. Mean Change/Percent Change in PGA at Week 24</li> <li>5. Percentage of Subjects Whose Average Prednisone Dose has been Reduced by <math>\geq 25\%</math> from Baseline to <math>&lt; 7.5</math> mg/day During Weeks 40 Through 52</li> </ol>
<p><b>Secondary Endpoints:</b></p> <p><u>Disease Activity:</u></p> <ul style="list-style-type: none"> <li>▪ Response rate at Weeks 12 and 24</li> <li>▪ Time to first response</li> <li>▪ Duration of first response</li> <li>▪ Percent of patients with <math>\geq 4</math> point reduction from baseline in SELENA SLEDAI at Weeks 12, 24 and 76.</li> <li>▪ Mean change in PGA at week 12 and 52</li> <li>▪ Percent change from baseline in SELENA SLEDAI score at Weeks 12, 24, and 52</li> <li>▪ Percent of patients with no worsening (increase of <math>&lt; 0.30</math> points from baseline) in PGA at Weeks 12, 24, 52 and 76</li> <li>▪ Percent of patients with not new BILAG A organ domain score or new 2 BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Weeks 12, 24, 52 and 76)</li> <li>▪ BILAG response rates at Weeks 12, 24, 52 and 76</li> <li>▪ Time to BILAG response</li> <li>▪ AUC of the SLENA SLEDAI score over 52 and 76 weeks</li> <li>▪ Change in the SLICC/ACR Damage Index at Weeks 52 and 76</li> <li>▪ Percent of patients with no new 1A/2B organ domain scores from Week 28 through Week 52</li> <li>▪ Percent of patients with no new 1A/2B organ domain scores from Week 52 through Week 76</li> </ul> <p><u>Flares:</u></p> <ul style="list-style-type: none"> <li>▪ Time to first SLE flares over 52 and 76 weeks</li> <li>▪ Time to first SLE flare after 24 weeks</li> <li>▪ Number of flares per subject and the rate of flares over 52 and 76 weeks</li> <li>▪ Number of flares per subject and the rate of flares from Week 24 to 52 and from Week 24 to 76</li> </ul> <p><u>Organ Specific Measures:</u></p> <ul style="list-style-type: none"> <li>▪ Renal flare rate and time to first renal flare</li> <li>▪ The rate and duration of renal remission and time to first renal remission</li> <li>▪ Percent change in proteinuria</li> </ul> <p><u>Steroid Reduction:</u></p> <ul style="list-style-type: none"> <li>▪ Percentage of patients with average steroid dose has been reduced by 25% from baseline to 7.5 mg/day or lower during Weeks 64 through 76</li> <li>▪ Percent change from baseline of prednisone dose at Weeks 12, 24, 52 and 76</li> <li>▪ Number of days of daily steroid dose <math>\leq 7.5</math> mg/day and/or reduced by 50% from baseline over time</li> <li>▪ Time to reduction of daily prednisone dose <math>\leq 7.5</math> mg/day and/or reduced by 50% from baseline over 52 weeks and 76 weeks at Weeks 12, 24, 52 and 76</li> <li>▪ Percent of patients with daily prednisone dose reduced <math>\leq 7.5</math> mg/day from <math>&gt; 7.5</math> mg/day at</li> </ul>

<p>baseline over time</p> <ul style="list-style-type: none"><li>▪ Percent of patients with daily steroid dose increased to &gt;7.5 mg/day from ≤ 7.5 mg/day at baseline over time</li></ul> <p><u>Biomarkers:</u></p> <ul style="list-style-type: none"><li>▪ Percent change from baseline in: total serum Ig, anti-dsDNA, ANA, anti-Sm, aCL, C3, C4, interferon expression signature and T lymphocytes (CD3<sup>+</sup>/4<sup>+</sup> and CD 3<sup>+</sup>/8<sup>+</sup>)</li><li>▪ Percent change in absolute B cell subsets (CD 20<sup>+</sup>, CD20<sup>+</sup>/27<sup>+</sup> memory, CD20<sup>+</sup>/27<sup>+</sup> naive, CD20<sup>+</sup>/69<sup>+</sup> activated, CD20<sup>+</sup>/138<sup>+</sup> plasmacytoid, CD19<sup>+</sup>/27<sup>BRIGHT</sup>/38<sup>BRIGHT</sup> SLE subset and CD20<sup>+</sup>/138<sup>+</sup> plasma cells) at Weeks 8, 24, 52 and 76</li></ul> <p><u>Patient Reported Outcomes:</u></p> <ul style="list-style-type: none"><li>▪ Mean change in SF-36 Health Survey PCS score at Weeks 12, 52 and 76</li><li>▪ Mean change in SF-36 Health Survey Score (8 domains) at Weeks 12, 24, 52 and 76</li><li>▪ Mean change in FACIT-Fatigue Scale score at Weeks 12, 24, 52 and 76</li><li>▪ EQ-5D Health Questionnaire at Weeks 12, 24, 52 and 76</li><li>▪ Workplace Productivity Questionnaire at Weeks 12, 24, 52 and 76</li><li>▪ Emergency room visits from Day 0 through Week 12, 24, 52, and 76</li></ul>
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Section 8.3 of the Sponsor's Analytical Plans for Protocols 1056 and 1057

## **Major Secondary Endpoints**

### **Week 76 Response Rate:**

If approved, belimumab would be potentially administered as a chronic treatment for SLE. In view of this, durability of treatment effect was evaluated by the group response to treatment by the SRI at Week 76 in Study 1056, which was a prespecified major secondary endpoint. As shown in Table 49, patients in the 1mg/kg and 10 mg/kg belimumab treatment groups had numerically higher response rates than placebo patients at Week 76, but these differences were not significant.

The results from the analyses of the subcomponents of the SRI endpoint at Week 76 for the 1mg/kg belimumab group showed numerical improvement for all subcomponents. The results from the analyses of the three subcomponents of the Week 76 response rate for the 10 mg/kg belimumab group were less robust as a result of the small numerical improvements observed for each subcomponent. Overall, these results differ with those from the Week 52 primary endpoint analyses where the results from the 10 mg/kg belimumab treatment group were more robust than those of the 1 mg/kg belimumab treatment group. Review of the reasons for failure to respond to treatment as Week 76 revealed that a higher proportion of subjects received prohibited/restrictive medications and were considered study medication failures in the placebo group (19%) as compared to the 1mg/kg and 10 mg/kg belimumab groups which had similar rates of subjects deemed medication failures (11-12%). This is again suggestive of a treatment effect associated with the administration of belimumab. The rate for drop-outs without being a medication failure at this time point were comparable for the three treatment groups. Overall, the proportion of subjects who fail on at least one component of the SRI is similar for the three treatment groups.

Table 49 - Overall Week 76 Responder Rate and Subcomponent Results for Study 1056

	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=272)
<b>Response:</b>			
<b>Observed Difference vs Placebo</b>	89 (32%)	106 (39%)	105 (39%)
<b>OR (95% CI)<sup>1</sup> vs Placebo</b>		7%	6%
<b>P-value</b>		1.34 (0.94, 1.91)	1.31 (0.92, 1.87)
		<b>0.1050</b>	<b>0.1323</b>
<b>Subcomponents</b>			
<b>4-Point Reduction in SELENA SLEDAI:</b>			
<b>OR (95% CI)<sup>2</sup> vs Placebo</b>	93 (33%)	114 (42%)	113 (41%)
<b>P-value</b>		1.42 (1.00, 2.02)	1.39 (0.98, 1.98)
		<b>0.0486</b>	<b>0.0660</b>
<b>No Worsening in PGA:</b>			
<b>OR (95% CI)<sup>3</sup> vs Placebo</b>	160 (58%)	178 (66%)	172 (63%)
<b>P-value</b>		1.40 (0.99, 1.99)	1.22 (0.86, 1.72)
		<b>0.0594</b>	<b>0.2703</b>
<b>No New 1A/2B BILAG Domain Scores</b>			
<b>OR (95% CI)<sup>4</sup> vs Placebo</b>	162 (59%)	187 (69%)	173 (63%)
<b>P-value</b>		1.58 (1.10, 2.25)	1.20 (0.84, 1.70)
		<b>0.0123</b>	<b>0.3123</b>
<b>Reasons for Failure</b>			
<b>Reasons for Failure:</b>			
<b>Medication Failure</b>	53 (19%)	30 (11%)	33 (12%)
<b>Drop-Out (not due to a Medication Failure)</b>	53 (19%)	50 (19%)	59 (22%)
<b>Failed to Satisfy ≥ 1 components (and not due to Medication Failure or Drop-Out)</b>	80 (29%)	85 (31%)	76 (28%)

OR=Odds Ratio; CI =Confidence Interval

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

<sup>2</sup>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

<sup>3</sup>OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline BILAG domain involvement (at least 1A/2B vs at most 1B)  
 Table 2.7.3-43 of Sponsor's Summary of Clinical Efficacy

### Reduction in Corticosteroids:

In view of the morbidity associated with corticosteroids, reduction in corticosteroid use in patients whose SLE was controlled was included as an important clinically relevant endpoint. This secondary endpoint was defined as the percentage of subjects whose average prednisone dose was reduced by  $\geq 25\%$  from baseline to  $\leq 7.5$  mg/day during Weeks 40 through 52 in subjects who were receiving  $>7.5$  mg/day prednisone at baseline. As noted previously in this review, fewer patients (46%) in Study 1056 were taking  $>7.5$  mg/day of prednisone as compared to patients (69%) in Study 1057 (refer to Table 8). As shown in Table 50, numerically more patients in both belimumab treatment groups were able to reduce their prednisone use by  $\geq 25\%$  as compared to placebo in Study 1056. Similarly, in Study 1057, a higher percentage of patients in the 1 mg/kg belimumab group and in the 10 mg/kg belimumab group were able to reduce their prednisone by  $\geq 25\%$  as compared to placebo.

**Table 50 - Proportion of Patients with Prednisone Reduction by  $\geq 25\%$  from Baseline to  $\leq 7.5$  mg/day During Weeks 40 through 52<sup>1</sup> 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)
<b>Response<sup>2</sup>:</b>	16 (13%)	25 (19%)	20 (17%)	23 (12%)	42 (21%)	36 (19%)
<b>Observed Difference vs Placebo</b>		7%	4%		9%	7%
<b>OR (95% CI)<sup>3</sup> vs Placebo</b>		1.57 (0.78, 3.14)	1.26 (0.61, 2.60)		1.89 (1.08, 3.31)	1.75 (0.99, 3.08)
<b>P-value<sup>3</sup></b>		<b>0.2034</b>	<b>0.5323</b>		<b>0.0252</b>	<b>0.0526</b>

<sup>1</sup>Includes only subjects with baseline prednisone > 7.5 mg/day

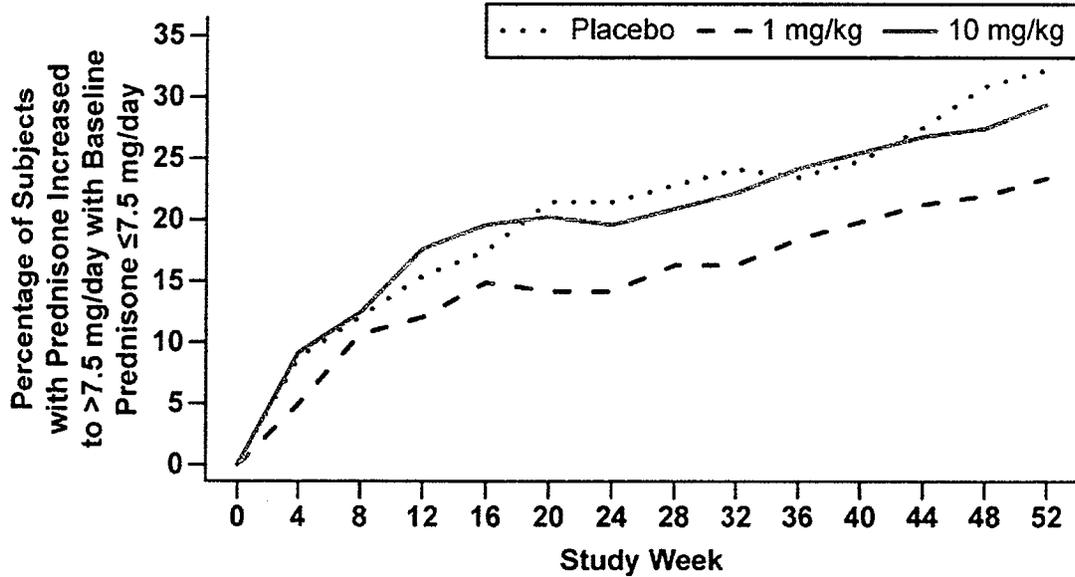
<sup>2</sup>Any subject who withdrew from the study prior to the Day 364 (Week 52) visit, missed the Day 364 (Week 52) visit ( $\pm$  28 day window allowed) and/or received a protocol-prohibited medication or a dose of allowable (but protocol-restricted) medication that resulted in treatment failure designation prior to the Day 364 (Week 52) visit was considered a treatment failure for prednisone reduction.

<sup>3</sup>OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline prednisone level and stratification factors.

Adapted Sponsor's Table 7-24; p. 135 and Sponsor's Table 7-15; p.114.

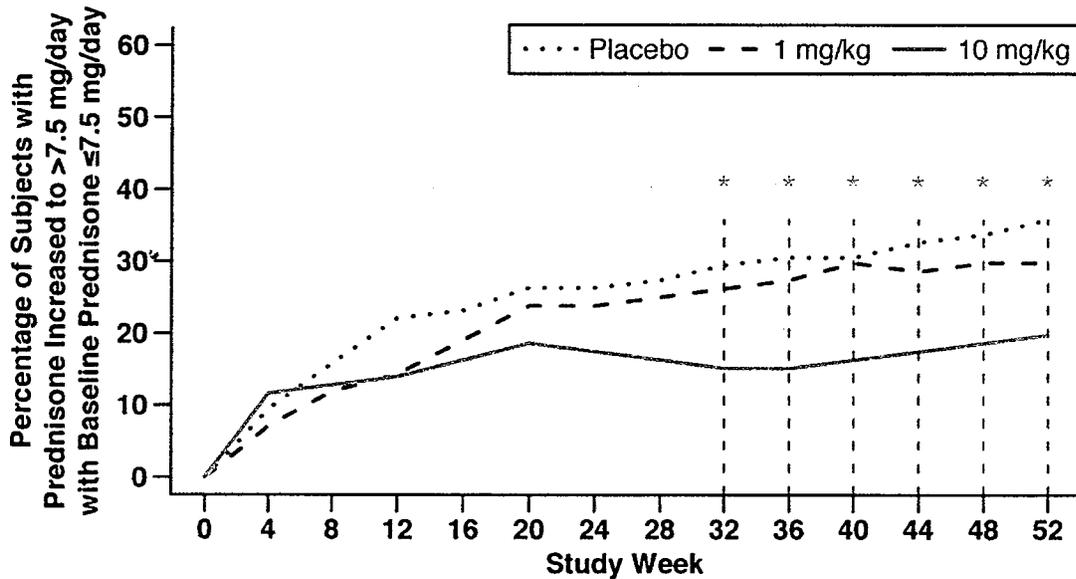
Subjects in these trials were also evaluated for increases in concomitant corticosteroids. The following Figure 4 and Figure 5 depict the percentage of subjects whose daily prednisone dose was increased to >7.5 mg/day from  $\leq 7.5$  mg/day at baseline over time in Studies 1056 and 1057, respectively. Over the course of Study 1056, a numerically smaller percentage of subjects in the belimumab 1 mg/kg group had their daily prednisone dose increased to > 7.5 mg/day as compared to placebo while the percentage of patients in the 10 mg/kg belimumab group whose daily prednisone dose was increased to > 7.5 mg/day was similar to that of the placebo group. In contrast, a smaller percentage of patients in the 10 mg/kg belimumab group had their daily prednisone dose increased to >7.5 mg/day as compared to the placebo group in Study 1057. The percent difference between the 10 mg/kg belimumab and placebo treatment groups was numerically different starting at Week 32 and appeared to sustain through Week 52 for this trial. The percentage of patients in the 1 mg/day group whose daily prednisone dose was increased to >7.5 mg/day was numerically smaller than the placebo group at all time points but the difference did not approach statistical significance. Although belimumab treatment appeared to be associated with a lower proportion of patients requiring a prednisone increase compared to placebo treatment in both studies, the inconsistency with respect to dose is difficult to explain.

Figure 4 - Percentage of Subjects Requiring an INCREASE in Daily Prednisone to >7.5 mg/day from <7.5 mg/day at Baseline (Imputation: Dropout=Failure) in Study 1056



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

Figure 5 - Percentage of Subjects Requiring an INCREASE in Daily Prednisone to >7.5 mg/day from <7.5 mg/day at Baseline (Imputation: Dropout=Failure) in Study 1057



#: p < 0.001 +: p < 0.01 \*: p < 0.05

HGS# 000-7711

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

**Patient Reported Outcomes:**

Another prespecified major secondary endpoint was the change from baseline to Week 24 in the SF-36 physical component score (PCS) for the belimumab groups as compared to placebo for both trials. As shown in Table 51, the change from baseline to Week 24 in the SF-36 physical component score (PCS) was comparable for all three treatment groups.

**Table 51 - Mean Change in SF-36 PCS Score from Baseline to Week 24 (LOCF)**

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

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

**Physician's Global Assessment (PGA):**

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

Table 52 - Percent Change and Absolute Change in PGA from Baseline to Week 24 for Studies 1056 and 1057

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

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

### 6.1.6 Other Endpoints

#### 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 53];
- 2) New BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline.

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

Table 54 displays the results from the flare analyses assessed by the modified SLE Flare Index. In Study 1056, the median time to first flare was similar for all three treatment groups with durations ranging from 82-85 days. In contrast, in Study 1057, the median time to flare for both the 1mg/kg (126 days) and 10 mg/kg (119 days) belimumab groups was longer as compared to placebo (84 days). In Study 1056, the risk for having a severe disease flare over 52 weeks was reduced only in the 1 mg/kg belimumab group, whereas in Study 1057 the risk was reduced only in the 10 mg/kg

belimumab group. The results suggest there may be a treatment benefit of belimumab with respect to flares.

Table 54 - SLE Flare Results over 52 Weeks in Studies 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
<b>Any Flare<sup>1</sup>:</b>						
n (%) <sup>2</sup>	228 (83%)	214 (79%)	215 (79%)	230 (80%)	203 (71%)	205 (71%)
Median Time to 1 <sup>st</sup> Flare in Days (Min, Max) <sup>3</sup>	82 (34,195)	85 (41, 249)	84 (35, 228)	84 (1,368)	126 (5, 375)	119 (1, 367)
Hazard Ratio (95% CI) vs PLO <sup>4</sup>		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 <sup>4</sup>		<b>0.2324</b>	<b>0.4796</b>	-	<b>0.0026</b>	<b>0.0036</b>
<b>Severe Flare<sup>1</sup>:</b>						
n (%) <sup>2</sup>	67 (24%)	44 (16%)	48 (18%)	66 (23%)	51 (18%)	40 (14%)
Median Time to 1 <sup>st</sup> Flare in Days (Min, Max) <sup>3</sup>	-(1,370)	-(3, 322)	-(10, 361)	-(5, 371)	-(5, 364)	-(1, 366)
Hazard Ratio (95% CI) vs PLO <sup>4</sup>		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 <sup>4</sup>		<b>0.0230</b>	<b>0.0867</b>	-	<b>0.1342</b>	<b>0.0055</b>
<b>Flare per Subject-Year<sup>5</sup></b>						
Mean ± SE	n=272 3.81 ± 0.18	n=267 3.33 ± 0.18	n= 270 3.42 ± 0.19	n=284 3.22 ±0.17	n=286 2.50 ± 0.17	n=287 2.37 ± 0.16
P-value <sup>6</sup>		<b>0.0632</b>	<b>0.1276</b>		<b>0.0012</b>	<b>0.0002</b>
<b>Severe Flares per Subject-Year<sup>5</sup></b>						
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 <sup>6</sup>		<b>0.3680</b>	<b>0.5775</b>		<b>0.3544</b>	<b>0.0381</b>

<sup>1</sup>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.

<sup>2</sup>Number (%) of subjects with at least 1 flare over 52 weeks.

<sup>3</sup>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.

<sup>4</sup>From Cox proportional hazards model for the comparison between each belimumab dose and placebo, adjusted for baseline stratification factors.

<sup>5</sup>Includes subjects who did not dropout or had medication failures before Day 28; 0 flares assigned for missing visits before exit/treatment failure date.

<sup>6</sup>From ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for baseline stratification factors.

Adapted Sponsor's Table 7-9; p. 99. Adapted Sponsor's Table 7-18; p. 120.

The occurrence of flares was also assessed from Weeks 24 to 52 following the implementation of background medication restrictions (Table 55 below). Decreases in the risk for experiencing a disease flare during this time period were observed in both belimumab groups in Study 1056 and Study 1057.

Table 55 - SLE Flare Results from Week 24 to Week 52 in Studies 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=238)	Belimumab 1mg/kg (N=245)	Belimumab 10 mg/kg (N=235)	Placebo (N=254)	Belimumab 1mg/kg (N=263)	Belimumab 10 mg/kg (N=271)
<b>Any Flare<sup>1</sup>:</b>						
<b>No. of Subjects<sup>2</sup></b>	176 (74%)	161 (66%)	150 (64%)	161 (63%)	117 (45%)	141 (52%)
<b>Median Time to 1<sup>st</sup> Flare in Days (Min, Max)<sup>3</sup></b>	76 (1, 218)	105 (1, 201)	98 (1, 204)	112 (3, 201)	207 (2, 207)	182 (2, 203)
<b>Hazard Ratio (95% CI) vs PLO<sup>4</sup></b>		0.81(0.66, 1.10)	0.78 (0.62, 0.97)		0.58(0.46,0.74)	0.71(0.56,0.89)
<b>P-value<sup>4</sup></b>		<b>0.0583</b>	<b>0.0226</b>		<b>&lt;0.0001</b>	<b>0.0027</b>
<b>Severe Flare:</b>						
<b>No. of Subjects<sup>2</sup></b>	43 (18%)	25 (10%)	28 (12%)	28 (11%)	21 (8%)	21 (8%)
<b>Median Time to 1<sup>st</sup> Flare in Days (Min, Max)<sup>3</sup></b>	-(1, 199)	-(1, 154)	-(6, 193)	-(3, 206)	-(2, 196)	-(7, 200)
<b>Hazard Ratio (95% CI) vs PLO<sup>4</sup></b>		0.55 (0.33, 0.90)	0.66 (0.41, 1.06)		0.72(0.41,1.26)	0.70(0.40,1.23)
<b>P-value<sup>4</sup></b>		<b>0.0167</b>	<b>0.0843</b>		<b>0.2476</b>	<b>0.2167</b>
<b>Flare per Subject-Year<sup>5</sup></b>	n= 227	n=236	n=229	n=246	n=257	N=264
<b>Mean ± SE</b>	3.89 ± 0.26	3.06 ± 0.21	2.95 ± 0.22	3.00 ± 0.24	1.92 ± 0.18	1.90 ± 0.15
<b>P-value<sup>6</sup></b>		<b>0.0091</b>	<b>0.0045</b>		<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
<b>Severe Flares per Subject-Year<sup>5</sup></b>						
<b>Mean ± SE</b>	1.09 ± 0.20	0.79 ± 0.17	0.82 ± 0.16	0.82 ± 0.18	0.58 ± 0.14	0.45 ± 0.10
<b>P-value<sup>6</sup></b>		<b>0.1898</b>	<b>0.3106</b>		<b>0.1851</b>	<b>0.0714</b>

<sup>1</sup>Censored at last available visit by Week 52 after Week 24. For 9 subjects who died, censored at death if no flares indicated after Week 24 and before death. Any increase of ≥ 3 points on SLEDAI score resulted in a mild/moderate flare.

<sup>2</sup>Number (%) of subjects with at least 1 flare between Week 24 and Week 52 among subjects with at least 1 visit after Week 24.

<sup>3</sup>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.

<sup>4</sup>From Cox proportional hazards model for the comparison between each belimumab dose and placebo, adjusted for baseline stratification factors.

<sup>5</sup>Includes subjects who did not dropout or had medication failures within 28 days post Week 24; 0 flares assigned for missing visits before exit/treatment failure date.

<sup>6</sup>From ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for baseline stratification factors.

Adapted Sponsor's Table 7-19; p. 122. Adapted Sponsor's Table 7-10; p. 101.

No reduction in risk for developing a BILAG 1A/2B organ domain flare over 52 weeks was observed in either of the belimumab treatment groups in Study 1056 as displayed in the following Table 56. Flares per subject years as assessed by the BILAG were also comparable for the 3 treatment groups and ranged from 1.3 to 1.5 flares/year in this trial. However in Study 1057, subjects in the 10 mg/kg belimumab treatment group had a reduction in flares per subject years as well as a reduction in risk for developing a BILAG 1A/2B organ flare as compared to placebo.

Table 56 - 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)
<b>Time to 1<sup>st</sup> BILAG 1A/2B Flare<sup>1</sup>:</b> n (%) <sup>2</sup>	94 (34%)	75 (28%)	86 (32%)	86 (30%)	77 (27%)	54 (19%)
<b>Median Time to 1<sup>st</sup> Flare in Days (Min, Max)<sup>3</sup></b>	385(27, 385)	- (15, 335)	- (26, 364)	-(24, 367)	-(27, 368)	-(1, 366)
<b>Hazard Ratio (95% CI) vs PLO<sup>4</sup></b>		0.78(0.58,1.06)	0.93(0.69,1.24)		0.89(0.66,1.22)	0.58(0.41,0.81)
<b>P-value<sup>4</sup></b>		<b>0.1191</b>	<b>0.6135</b>		<b>0.4804</b>	<b>0.0016</b>
<b>Time to 1<sup>st</sup> BILAG 1A Flare (post hoc analysis):</b> No. of Subjects <sup>2</sup>	72 (26%)	52 (19%)	62 (23%)	58 (20%)	54 (19%)	29 (10%)
<b>Median Time to 1<sup>st</sup> Flare in Days (Min, Max)<sup>3</sup></b>	385(27, 385)	-(15, 315)	-(27, 364)	-(24, 367)	-(27, 351)	-(1, 366)
<b>Hazard Ratio (95% CI) vs PLO<sup>4</sup></b>		0.71(0.50,1.01)	0.88(0.63,1.24)		0.88(0.61,1.28)	0.45(0.28,0.70)
<b>P-value<sup>4</sup></b>		<b>0.0593</b>	<b>0.4744</b>		<b>0.4997</b>	<b>0.0004</b>
<b>Flare per Subject-Year<sup>5</sup></b>	n=272	n=267	N=270	n=284	n=286	n=287
<b>Mean ± SE</b>	1.5 ± 0.16	1.3 ± 0.17	1.39 ± 0.16	1.21 ± 0.14	1.04 ± 0.14	0.75 ± 0.11
<b>P-value<sup>6</sup></b>		<b>0.4616</b>	<b>0.5828</b>		<b>0.3225</b>	<b>0.0104</b>

<sup>1</sup> Censored at last available visit by Week 52 visit. For 9 subjects who died, censored at death if no flares indicated before death.

<sup>2</sup> Number (%) of subjects with at least 1 flare over 52 weeks.

<sup>3</sup> 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

<sup>4</sup> 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.

<sup>5</sup> Includes subjects who did not dropout or had medication failures before Day 28; 0 flares assigned for missing visits before exit/treatment failure date.

<sup>6</sup> From ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for baseline BILAG domain involvement (at least 1A/2B vs at most 1B) and stratification factors.

Adapted Sponsor's Table 7-21; p. 130. Adapted Sponsor's Table 7-12; p. 110.

The occurrence of BILAG flares was also assessed from Weeks 24 to 52. Decreases in the risk for experiencing a disease flare during this time period were observed in both belimumab groups in Study 1056 and in Study 1057 (Table 57).

Table 57 - BILAG Flares from Week 24 to Week 52 in Studies 1056 and 1057

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

<sup>1</sup> Censored at last available visit. For 9 subjects who died, censored at death if no flares indicated before death.

<sup>2</sup> Number (%) of subjects with at least 1 flare over 52 weeks.

<sup>3</sup> 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.

<sup>4</sup> 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.

<sup>5</sup> Includes subjects who did not dropout or had medication failures before Day 28; 0 flares assigned for missing visits before exit/treatment failure date.

<sup>6</sup> From ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for baseline BILAG domain involvement (at least 1A/2B vs at most 1B) and stratification factors.

Adapted Sponsor's Table 7-22; p. 132. Adapted Sponsor's Table 7-13; p. 111.

### Improvement and Worsening by Organ Domains:

Although the SLEDAI is not grouped by organ systems, in order to facilitate analysis of treatment effect by systems, the Applicant grouped individual items into organ systems similar to BILAG organ domains for exploratory analyses. (Improvement and worsening by actual BILAG organ domains is summarized in Table 60 and Table 61 below). With the exception of the "Immunology" domain, which consists of anti-dsDNA and complement laboratory tests, there was no consistent pattern of improvement and worsening that would support a treatment benefit in favor of belimumab as assessed by the SELENA SLEDAI (Table 58 and Table 59). For most organ systems (notable exceptions—cardiorespiratory in Study 1056, hematological and fever in Study 1057) there was at least a numeric trend suggestive of an improvement with belimumab.

Table 58- Improvement by SELENA-SLEDAI Organ Systems

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

CNS items include: Cranial nerve disorder, lupus headache, organic brain syndrome, psychosis, seizure, visual disturbance

Cardio-respiratory items include: pericarditis and pleurisy

Vascular items include: CVA and vasculitis

Musculoskeletal items include: arthritis and myositis

Immunology items include: increased DNA binding and low complement

Hematology and Fever items include: leucopenia, thrombocytopenia and fever

Renal items include: hematuria, proteinuria, pyuria, and urinary casts

Mucocutaneous items include: alopecia, mucosal ulcers, and rash

P-values from logistic regression for the comparison between each belimumab dose and placebo

Modified from Sponsor's tables TA46.1, TA46.2, TA46.3, TA46.4, TA46.5, TA46.6, TA46.7, and TA46.8

Table 59: Worsening (New Involvement) by SELINA-SLEDAI Organ Domains

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

CNS items include: Cranial nerve disorder, lupus headache, organic brain syndrome, psychosis, seizure, visual disturbance

Cardio-respiratory items include: pericarditis and pleurisy

Vascular items include: CVA and vasculitis

Musculoskeletal items include: arthritis and myositis

Immunology items include: increased DNA binding and low complement

Hematology and Fever items include: leucopenia, thrombocytopenia and fever

Renal items include: hematuria, proteinuria, pyuria, and urinary casts

Mucocutaneous items include: alopecia, mucosal ulcers, and rash

P-values from logistic regression for the comparison between each belimumab dose and placebo

Modified from Sponsor's tables TA47.1, TA47.2, TA47.3, TA47.4, TA47.5, TA47.6, TA47.7, and TA47.8

With respect to new organ involvement, as summarized in Table 59 above, for most organ groupings there was a trend toward more new organ involvement in the placebo group, particularly in Study 1056. There was again some inconsistency, with more new mucocutaneous involvement occurring in the belimumab treatment groups of Study 1057.

When using BILAG domains to assess improvement or worsening, results are similar in that there appears to be a numeric trend in favor of belimumab in most organ domains, with the exception of the cardiorespiratory subgroup in Study 1057 and the vasculitis subgroup of study 1056 (Table 60).

Table 60 - BILAG Organ Domain Improvement from Baseline to Week 52

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

Dropouts/Medication failure = No Improvement

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

Modified Sponsor's Tables T38, T40, T42, T44, T46, T48, T50, T52 from Summary of Clinical Efficacy Appendices

However, the proportion of patients experiencing worsening in BILAG organ domain scores was similar among all three treatment groups of each study (Table 61).

Table 61 – BILAG Organ Domain Worsening from Baseline to Week 52

	Study 1056			Study 1057		
	Placebo n = 275	Belimumab 1 mg/kg n = 271	Belimumab 10 mg/kg n = 273	Placebo n = 287	Belimumab 1 mg/kg n = 288	Belimumab 10 mg/kg n = 290
<b>BILAG: General</b>						
Baseline Domain Score	n = 273	n = 270	n = 273	n = 284	n = 288	n = 287
Number of pts with B	36 (13)	29 (11)	38 (14)	25 (9)	23 (8)	23 (8)
Number of pts with C	164 (60)	176 (65)	162 (59)	106 (37)	99 (34)	94 (33)
Number of pts with D	11 (4)	7 (3)	4 (1)	11 (4)	11 (4)	13 (5)
Number of pts with E	62 (23)	58 (21)	69 (25)	142 (50)	155 (54)	157 (55)
Number (%) worsened at Wk 52	9 (3)	10 (4)	8 (3)	9 (3)	6 (2)	11 (4)
p-value of difference		0.7963	0.8053		0.4151	0.6659
<b>BILAG: Mucocutaneous</b>						
Baseline Domain Score	n = 260	n = 255	n = 261	n = 278	n = 276	n = 280
Number of pts with B	163 (63)	143 (56)	129 (49)	163 (59)	155 (56)	164 (59)
Number of pts with C	67 (26)	82 (32)	85 (33)	84 (30)	75 (27)	81 (29)
Number of pts with D	7 (3)	3 (1)	7 (3)	2 (1)	4 (1)	5 (2)
Number of pts with E	23 (9)	27 (11)	40 (15)	29 (10)	42 (15)	30 (11)
Number (%) worsened at Wk 52	10 (4)	11 (4)	15 (6)	14 (5)	12 (4)	14 (5)
p-value of difference		0.7885	0.3085		0.7016	0.9845
<b>BILAG: Musculoskeletal</b>						
Baseline Domain Score	n = 261	n = 260	n = 263	n = 254	n = 255	n = 265
Number of pts with B	181 (69)	166 (64)	169 (64)	114 (45)	117 (46)	135 (51)
Number of pts with C	50 (19)	66 (25)	63 (24)	68 (27)	79 (31)	65 (25)
Number of pts with D	5 (2)	5 (2)	7 (3)	3 (1)	3 (1)	5 (2)
Number of pts with E	25 (10)	23 (9)	24 (9)	69 (27)	56 (22)	60 (23)
Number (%) worsened at Wk 52	17 (7)	11 (4)	17 (6)	9 (4)	3 (1)	26 (5)
p-value of difference		0.2462	0.9816		0.9932	0.0622
<b>BILAG: Neurological</b>						
Baseline Domain Score	n = 275	n = 268	n = 272	n = 287	n = 288	n = 290
Number of pts with B	6 (2)	4 (1)	6 (2)	0	1 (0.3)	0
Number of pts with C	36 (13)	40 (15)	55 (20)	20 (7)	26 (9)	22 (8)
Number of pts with D	7 (3)	5 (2)	2 (1)	5 (2)	2 (1)	3 (1)
Number of pts with E	226 (82)	219 (82)	209 (77)	262 (91)	259 (90)	265 (91)
Number (%) worsened at Wk 52	3 (1)	2 (1)	5 (2)	1 (0.3)	1 (0.3)	1 (0.3)
p-value of difference		1.0000	0.5026		1.0000	1.0000
<b>BILAG: CardioRespiratory</b>						
Baseline Domain Score	n = 273	n = 269	n = 272	n = 285	n = 285	n = 289
Number of pts with B	7 (3)	11 (4)	14 (5)	10 (4)	3 (1)	5 (2)
Number of pts with C	51 (19)	48 (18)	47 (17)	23 (8)	21 (7)	25 (9)
Number of pts with D	9 (3)	8 (3)	10 (4)	4 (1)	4 (1)	3 (1)
Number of pts with E	206 (75)	202 (75)	201 (74)	248 (87)	257 (90)	256 (89)
Number (%) worsened at Wk 52	3 (1)	4 (1)	6 (2)	2 (1)	1 (0.4)	0
p-value of difference		0.7230	0.3392		1.0000	0.2461

Dropouts/Medication failure = No Improvement

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

Modified Sponsor's Tables T39, T41, T43, T45, T47, T49, T51, T53 from Summary of Clinical Efficacy Appendices

Table 61 – BILAG Organ Domain Worsening from Baseline to Week 52 (cont.)

	Study 1056			Study 1057		
	Placebo n = 275	Belimumab 1 mg/kg n = 271	Belimumab 10 mg/kg n = 273	Placebo n = 287	Belimumab 1 mg/kg n = 288	Belimumab 10 mg/kg n = 290
<b>BILAG: Vasculitis</b>						
Baseline Domain Score	n = 268	n = 262	n = 270	n = 280	n = 281	n = 274
Number of pts with B	23 (9)	14 (5)	15 (6)	15 (5)	18 (6)	17 (6)
Number of pts with C	106 (40)	113 (43)	108 (40)	102 (36)	100 (36)	88 (32)
Number of pts with D	4 (1)	6 (2)	10 (4)	6 (2)	8 (3)	5 (2)
Number of pts with E	135 (50)	129 (49)	137 (51)	157 (56)	155 (55)	164 (60)
Number (%) worsened at Wk 52	5 (2)	1 (0.4)	1 (0.4)	4 (1)	1 (0.4)	2 (1)
p-value of difference		0.2163	0.1219		0.2162	0.6859
<b>BILAG: Renal</b>						
Baseline Domain Score	n = 275	n = 270	n = 272	n = 286	n = 283	n = 288
Number of pts with B	21 (8)	13 (5)	23 (8)	37 (13)	43 (15)	32 (11)
Number of pts with C	68 (25)	60 (22)	57 (21)	90 (31)	79 (28)	87 (30)
Number of pts with D	13 (5)	16 (6)	15 (6)	23 (8)	20 (7)	17 (6)
Number of pts with E	173 (63)	181 (67)	177 (65)	136 (48)	141 (50)	152 (53)
Number (%) worsened at Wk 52	23 (8)	10 (4)	14 (5)	19 (7)	17 (6)	20 (7)
p-value of difference		<b>0.0208</b>	0.1323		0.7552	0.8860
<b>BILAG: Hematology</b>						
Baseline Domain Score	n = 275	n = 271	n = 272	n = 286	n = 286	n = 287
Number of pts with B	36 (13)	40 (15)	34 (12.5)	51 (18)	54 (19)	50 (17)
Number of pts with C	79 (29)	72 (27)	84 (31)	63 (22)	67 (23)	77 (27)
Number of pts with D	21 (8)	17 (6)	17 (6)	12 (4)	16 (6)	24 (8)
Number of pts with E	139 (51)	142 (52)	137 (50)	160 (56)	149 (52)	136 (47)
Number (%) worsened at Wk 52	26 (9)	11 (4)	16 (6)	25 (9)	20 (7)	21 (7)
p-value of difference		<b>0.0110</b>	0.1150		0.4370	0.5302

Dropouts/Medication failure = No Improvement

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

Modified Sponsor's Tables T39, T41, T43, T45, T47, T49, T51, T53 from Summary of Clinical Efficacy Appendices

Whereas instruments such as SLEDAI and BILAG assess disease activity, they do not capture accumulated damage in SLE, which is an important factor related to overall morbidity and ultimately prognosis. To this end, the American College of Rheumatology and European counterparts developed a damage index to capture permanent end-organ-dysfunction in 12 different organ systems affected by SLE (Table 62):

Table 62 – Systemic Lupus International Collaborating Clinics (SLICC/American College of Rheumatology  
Damage Index for SLE)

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

The SLICC/ACR Damage Index records damage occurring in patients with SLE regardless of the cause. The damage index does not include hematologic items, such as cytopenias, since these can be waxing and waning phenomena; other manifestations need to have been present for at least 6 months. As shown in Table 63, the results were not consistent with respect to progression in the damage index and therefore definitive conclusions cannot be made.

Table 63 - Change in SLICC/ACR Damage Index at Week 52

	Study 1056			Study 1057		
	Placebo n = 275	Belimumab 1 mg/kg n = 271	Belimumab 10 mg/kg n = 273	Placebo n = 287	Belimumab 1 mg/kg n = 288	Belimumab 10 mg/kg n = 290
<b>Baseline</b>						
<b>Mean (<math>\pm</math>SE)</b>	0.99 (0.09)	1.04 (0.08)	0.94 (0.08)	0.55 (0.05)	0.60 (0.06)	0.55 (0.06)
<b>Change at Week 52</b>						
<b>Mean (<math>\pm</math>SE)</b>	0.06(0.02)	0.04 (0.02)	0.04 (0.01)	0.05 (0.02)	0.07 (0.02)	0.03 (0.01)
<b>LS mean (<math>\pm</math>SE)</b>	0.08 (0.03)	0.07 (0.03)	0.06 (0.03)	0.1 (0.02)	0.12 (0.02)	0.08 (0.02)
<b>P-value (Difference vs PLO)</b>		0.5136	0.3415		0.3278	0.4222

Adapted Sponsor's Table T37 in Summary of Clinical Efficacy Appendices

### 6.1.7 Subpopulations

Pre-specified subgroup analyses of the primary efficacy endpoint by region, stratification factors, baseline C3, baseline C4, average steroid use and anti-dsDNA were provided by the Applicant. For each subgroup analysis, consistency of the treatment effect across subgroups was evaluated using logistic regression with main effects for treatment, subgroup, and the treatment-by-subgroup interaction. A significant treatment-by-subgroup interaction is evidence that the treatment effect is (either quantitatively or qualitatively) different in the subgroups being considered. The results of these analyses are displayed in Table 64. Statistically significant **qualitative** treatment-by-subgroup interactions were observed in the analyses comparing each belimumab treatment group versus placebo for race (stratification factor) in Study 1056 suggesting that there are differences in the direction of the treatment effect in the racial subgroups. Statistically significant **quantitative** treatment-by-subgroup interactions were observed in the analyses comparing each belimumab treatment group versus placebo for baseline SELENA SLEDAI score (stratification factor), and in the analyses comparing the belimumab 10 mg/kg versus placebo for baseline C3 and baseline C4 levels in Study 1057. A quantitative interaction refers to cases where there may be a difference in the magnitude of the treatment effect in the subgroups but the direction of the treatment effect does not vary across subgroups.

Table 64 - Subgroup Analyses of the Primary Efficacy Endpoint for Trials 1056 and 1057

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

AIA = African descent or indigenous American descent

<sup>1</sup>For treatment by subgroup interaction effect from logistic regression.

Adapted Sponsor's Table L9-1; Appendix 17.2.6 from the Study Reports for Trials 1056 and 1057.

SLE patients of African American or African heritage have been reported to have more aggressive disease, often leading to worse outcomes. Therefore the significant qualitative treatment-by-race interactions observed for comparison of each belimumab group to placebo merit special attention. To this end, the Applicant provided post hoc exploratory analysis of treatment effect on race, summarized in Table 65 below. The

results of this analysis for Studies 1056 and 1057 suggest that there may be a reversal in the direction of the treatment effect in subjects of African American or African heritage. A similar finding was noted in the Native American subgroup of Study 1056 but not the same subgroup of Study 1057. This illustrates the difficulty of drawing conclusions from these subgroup analyses when subgroups are small.

**Table 65 - Primary Efficacy Endpoint Results by Racial Subgroups for Studies 1056 and 1057**

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

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.

Table 66 lists additional subgroup analyses for gender and age of the primary endpoint based on populations pooled from studies 1056 and 1057. Since most of the subjects who participated in these trials were  $\leq 45$  years of age (74%) with relatively few patients age 65 years and older (< 2%), the Applicant used 45 years as the cut-point for the age analysis. Review of the data presented in this table did not reveal any subgroup that did not exhibit a treatment effect of belimumab. However, ability to detect small differences in effects is limited by the small number of subjects involved in each analysis.

Table 66 – Primary Response at Week 52 by Gender and Age Pooled Subgroups

	Gender					
	Male			Female		
	Placebo (N=40)	Belimumab 1mg/kg (N=35)	Belimumab 10 mg/kg (N=24)	Placebo (N=522)	Belimumab 1mg/kg (N=524)	Belimumab 10 mg/kg (N=539)
Response: Observed Difference vs PLO OR (95% CI) <sup>1</sup> vs PLO P-value <sup>2</sup>	15 (38%)	15 (43%) 5.4 1.5 (0.5, 4.1) 0.8989	13 (54%) 16.7 2.4 (0.8, 7.4) 0.5507	203 (39%)	243 (46%) 7.5 1.4 (1.1, 1.8) NA	272 (51%) 11.6 1.7 (1.3, 2.3) NA
	Age (Baseline)					
	Age < 45 years			Age > 45 years		
	Placebo (N=414)	Belimumab 1mg/kg (N=420)	Belimumab 10 mg/kg (N=414)	Placebo (N=148)	Belimumab 1mg/kg (N=139)	Belimumab 10 mg/kg (N=149)
Response: Observed Difference vs PLO OR (95% CI) <sup>1</sup> vs PLO P-value <sup>2</sup>	164 (40%)	193 (46%) 6.3 1.4 (1.0, 1.9) 0.7790	219 (53%) 13.3 1.8 (1.3, 2.4) 0.5363	54 (37%)	65 (47%) 10.3 1.6 (1.9, 2.5) NA	66 (44%) 7.8 1.5 (0.9, 2.4) NA

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

<sup>2</sup>For treatment by subgroup interaction effect from a logistic regression model by adding the subgroup and interaction effect to the above model.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As part of their clinical development program for belimumab, the Applicant conducted Phase 1 and 2 dose-ranging studies to identify a safe and efficacious dose for evaluation in their Phase 3 studies. Study LBSL01 was a Phase 1 dose-ranging trial that evaluated 1, 4, 10 and 20 mg/kg doses of belimumab administered as a single dose or two doses 21 days apart in patients with active SLE. Based on analysis of belimumab's effects on a variety of biomarkers, a clear dose response was not demonstrated in this trial. Study LBSL02 was a Phase 2 dose-ranging trial that also evaluated 1, 4, 10 and 20 mg/kg doses of belimumab administered on Days 0, 14, and 28 and then every 28 days via IV infusion. A consistent dose response for efficacy or safety was also not observed in this study. However, results of post hoc analyses of LBSL02 suggested a greater treatment effect associated with the 10 mg/kg dose versus the 1 mg/kg dose of belimumab in a subgroup of patients who were autoantibody positive. The Applicant decided to evaluate both the 1mg/kg and 10 mg/kg doses of belimumab in the pivotal Phase 3 trials since they were shown to be biologically active, safe and well tolerated, and resulted in steady state trough levels of active drug in excess of BLyS concentrations in the peripheral circulation.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

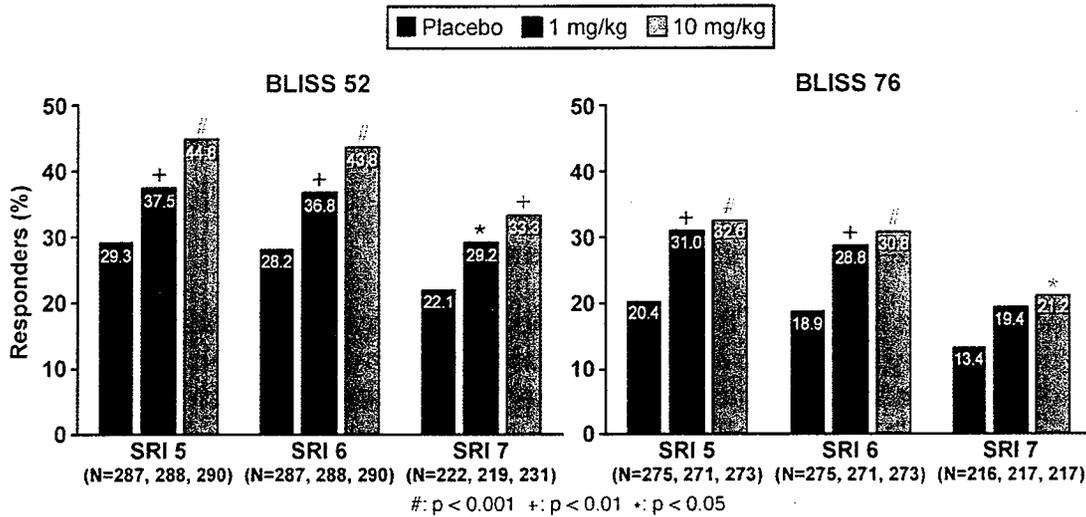
In support of persistence of efficacy, the Applicant submitted an interim analysis of 48 months of data collected from the ongoing open-label extension study, LBSL99. The

efficacy data contained in this interim report should not be used to support persistence of belimumab's efficacy since this trial is an uncontrolled extension of LBSL02 which was a failed Phase 2 study. Durability of treatment effect was also evaluated by the group response to treatment by the SRI at Week 76 in Study 1056, which was a prespecified major secondary endpoint. As discussed in section 6.1.5, patients in the 1mg/kg and 10 mg/kg belimumab treatment groups had numerically higher response rates than placebo patients at Week 76, but these differences were not significant (see Table 49).

#### 6.1.10 Additional Efficacy Issues/Analyses

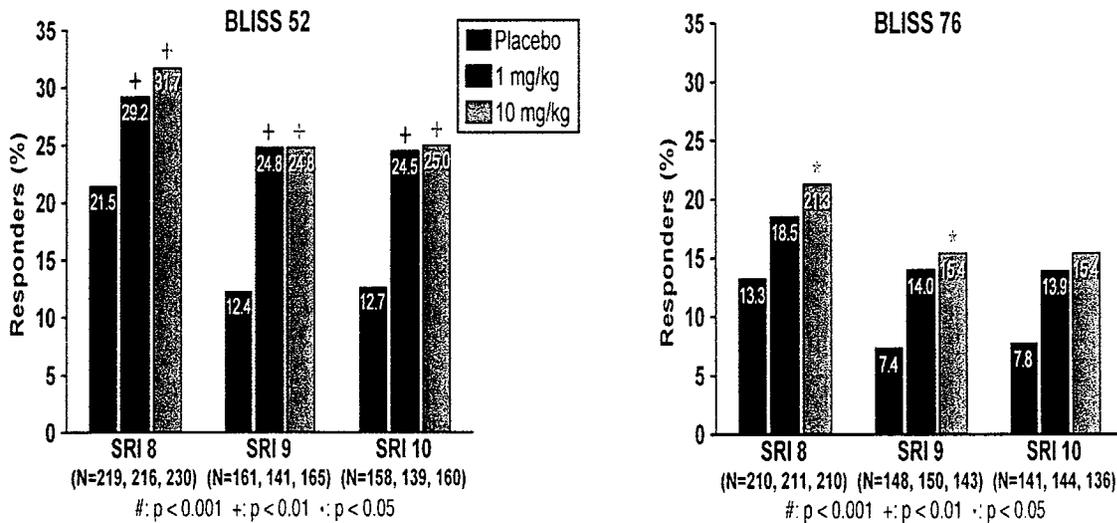
Post hoc analyses for time to BILAG flare and organ or system disease involvement were conducted by the Applicant and are presented above in Section 6.1.6. Since the literature suggests that reductions greater than 4 points in the SELENA SLEDAI score are indicative of clinically relevant reductions in SLE disease activity, the sponsor also submitted the results from other post hoc analyses that employed higher reductions in SELENA SLEDAI thresholds (e.g., SELENA SLEDAI  $\geq 5$  through  $\geq 10$ ) for the SRI responder analysis for both Studies 1056 and 1057 at the Week 52 time point. As shown in Figure 6 and Figure 7 below, numerically higher response rates were observed for both the 10 mg/kg and 1 mg/kg groups compared to placebo in both studies for the SRI 5 through SRI 10 at Week 52. In addition to supporting the robustness of the primary efficacy analysis for both studies, these results are suggestive that a higher magnitude of treatment effect may have been observed if patients with higher levels of SLE disease activity at baseline had been enrolled in these two pivotal trials.

Figure 6 - Week 52 Post Hoc Analyses of SRI with Higher SELENA SLEDAI Thresholds of Improvement ( $\geq 5$  through  $\geq 7$ ) for Studies 1056 and 1057 (ITT Population for SRI 5 and 6; MITT Population SRI 7)



Sponsor's Fig. 9-10; p. 108 AAC Meeting Briefing Package

Figure 7 - Week 52 Post Hoc Analyses of SRI with Higher SELENA SLEDAI Thresholds of Improvement ( $\geq 8$  through  $\geq 10$ ) for Studies 1056 and 1057 (MITT Population)



Sponsor's Fig. 16-2 and 16-3; p. 252-3 AAC Meeting Briefing Package

## 7 Review of Safety

### Safety Summary

The review of belimumab's safety database identified concerns in four main areas: 1) a higher incidence of deaths, 2) a higher rate of serious adverse events 3) a higher incidence of serious infections 3) and an increase in psychiatric adverse events including depression and suicide.

Although the types of death are consistent with immunosuppressive therapies (e.g., infection) and with the risks related to the underlying and concomitant medical conditions (e.g., cardiovascular disease), numerically more deaths occurred during the controlled studies in the 1 mg/kg and 10 mg/kg belimumab treatment groups as compared to the placebo group. An exposure-adjusted analysis of mortality for these trials revealed that the point estimate for death was nearly double for belimumab-treated patients as compared to placebo patients but their confidence intervals overlapped suggesting that there is no real difference between the two groups. Additionally, the exposure-adjusted mortality rates for both the placebo and belimumab-treated groups in these studies are lower than what has been reported in the literature for SLE patients providing some reassurance to this medical reviewer that the increased magnitude for this finding may be lower than perceived but still needs further investigation.

A numeric imbalance in the number of serious adverse events in a number of organ systems for the 10 mg/kg belimumab group as compared to placebo was also observed during this review of the controlled SLE studies conducted in support of belimumab. However, examination of these data revealed that many of these events could be related to underlying SLE disease activity or as a result of infections. The exposure-adjusted incidence of serious infections for these trials was higher in the combined belimumab groups as compared to placebo. This is not an unexpected finding since belimumab is an immunosuppressive agent. What is surprising is that the rate of serious infection was not higher given that belimumab is a B-cell modulating agent. Although decreases in immunoglobulins were observed in belimumab-treated patients, no associated increases in infections or serious infections were observed in belimumab-treated patients with treatment-related reductions in immunoglobulins as compared to placebo patients who participated in these trials.

An unexpected safety finding was the increase in psychiatric adverse events including depression and suicide observed in the belimumab-treatment group. Although SLE patients with central nervous system involvement were prohibited from participating in the controlled studies, there was both a numeric and exposure-adjusted imbalance in reported psychiatric serious adverse events (including suicide) and common adverse events. A consultant from the Agency's Division of Psychiatric Products found no convincing evidence of a signal for belimumab-related psychiatric experiences on his review of these data, however, based on the two suicides that occurred in patients

treated with belimumab, he could not conclude that treatment with the product plays a significant etiologic role in suicide. He did recommend that future studies conducted with belimumab rate patients use the Columbia Suicide-Severity Rating Scale (C-SSRS) at baseline and at each visit to improve the timely ascertainment of suicidality-related events. Although a retrospective assessment of suicidality, conducted according to the Columbia Algorithm for Suicide (C-CASA) that was submitted as an amendment by the Applicant, showed no difference in the primary safety population with regard to suicidal behaviors, additional evaluation should be done to further delineate the potential risk for these types of events to occur with belimumab treatment.

Since many patients who participated in these trials were taking concomitant corticosteroids, and inconsistently received prophylaxis for infusion reactions at the discretion of study investigators coupled with the lack of an acceptable methodology to classify infusion reactions, hypersensitivity reactions, and anaphylactic events contained in the safety database may have resulted in an underestimation of the risk for anaphylaxis associated with the administration of belimumab. However, final review of these type of events did not suggest that prophylactic premedication was warranted for all patients undergoing belimumab therapy.

No discernable pattern or increase in risk for malignancies associated with belimumab exposure was identified during this review of the product's safety database. However, the controlled trials were not designed to determine the risk for developing a malignancy as a result of treatment with belimumab. In view of the Agency's safety experience with other immunosuppressive therapies, it would be prudent to continue monitoring safety data from the ongoing open-label extensions studies for the development of potential safety signals such as malignancies to occur with increasing exposure to belimumab.

Other than expected decreases in lymphocytes and immunoglobulins, review of the clinical lab test parameters or vital sign data showed no evidence of an adverse effect of belimumab on these assessments. Examination of long-term safety data generated from the ongoing open-label extension studies in SLE as well as safety data from the Phase 1 studies and RA clinical development program for belimumab also did not reveal any new safety signals.

Although protocols for the studies conducted in support of belimumab's safety and efficacy mandated that subjects of childbearing potential practice effective forms of contraception for the duration of their study participation, a large number of pregnancies (i.e., 47) occurred during the Phase 2 and 3 SLE trials. Since SLE typically affects young women of childbearing potential, additional explorations to assess the potential effects of belimumab during pregnancy should be done.

Limitations associated with the belimumab safety database include the inconclusive results from the small vaccination substudy, the lack of concomitant immunosuppressives such as mycophenolate and cyclophosphamide, the lack of

patients with severe renal lupus and central nervous system disease, and the small numbers of patients available for subgroup analyses of gender (males) and age ( $\geq 65$  years of age as well as children  $\leq 17$  years of age) which precludes determination of the product's safety profile in these subgroups.

In view of the inconsistent dose-response effect and the marginal efficacy demonstrated in the pivotal Phase 3 trials, the risk/benefit assessment favors the 10 mg/kg belimumab dosing regimen when administered as an intravenous infusion every 2 weeks for the first 3 doses and at 4-week intervals thereafter.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In support of this BLA, submitted safety data from a total of 9 SLE studies: two Phase 1 trials (LBSL02 and C1058), two Phase 2 trials (LBSL02 and 1070), two Phase 3 trials (1056 and 1057), and three open-label extension trials (LBSL99, 1066 and 1074). A tabular summary of these trials can be found in the in Section 5. Since 1056 was a 76-week study, interim safety data from Week 53 through Week 76 as of the cut-off date June 25, 2009 were also provided. Additional interim long term safety data generated from the 24-week extension of LBSL02 and the ongoing open-label extension study LBSL99 were also provided as of the cut-off date March 6, 2009. Reports of serious adverse events that occurred in ongoing SLE trials (e.g., LBSL99, 1056, 1066 and 1074) after these cut-off dates through December 31, 2009 were also included in this submission.

The Applicant also provided safety data from the RA clinical development program (Studies LBRA01, LBRA99 and 1089) and five investigator-initiated trials (e.g., 2 trials in Sjogren's syndrome, 2 trials in pre-renal transplant desensitization and 1 trial in Waldenström's macroglobulinemia) that are only considered where pertinent in the discussion that follows.

Deaths and SAEs occurring January 1, 2010 through July 9, 2010 from ongoing trials in the SLE (LBSL99, 1056, 1066, 1074 and 1070) and RA (1089) belimumab clinical development plan as well as the 5 investigator-initiated trials with belimumab were submitted in the 120-day safety update on October 6, 2010 and are included in pertinent areas of the following discussion.

Safety data from the 17 studies were summarized in the individual trial reports, the Integrated Summary of Safety and the electronic datasets for adverse events, lab data and vital signs. All safety analyses were performed on the double-blind safety population from the 52-week trials (LBSL02, 1056 and 1057) and the single and multiple

dose Phase 1 and 2 studies and ongoing open label studies in SLE and RA conducted by the Applicant as well as the data from the investigator initiated studies and contained in the 120-day safety update were examined by this medical officer.

### 7.1.2 Categorization of Adverse Events

Verbatim terms of AEs recorded in the case report forms (CRF) by investigators was coded by the Applicant using MedDRA dictionary Preferred Term and System Organ Class (SOC) (version 12.0). A listing of all AEs coded in this manner including the corresponding verbatim terms was included in the CRF for review. The MedDRA coding of the information generated from clinical trials conducted by the applicant was generally acceptable. Additionally, the clinical lab and vital sign ranges for clinically significant abnormal results was reviewed and appeared to be appropriate.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This application contained 52-weeks of double-blind safety data generated from the following 3 trials: LBSL02, 1056 and 1057. These trials were of sufficiently similar design to allow for pooled analyses of the controlled safety data by treatment group. It should be noted, however, that the 4 mg/kg belimumab group was only present in Study LBSL02, which evaluated a somewhat different population of SLE patients (including approximately 30% ANA-negative patients) than did Studies 1056 and 1057. Analyses of the safety data were performed on the modified intention-to-treat (MITT) population which was defined as all patients who received at least 1 dose of study medication.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

At the time of data cut-off for the ongoing trials LBSL99 and 1056 (June 25, 2009), the extent of exposure to intravenous (IV) belimumab for the five multiple dosing SLE studies was as shown in Table 67 below. A total of 1,603 patients with SLE had been exposed to belimumab in these trials, out of which 946 patients had been treated with the to-be-marketed dose of 10 mg/kg. Approximately 828 of these subjects had received 10 mg/kg of belimumab for  $\geq 6$  months, 677 subjects for  $\geq 12$  months, and 73 patients  $\geq 24$  months. These numbers exceed minimum safety database recommendations for chronic use products as outlined in the ICH E1A guidance document.

Table 67 - Exposure to Belimumab in the IV SLE studies (LBSL01, LBSL02, LBSL99, 1056 & 1057)

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

<sup>1</sup>Duration is calculated as last infusion date – first infusion date = 28 days. A 3-month interval is defined as 13 weeks.

<sup>2</sup>Includes subjects who were randomized to the 10mg/kg group and subjects who switched to the 10mg/kg group. For subjects who switched to the 10mg/kg, exposure was calculated after their 1<sup>st</sup> dose of 10mg/kg belimumab treatment.

<sup>3</sup>In the “10mg/kg” column: Only the exposure to belimumab 10 mg/kg treatment was counted. In the “All Active column”: For patients who switched to belimumab 10 mg/kg group from belimumab 1 mg/kg or 4 mg/kg groups, the initial exposure to belimumab 1 mg/kg or 4 mg/kg treatment was counted in addition to the exposure to belimumab 10 mg/kg treatment.

Adapted Sponsor’s Table T5; Appendix 15 of the Summary of Clinical Safety.

## 7.2.2 Explorations for Dose Response

As part of their product development program for belimumab, the Applicant conducted a Phase 1, single and double dose-escalation study (LBSL01) and two Phase 2 multiple, repeat dose-ranging studies (LBRA01 and LBSL02) in order to identify an efficacious and safe dose of belimumab for evaluation in the pivotal Phase 3 trials. A clear dose response for safety or pharmacodynamic biomarkers (e.g., anti-dsDNA, ANA, complement, CD20+ and CD138+ peripheral B cells) was not observed in Study LBSL01 which evaluated 1, 4, 10 and 20 mg/kg doses of belimumab IV. Analysis of pharmacokinetic data from this trial also revealed that serum belimumab exposure following IV dosing was approximately dose proportional over the 20-fold dose range evaluated. In order to achieve steady state levels within the first month of dosing, a loading dose regimen (Days 0, 14, 28 and every 28 days thereafter) was selected by the Applicant for study in the Phase 2 studies LBRA01 and LBSL02 which also evaluated 1, 4, and 10 mg/kg doses of belimumab IV. A consistent dose response was also not observed in these 2 studies, however, post hoc analysis data from patients treated with the 10mg/kg dose of belimumab was suggestive of a faster onset of effect and greater reduction of corticosteroids in autoantibody positive SLE patients in LBSL02. Since data from the 6-month monkey toxicology study was also suggestive of a faster onset of effect with higher doses based on decreases in CD20+ and mature

CD20+/CD21+ peripheral B cells, the Applicant decided to further explore both the 1 mg/kg and 10 mg/kg doses in the Phase 3 trials since these doses were both shown to be biologically active and produced trough levels of belimumab in excess of BLYS concentrations in the peripheral circulation.

### 7.2.3 Special Animal and/or In Vitro Testing

The Applicant did not conduct any special animal and/or in vitro testing with belimumab to support its safety profile.

### 7.2.4 Routine Clinical Testing

The following clinical and lab testing were conducted in all the studies except where noted submitted in support of belimumab's safety profile:

- Symptom driven physical exam and weight
- Vital signs: systolic and diastolic blood pressure, respiratory rate (Study LBSL02 only), and temperature (Study LBSL02 only)
- Complete cell count (CBC) with differential and platelet count, hemoglobin and hematocrit; PT/PTT
- Serum chemistries; albumin, alkaline phosphatase, ALT, AST, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, lactic dehydrogenase, phosphorus, potassium, sodium, direct bilirubin, total bilirubin, and total protein
- Urinalysis: including pH, specific gravity, protein, glucose, ketones, nitrite, occult blood, bilirubin, urobilinogen
- Spot urine for protein to creatinine ratio
- Pregnancy testing
- Serum immunoglobulins (IgG, IgM and IgA), autoantibodies (ANA, anti-dsDNA, anti-Sm, aCI), serum complement (C3 and C4), CRP
- BLYS protein and immunogenicity
- FACS of peripheral lymphocytes (B cells: CD20+, CD20+/27-naïve, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27bright/38bright SLE subset and CD20-/138+ plasma cells) (T cells: CD3+/4+ and CD3+/8+)
- Pre- and post- vaccine antibody response; test for functional antibody to previous vaccines (Study 1056 only)
- Interferon expression signature

Overall, the types of clinical lab testing and physical assessments as well as the timing of these assessments were appropriate for the population studied in these trials.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this application since belimumab is a therapeutic biologic protein and is cleared via the reticuloendothelial system.

## 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable for this application since there are no other members of the B lymphocyte stimulator (BLyS) antagonist pharmacologic class currently marketed.

## 7.3 Major Safety Results

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

Table 68 - Summary of Adverse Events and Deaths in the Controlled 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
Number of Subjects with at Least 1 AE	624 (92%)	626 (93%)	107 (96%)	625 (93%)	1358 (93%)
Number of Subjects with At Least 1 Serious AE	107 (16%)	125 (19%)	15 (14%)	117 (17%)	257 (18%)
Number of Subjects with at Least 1 Infection	450 (67%)	478 (71%)	88 (79%)	471 (70%)	1037 (71%)
Number of Subjects with at Least 1 Serious Infection	35 (5%)	46 (7%)	7 (6%)	35 (5%)	88 (6%)
Number of Subjects with at Least 1 Malignancy	3 (0.4%)	3 (0.4%)	0	3 (0.4%)	6 (0.4%)
Number of Subjects with at Least 1 AE Leading to Dosing Interruption	85 (13%)	86 (13%)	25 (23%)	91 (14%)	202 (14%)
Number of Subjects with at Least 1 AE Leading to Discontinuation	48 (7%)	42 (6%)	4 (4%)	45 (7%)	91 (6%)
Deaths	3 (0.4%)	6* (0.9%)	--	6 (0.9%)	12 (0.8%)

Source: Table 2.7.4-8 of Summary of Clinical Safety

\*One SLE -related death occurred more than 15 weeks after patients' last dose of belimumab—per Sponsor's AC briefing document.

### 7.3.1 Deaths

There were 14 deaths reported in the controlled period of the IV SLE trials, with one additional death occurring in a patient 15 weeks post treatment discontinuation, for a total of 15 deaths, as follows: 3 patients died of cardiovascular (including stroke) events, 5 patients died of infectious etiologies, 2 patients committed suicide, 2 patients died of unknown causes, 2 patients died of SLE-related complications, and 1 patient died of a malignancy. Table 69 below lists these 15 deaths and the 15 deaths that occurred in the open-label extension studies and RA clinical development program, by treatment group.

Table 69 - Deaths in the SLE Studies

Subject Number	Age/Sex	Cause of Death	Days Since 1 <sup>st</sup> Infusion	Days Since Last Infusion	Pertinent History
<b>Placebo</b>					
CL002-001	45yo/F	Myocardial Infarction	328	19	Presented to ER with new onset chest and epigastric pain and had a cardiopulmonary arrest.
CO001-016	25yo/F	Cardiac Arrest Secondary to Sepsis	70	11	Concomitant Meds: Prednisolone, methotrexate, diclofenac and ibuprofen. Developed bacterial gastroenteritis and dehydration complicated by vasculitis and became septic (blood culture positive for Staph. Saprophyticus) despite antibiotics and supportive medical care.
IN005-015	18yo/F	Unknown	225	84	Hospitalized 2 months prior to death for acute abdominal pain secondary to portal/mesenteric/renal vein and vena cava thrombosis and acute pancreatitis.
<b>Belimumab 1 mg/kg</b>					
US034-002	43yo/F	Suicide	32	20	H/O Depression on antidepressant (citalopram). Reported to have worsening depression prior to committing suicide
US014-006	46yo/F	Unknown	56	28	H/O Asthma, clostridial gastroenteritis, eosinophilia and QT prolongation on EKG. Concomitant Meds: ibuprofen, hydroxychloroquine, mycophenolate, prednisone and lisinopril. Pt. developed nausea, vomiting and weakness while camping and was found to be dehydrated due to unspecified gastrointestinal illness at local ER where she died despite resuscitative measures.
JS042-006	52yo/F	Ovarian Cancer	21	7	Positive family H/O ovarian cancer. H/O Vaginal bleeding prior to study entry that evolved to include left lower abdominal pain, vaginal pain, pelvic cramping and diarrhea by the 9 <sup>th</sup> dose of study medication that was followed by a diagnosis of advanced ovarian cancer on laparotomy.
AR005-006	32yo/F	Sepsis Secondary to Cellulitis	13	13	Concomitant Meds: Methylprednisolone, mycophenolate, thalidomide, and ibuprofen. Developed cellulitis and died as a result of sepsis despite antibiotics and supportive medical care.
RU005-010	58yo/F	Ischemic Stroke	345	34	H/O hypertension. Anti-cardiolipin antibody negative at screening. Concomitant meds: Prednisolone, hydroxychloroquine, bioprolol.
CL001-007	25yo/F	Respiratory Failure/SLE Flare	216	104	Patient died due to respiratory arrest more than 15 weeks after the patient discontinued the trial due to acute renal failure. Post study withdrawal, the patient was hospitalized and experienced oligouria, uremic syndrome, sepsis, polyserositis, ascites, intestinal edema, anemia, and alveolar hemorrhage.

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

Table 69- Deaths in the SLE Studies (conti.)

Subject Number	Age/Sex	Cause of Death	Days Since 1 <sup>st</sup> Infusion	Days Since Last Infusion	Pertinent History
<b>Belimumab 10 mg/kg</b>					
US041-013	40yo/F	Respiratory Failure Secondary to Sepsis	257	33	Pt. developed aspiration pneumonia status post seizure, became septic and died due to respiratory failure despite antibiotics and aggressive supportive medical care (respirator).
MX001-005	47yo/F	Cardiac Arrest (SLE Flare)	77	21	H/O Diabetes mellitus, pericardial excision, serositis, antiphospholipid syndrome, pulmonary hypertension, and heart failure. Concomitant Meds: Azathioprine, methotrexate and prednisone. Hospitalized after c/o severe headache with vomiting associated with fever, chills and productive cough with bilateral pleural effusions and lymphopenia attributed to SLE flare with CNS involvement. She was treated with corticosteroids and NSAIDs but died due to cardiac arrest.
CL001-024	53yo/F	Bacterial Sepsis	331	25	H/O Obesity, pulmonary fibrosis. Developed septic shock (blood cultures positive for MRSA) and multi-organ failure secondary to infected herpes zoster lesions despite antibiotics. Concomitant meds: Methylprednisolone, azathioprine, chloroquine, salbutamol, acenocoumarol, sertraline, and omeprazole
IN004-002	20yo/F	Infectious Diarrhea	336	28	Had SLE flare with cutaneous vasculitis and hypochromic anemia. Started on antibiotics and increased corticosteroids but developed infectious diarrhea and died en route to hospital. Concomitant meds: Prednisolone, azathioprine, hydroxychloroquine, levofloxacin, iron, ciprofloxin/tinidazole, and fluconazole.
KR008-001	23yo/F	Suicide		(b) (6)	H/O Depressed mood and psychotic disorder; autoimmune thyroiditis, and drug-induced hepatitis. Committed suicide following conflict with parent. Concomitant meds: methylprednisone, azathioprine, hydroxychloroquine, meloxicam, levothyroxine, and rebamipide
PE002-001	33yo/F	Respiratory Failure From Presumed Pulmonary Embolus	128	8	H/O chronic cholecystitis. Pt. developed dyspnea eight days after her last study infusion and died en route to the hospital. (No autopsy.) Concomitant meds: Prednisone, levothyroxine, and ceftriaxone.

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

Table 69 - Deaths in the SLE Studies (conti.)

Subject Number	Age/Sex	Cause of Death	Days Since 1 <sup>st</sup> Infusion	Days Since Last Infusion	Pertinent History
<b>OLE Trial LBSL99 (Belimumab 10 mg/kg)</b>					
US023-005	65yo/F	Suicide	200	25	H/O Hypertension, fibromyalgia, insomnia and ruptured cerebral aneurysm. Negative history of depression. Death attributed to oxycodone and alcohol intoxication. Concomitant meds: Hydroxychloroquine, valsartan, HCTZ, celecoxib, oxycodone, cyclobenzaprine, trazadone, and APAP/codeine.
US032-002	64yo/F	CMV pneumonia	703	32	Diagnosed with pulmonary fibrosis and pneumonitis. Pt. developed pneumonia secondary to CMV and died despite antivirals, antibiotics, and steroids. Concomitant meds: methotrexate, leflunomide, hydroxychloroquine and prednisone.
US062-002	52yo/F	Coronary atherosclerotic heart disease	44	9	H/O Cardiomyopathy, CHF, CAD, CVA, TIA, hypertension and S/P mitral valve replacement. Pt. found dead in bed. Autopsy listed cause of death as coronary artery arteriosclerosis.
US016-007	71yo/M	Cerebral Hemorrhage	1412	424	H/O Hypertension, seizure disorder, ascending aortic aneurysm chronic diarrhea, anemia, colon CA and S/P right colectomy. Pt. developed a fatal cerebral hemorrhage secondary to head trauma sustained in fall following surgery and died. Concomitant meds: Prednisone, hydroxychloroquine, amlodipine, valsartan, atenolol furosemide, levetiracetam and doxazosin.
<b>OLE Trials 1074 and 1066</b>					
BR002-002	31yo/F	Bronchopneumonia	67	4	H/O Hypertension. Four days after last study infusion was hospitalized for bronchopneumonia. Developed worsening shortness of breath and died. Concomitant meds: Prednisone, captopril, nifedipine and atenolol.
TW011-017	30yo/F	Pulmonary hemorrhage	101	13	H/O Renal failure secondary to lupus nephritis (class V, stage II), nephritic syndrome, renal vein thrombosis, hypertension. Pt. was hospitalized for worsening renal failure and went on to develop multiple fungal and bacterial infections that resulted in septic shock, multiorgan failure and death despite aggressive medical care, hemodialysis, mechanical ventilation and antibiotics.
PH004-002	23yo/F	Septic Shock	~1.8 years	48	Presented to ER with worsening dyspnea and renal failure, ultimately requiring mechanical ventilation and dialysis. Patient developed hypotension, necrotic vasculitic lesions, and worsening lupus nephritis, followed by multi-organ failure, with positive cultures.
RO007-003	43yo/F	TTP	~2 years		Patient presented with new onset aphasia and confusion, diagnosed with acute neuropsychiatric syndrome, concurrent with severe thrombocytopenia, thrombotic thrombocytopenic purpura, and hemolytic anemia. Patient died of multi-organ failure
PH001-004	39yo/F	Pneumonia	2.2 years	29	Worsening month-long community acquired pneumonia, complicated by DIC, pulmonary embolism and SLE flare (myocarditis, hemolytic anemia, nephritis, and peripheral vasculitis). Concomitant meds: Prednisone.

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

Table 69 - Deaths in the SLE Studies (conti.)

Subject Number	Age/Sex	Cause of Death	Days Since 1 <sup>st</sup> Infusion	Days Since Last Infusion	Pertinent History
<b>OLE Trials 1074 and 1066 (cont.)</b>					
US018-003	69yo/M	Cardiovascular Disease	1.9 years	29	Found unconscious at home, diagnosed with metabolic encephalopathy. Hospitalized with improvement and discharged to skilled nursing facility. Eighteen days after hospital discharge patient was found dead in his apartment. Cardiovascular disease noted on autopsy.
<b>RA Studies: Placebo</b>					
US004-003	51yo/F	Cardiac Arrest	105	22	H/O Hypercholesterolemia, diabetes mellitus, hypothyroidism. Positive family H/O heart disease. Concomitant meds: Auranofin, prednisone, insulin, estrogen, and levothyroxine. Pt. was found dead at home after having 'chest discomfort' for a few days. (No autopsy.)
<b>RA Studies 10mg/kg</b>					
US007-004	51yo/M	Pneumonia	286	176	H/O COPD and pulmonary fibrosis. Concomitant meds: Leflunomide, albuterol, diazepam, carbamazepine, methadone, olanzapine, Phenobarbital, diazepam, tramadol, cyclobenzaprine, exomeprazole and trihexyphenidyl. Pt. died of pneumonia at another hospital.
US040-004	67yo/F	Respiratory Failure	1211	9	H/O COPD, dyspnea on exertion, angina, and coronary artery arteriosclerosis. Pt. developed aspiration pneumonia, pulmonary edema, atelectasis, pleural effusion and sepsis following surgery to repair a hiatal hernia. Died due to worsening respiratory failure.
US016-008	61yo/M	Coronary Artery Thrombosis	46	20	H/O COPD, deep vein thrombosis, pericarditis and vasculitis. Concomitant meds: methotrexate, leflunomide, prednisone, chlorpheniramine, and hydrocodone. Pt found dead attributed to acute coronary artery thrombosis on autopsy.
US016-004	49yo/M	Coronary Artery Disease	1521	219	H/O hypothyroidism, kidney stones and migraines. Concomitant meds: Prednisone, pantoprazole and levothyroxine. Pt. found dead attributed to coronary artery disease on autopsy.

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

Based on 14 deaths observed in the controlled period of the IV SLE clinical trials, and one death occurring 15 weeks after patient withdrawal, the death incidence rate per 100 subject-years was almost twice as high for belimumab as for placebo treated subjects, as shown in Table 70. Although the types of death are consistent with immunosuppressive therapies and with the risks related to the underlying and concomitant medical conditions, the apparent increased mortality risk with belimumab remains concerning, particularly in light of the marginal efficacy observed. Even if the single patient who died 15 weeks post study withdrawal was removed from the exposure-adjusted analysis, the mortality rate with belimumab remains much higher

than for the placebo group (0.73/100 pt-years). However, the confidence intervals for the point estimates for death for the placebo and belimumab treatment groups overlap suggesting that there may be no real difference between the two groups. Additionally both of these exposure-adjusted mortality rates are lower than what has been reported in the literature for SLE patients (1.63/100 pt-years) by Bernatsky et al<sup>4</sup> which suggests that the increased magnitude of this finding may be lower than perceived.

**Table 70 - Exposure-Adjusted Incidence of Death in the Studies LBSL02, 1056, and 1057**

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

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

Analyses that incorporate the uncontrolled-long term extension data are difficult to interpret, given that there may be unquantifiable survival bias related to patients who are in the best condition or tolerating treatment the best remaining in long-term follow-up. Therefore only the exposure-adjusted incidence from the controlled period of the studies is presented here.

### 7.3.2 Nonfatal Serious Adverse Events

Table 71 is an abridged summary of the serious adverse events (SAE) observed during the controlled IV SLE studies. Overall, the proportions of patients who had a SAE were similar for the placebo and belimumab treatment groups with a slightly higher number of SAEs reported in the belimumab 1 mg/kg group. Numeric imbalances in the number of SAEs were noted, with a higher incidence in the 10 mg/kg belimumab treatment group as compared to placebo in the following system organ classes: Blood and Lymphatic System disorders, General Disorders and Administration Site Conditions, Immune System Disorders, Infections and Infestations, Nervous System Disorders, Pregnancy, Puerperium and Perinatal Conditions, Psychiatric Disorders, Renal and Urinary disorders, Reproductive System and Breast Disorders, and Vascular Disorders. Serious adverse events related to infections, immune system, nervous and psychiatric disorders are discussed separately in other sections of this review.

<sup>4</sup> Bernatsky S, Boivin JF, Joseph L, et al. Mortality in Systemic Lupus Erythmetosus. *Arth Rheu* 2006;54(8):2550-7.

Table 71 - Serious Adverse Events in Studies LBSL02, 1056 and 1057

MedDRA System Organ Class	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=674	Total Belimumab N= 1458
<b>Number of Subjects with ≥ 1 SAE: Exposure-Adjusted Incidence<sup>1</sup> per 100 patient-years</b>	<b>107 (16%) 15.9</b>	<b>125 (19%)</b>	<b>15 (14%)</b>	<b>117 (17%)</b>	<b>257 (18%) 17.4</b>
<b>Blood and Lymphatic System Dis.:</b>	<b>7 (1%)</b>	<b>4 (1%)</b>	<b>0</b>	<b>11 (2%)</b>	<b>15 (1%)</b>
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%)
<b>Cardiac Disorders</b>	<b>13 (2%)</b>	<b>6 (1%)</b>	<b>2 (2%)</b>	<b>11 (2%)</b>	<b>19 (1.3%)</b>
<b>Ear and Labyrinth Disorders</b>	<b>0</b>	<b>1 (0.1%)</b>	<b>0</b>	<b>0</b>	<b>1 (0.07%)</b>
<b>Endocrine Disorders:</b>	<b>0</b>	<b>2 (0.3%)</b>	<b>0</b>	<b>1 (0.1%)</b>	<b>3 (0.2%)</b>
Hypothyroidism	0	2 (0.3%)	0	0	2 (0.1%)
Adrenal Insufficiency	0	0	0	1 (0.1%)	1 (0.1%)
<b>Eye Disorders</b>	<b>0</b>	<b>2 (0.3%)</b>	<b>0</b>	<b>1 (0.1%)</b>	<b>3 (0.2%)</b>
<b>Gastrointestinal Disorders</b>	<b>17 (3%)</b>	<b>13 (2%)</b>	<b>3 (3%)</b>	<b>10 (2%)</b>	<b>26 (2%)</b>
<b>General Disorders and Administrative Site Conditions:</b>	<b>13 (2%)</b>	<b>10 (2%)</b>	<b>0</b>	<b>17 (3%)</b>	<b>27 (2%)</b>
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%)
<b>Hepatobiliary Disorders:</b>	<b>6 (1%)</b>	<b>8 (1%)</b>	<b>2 (2%)</b>	<b>5 (1%)</b>	<b>15 (1%)</b>
<b>Immune System Disorders:</b>	<b>1 (0.1%)</b>	<b>2 (0.3%)</b>	<b>0</b>	<b>2 (0.3%)</b>	<b>4 (0.3%)</b>
Anaphylactic Reaction	0	2 (0.3%)	0	1 (0.1%)	3 (0.2%)
Drug Hypersensitivity	0	0	0	1 (0.1%)	1 (0.1%)
<b>Infections and Infestations:</b>	<b>35 (5%)</b>	<b>46 (7%)</b>	<b>7 (6%)</b>	<b>35 (5%)</b>	<b>88 (6.0%)</b>
<b>Injury, Poisoning and Procedural Complications</b>	<b>7 (1%)</b>	<b>6 (1%)</b>	<b>3 (3%)</b>	<b>7 (1%)</b>	<b>16 (1%)</b>
<b>Investigations</b>	<b>1 (0.1%)</b>	<b>0</b>	<b>0</b>	<b>3 (0.4%)</b>	<b>3 (0.2%)</b>
<b>Metabolism and Nutrition Disorders</b>	<b>3 (0.4%)</b>	<b>3 (0.4%)</b>	<b>0</b>	<b>1 (0.1%)</b>	<b>4 (0.3%)</b>

Modified Sponsor's Table T62; Appendix 15 of the Summary of Clinical Safety.

<sup>1</sup>Exposure is 672.3 subject-years for placebo and 1472.9 subject-years for combined belimumab groups

Table 71 - Serious Adverse Events in Studies LBSL02, 1056 and 1057 (conti.)

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
<b>Number of Subjects with ≥ 1 SAE: Exposure-Adjusted Incidence<sup>1</sup> per 100 patient-years</b>	<b>107 (16%) 15.9</b>	<b>125 (19%)</b>	<b>15 (14%)</b>	<b>117 (17%)</b>	<b>257 (18%) 17.4</b>
<b>Musculoskeletal and Connective Tissue Disorder</b>	<b>14 (2%)</b>	<b>16 (2%)</b>	<b>1 (1%)</b>	<b>13 (2%)</b>	<b>30 (2%)</b>
<b>Neoplasms Benign, Malignant and Unspecified (incl. cysts/polyps)</b>	<b>3 (0.4%)</b>	<b>5 (1%)</b>	<b>0</b>	<b>1 (0.1%)</b>	<b>6 (0.4%)</b>
<b>Nervous System Disorders:</b>	<b>8 (1%)</b>	<b>10 (2%)</b>	<b>1 (1%)</b>	<b>16 (2%)</b>	<b>27 (2%)</b>
<b>Pregnancy, Puerperium and Perinatal Conditions:</b>	<b>1 (0.1%)</b>	<b>2 (0.2%)</b>	<b>0</b>	<b>5 (1%)</b>	<b>7 (0.5%)</b>
Abortion Spontaneous	1 (0.1%)	1(0.1%)	0	5 (1%)	6 (0.4%)
Pregnancy	0	1 (0.1%)	0	0	1 (0.1%)
<b>Psychiatric Disorders</b>	<b>3 (0.4%)</b>	<b>4 (1%)</b>	<b>0</b>	<b>8 (1%)</b>	<b>12 (0.8%)</b>
<b>Renal and Urinary Disorders:</b>	<b>12 (2%)</b>	<b>9 (1%)</b>	<b>0</b>	<b>14 (2%)</b>	<b>23 (1.6%)</b>
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
<b>Reproductive System and Breast Disorders:</b>	<b>5 (1%)</b>	<b>3 (0.4%)</b>	<b>0</b>	<b>7 (1%)</b>	<b>10 (0.7%)</b>
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%)
Cervical 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%)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	<b>11 (2%)</b>	<b>7 (1%)</b>	<b>1 (1%)</b>	<b>8 (1%)</b>	<b>16 (1.1%)</b>

Modified Sponsor's Table T62; Appendix 15 of the Summary of Clinical Safety.

<sup>1</sup>Exposure is 672.3 subject-years for placebo and 1472.9 subject-years for combined belimumab groups

**Table 71 - Serious Adverse Events in Studies LBSL02, 1056 and 1057 (conti.)**

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
<b>Number of Subjects with ≥ 1 SAE: Exposure-Adjusted Incidence<sup>1</sup> per 100 patient-years</b>	<b>107 (16%) 15.9</b>	<b>125 (19%)</b>	<b>15 (14%)</b>	<b>117 (17%)</b>	<b>257 (18%) 17.4</b>
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>6 (1%)</b>	<b>5 (1%)</b>	<b>0</b>	<b>5 (1%)</b>	<b>10 (0.7%)</b>
<b>Surgical and Medical Procedures</b>	<b>1 (0.1%)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Vascular Disorders:</b>	<b>7 (1%)</b>	<b>6 (1%)</b>	<b>2 (2%)</b>	<b>11(2%)</b>	<b>19 (1.3%)</b>
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.

<sup>1</sup>Exposure is 672.3 subject-years for placebo and 1472.9 subject-years for combined belimumab groups

It should be noted that many of the SAEs seen in the Blood and Lymphatic System Disorders, Renal and Urinary Disorders and Vascular Disorders SOC are of the type that are known to occur with the underlying disease of SLE (i.e., anemias, leukopenias, lymphopenias, thrombocytopenias, lupus nephritis, glomerulonephritis, proteinuria, thrombotic and embolic events), thus their occurrence is not unexpected. The higher rates of SAEs observed in the Pregnancy, Puerperium and Perinatal Conditions and Reproductive System and Breast Disorders is not unexpected since the majority of the subjects who participated in these trials are female and of childbearing potential.

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

Table 72 lists SAEs that occurred in ≥ 5 subjects treated with belimumab during the controlled IV SLE trials. Pyrexia, urinary tract infection, lupus nephritis, cholelithiasis, cellulitis, and anemia were the most commonly observed SAEs in patients who received

belimumab in these trials. As noted previously, the majority of these SAEs could have been related to underlying SLE disease activity or as a result of infections.

Table 72 - 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
<b>Number of Subjects with at Least 1SAE</b>	<b>107 (16%)</b>	<b>125 (19%)</b>	<b>15 (14%)</b>	<b>117 (17%)</b>	<b>257 (18%)</b>
Pyrexia	3 (0.4%)	5 (0.7%)	0	9 (1.3%)	14 (1.0%)
Urinary Tract Infection	4 (0.6%)	7 (1.0%)	1 (0.9%)	5 (0.7%)	13 (0.9%)
Lupus Nephritis	5 (0.7%)	5 (0.7%)	0	6 (0.9%)	11 (0.8%)
Cholelithiasis	4 (0.6%)	5 (0.7%)	2 (1.8%)	2 (0.3%)	9 (0.7%)
Cellulitis	2 (0.2%)	7 (1.0%)	1 (0.9%)	1 (0.1%)	8 (0.5%)
Anemia	1 (0.1%)	2 (0.3%)	0	6 (0.9%)	8 (0.5%)
Infusion Related Reaction	2 (0.2%)	2 (0.3%)	0	4 (0.4%)	6 (0.4%)
Bronchitis	1 (0.1%)	2 (0.3%)	1 (0.9%)	3 (0.4%)	6 (0.4%)
Depression	1 (0.1%)	3 (0.4%)	0	3 (0.4%)	6 (0.4%)
SLE Arthritis	2 (0.2%)	1 (0.1%)	0	4 (0.6%)	5 (0.3%)
Abortion Spontaneous	1 (0.1%)	1 (0.1%)	0	4 (0.6%)	5 (0.3%)
Osteonecrosis	1 (0.1%)	4 (0.6%)	0	1 (0.1%)	5 (0.3%)

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

Overall there was a numeric imbalance, with a higher incidence of SAE occurring with belimumab treatment compared to placebo. Although there are confounding factors, such as less duration of exposure with placebo (e.g., due to drop-out), it is not possible to rule out inherent toxicities associated with belimumab treatment played a major factor in the increased risk observed. No other safety signals were identified on review of the data collected from the on-going open-label extension (OLE) studies in SLE, the Phase 1 SLE trials or the RA development program.

### 7.3.3 Dropouts and/or Discontinuations

Table 73 is an abridged summary of adverse events by system organ class and preferred term that resulted in patients discontinuing from the controlled SLE studies LBSL02, 1056, and 1057. Overall, the proportions of patients who discontinued due to an AE were comparable for the placebo and belimumab 1 mg/kg and 10 mg/kg treatment groups with fewer patients discontinuing study treatment in the 4 mg/kg group as a result of an adverse event. Renal and Urinary Disorders, Nervous System Disorders, Infections and Infestations, Skin and Subcutaneous Tissue and General Disorders and Administrative Site Conditions were the most common types of adverse events resulting in patients withdrawing from these studies. The higher rate of discontinuations from study treatment seen in the Renal and Urinary Disorders was due to flares of lupus nephritis which occurred more frequently in the placebo group as

compared to the belimumab treatment groups. Similarly, the higher rate of study discontinuation observed in the Skin and Subcutaneous Tissue Disorders was primarily due to skin manifestations of patients' underlying disease. The higher rate of withdrawal due to Nervous System Disorders is attributable to single cases of adverse events that did not appear to comprise a pattern. Withdrawals due to infection are an expected finding in clinical trials evaluating immunosuppressive therapies. Review of study withdrawal data due to adverse events from the on-going OLE studies and other trials conducted with belimumab did not identify any other safety concerns.

Table 73 - 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
<b>Number of Subjects with ≥ 1 AE Leading to Discontinuation:</b>	<b>48 (7%)</b>	<b>42 (6%)</b>	<b>4 (4%)</b>	<b>45 (7%)</b>	<b>91 (6%)</b>
<b>Blood and Lymphatic System Dis.</b>	4 (0.6%)	0	0	0	0
<b>Cardiac Disorders:</b>	3 (0.4%)	1 (0.1%)	0	3 (0.4%)	4 (0.3%)
Myocardial Infarction	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Cardiac Arrest	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Bradycardia	0	1 (0.1%)	0	0	1 (0.1%)
Pericarditis Lupus	0	0	0	1 (0.1%)	1 (0.1%)
<b>Eye Disorders:</b>	0	1 (0.1%)	0	0	1 (0.1%)
Ocular Vasculitis	0	1 (0.1%)	0	0	1 (0.1%)
<b>Gastrointestinal Disorders:</b>	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Dysphagia	0	0	0	1 (0.1%)	1 (0.1%)
<b>General Disorders and Administrative Site Conditions:</b>	3 (0.4%)	4 (0.6%)	0	5 (0.7%)	9 (0.6%)
Infusion Related Reaction	1 (0.1%)	2 (0.3%)	0	5 (0.7%)	7 (0.5%)
Pyrexia	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)
Death	0	1 (0.1%)	0	0	1 (0.1%)
<b>Hepatobiliary Disorders:</b>	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Cholelithiasis	0	0	1 (0.1%)	0	1 (0.1%)
<b>Immune System Disorders:</b>	0	3 (0.4%)	0	2 (0.3%)	5 (0.3%)
Anaphylactic Reaction	0	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Drug Hypersensitivity	0	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Hypogammaglobulinemia	0	1 (0.1%)	0	0	1 (0.1%)
<b>Infections and Infestations:</b>	7 (1.0%)	5 (0.7%)	1 (0.9%)	4 (0.6%)	10 (0.7%)
Pneumonia	0	2 (0.3%)	0	1 (0.1%)	3 (0.3%)
Urinary Tract Infection	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Erysipelas	1 (0.1%)	1 (0.1%)	0	0	1 (0.1%)
Furuncle	0	0	0	1 (0.1%)	1 (0.1%)
Herpes Zoster	0	0	0	1 (0.1%)	1 (0.1%)
Kidney Infection	0	0	0	1 (0.1%)	1 (0.1%)
Sepsis	0	1 (0.1%)	0	0	1 (0.1%)
Septic Arthritis Streptococcal	0	1 (0.1%)	0	0	1 (0.1%)
<b>Injury, Poisoning and Procedural Complications:</b>	0	0	1 (0.9%)	0	1 (0.1%)
Road Traffic Accident	0	0	1 (0.9%)	0	1 (0.1%)

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

Table 73 - Discontinuations due to Adverse Events in Studies LBSL02, 1056, and 1057 (conti.)

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
<b>Number of Subjects with ≥ 1 AE Leading to Discontinuation:</b>	<b>48 (7%)</b>	<b>42 (6%)</b>	<b>4 (4%)</b>	<b>45 (7%)</b>	<b>91 (6%)</b>
<b>Investigations:</b>	0	1 (0.1%)	0	3 (0.4%)	4 (0.3%)
Alanine Aminotransferase Increased	0	0	0	1 (0.1%)	1 (0.1%)
Hepatic Enzyme Increased	0	1(0.1%)	0	0	1 (0.1%)
Weight Decreased	0	0	0	1 (0.1%)	1 (0.1%)
Weight Increased	0	0	0	1 (0.1%)	1 (0.1%)
<b>Musculoskeletal and Connective Tissue Disorder:</b>	5 (0.7%)	2 (0.3%)	0	1 (0.1%)	3 (0.2%)
SLE Arthritis	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)
Myalgia	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Osteonecrosis	0	1 (0.1%)	0	0	1 (0.1%)
<b>Neoplasms Benign, Malignant and Unspecified (incl. cysts/polyps):</b>	1 (0.1%)	2 (0.3%)	0	0	2 (0.1%)
Breast Cancer	0	1 (0.1%)	0	0	1 (0.1%)
Cervix Carcinoma Stage 0	0	1 (0.1%)	0	0	1 (0.1%)
<b>Nervous System Disorders:</b>	4 (0.4%)	5 (0.7%)	0	6 (0.9%)	11 (0.8%)
Headache	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Convulsion	0	0	0	1 (0.1%)	1 (0.1%)
Ischemic Stoke	0	1 (0.1%)	0	0	1 (0.1%)
Lupus Encephalitis	0	0	0	1 (0.1%)	1 (0.1%)
Myasthenia Gravis	0	0	0	1 (0.1%)	1 (0.1%)
Myelitis Transverse	0	1 (0.1%)	0	0	1 (0.1%)
Neuritis	0	1 (0.1%)	0	0	1 (0.1%)
Neuropsychiatric Lupus	0	0	0	1 (0.1%)	1 (0.1%)
Peripheral Sensory Neuropathy	0	1 (0.1%)	0	0	1 (0.1%)
Transient Ischemic Attack	0	0	0	1 (0.1%)	1 (0.1%)
<b>Pregnancy, Puerperium and Perinatal Conditions:</b>	2 (0.3%)	2 (0.3%)	0	1 (0.1%)	3 (0.2%)
Pregnancy	1 (0.1%)	2 (0.3%)	0	1 (0.1%)	3 (0.2%)
<b>Psychiatric Disorders:</b>	0	1 (0.1%)	0	2 (0.3%)	3 (0.2%)
Mania	0	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Completed Suicide	0	0	0	1 (0.1%)	1 (0.1%)
<b>Renal and Urinary Disorders:</b>	8 (1.2%)	6 (0.9%)	0	8 (1.2%)	14 (1%)
Lupus Nephritis	8 (1.2%)	4 (0.6%)	0	6 (0.9%)	10 (0.7%)
Nephropathy	0	1 (0.1%)	0	0	1 (0.1%)
Nephrotic Syndrome	0	0	0	1 (0.1%)	1 (0.1%)
Proteinuria	0	0	0	1 (0.1%)	1 (0.1%)
Renal Failure Acute	0	1 (0.1%)	0	0	1 (0.1%)
<b>Reproductive System and Breast Disorders:</b>	0	1 (0.1%)	0	0	1 (0.1%)
Cervical Dysplasia	0	1 (0.1%)	0	0	1 (0.1%)
<b>Respiratory, Thoracic and Mediastinal Disorders:</b>	2 (0.3%)	2 (0.3%)	0	4 (0.6%)	6 (0.45)
Pleurisy	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Respiratory Failure	0	0	0	2 (0.3%)	2 (0.2%)
Acute Respiratory Distress Syndrome	0	1 (0.1%)	0	0	1 (0.1%)
Dyspnea	0	0	0	1 (0.1%)	1 (0.1%)

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

Table 73 - Discontinuations due to Adverse Events in Studies LBSL02, 1056, and 1057 (conti.)

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
<b>Number of Subjects with ≥ 1 AE Leading to Discontinuation:</b>	<b>48 (7%)</b>	<b>42 (6%)</b>	<b>4 (4%)</b>	<b>45 (7%)</b>	<b>91 (6%)</b>
<b>Skin and Subcutaneous Tissue Disorders:</b>	6 (0.9%)	3 (0.4%)	1 (0.9%)	5 (0.7%)	9 (0.6%)
Angioedema	0	1 (0.1%)	1 (0.9%)	1 (0.1%)	3 (0.2%)
Systemic Lupus Erythematosus Rash	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Eczema	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Cutaneous Lupus Erythematosus	0	0	0	1 (0.1%)	1 (0.1%)
Pruritus	0	1 (0.1%)	0	0	1 (0.1%)
Pruritus Allergic	0	0	0	1 (0.1%)	1 (0.1%)
Skin Ulcer	0	0	0	0	0
<b>Vascular Disorders:</b>	1 (0.1%)	4 (0.6%)	0	0	4 (0.3%)
Vasculitis	1 (0.1%)	2 (0.1%)	0	0	2 (0.1%)
Aortic Dissection	0	1 (0.1%)	0	0	1 (0.1%)
Hypertension	0	1 (0.1%)	0	0	1 (0.1%)

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

### 7.3.4 Significant Adverse Events

Table 74 is a tabular listing of adverse events observed during the controlled studies 1056, 1057 and LBSL02 by treatment arm that were rated as severe in nature by study investigators. The most common severe adverse events during these controlled trials as compared to placebo were: headache (1.2% for total belimumab versus for 0.9% placebo), pneumonia (0.7% for total belimumab versus for 0.4% for placebo), anemia (0.5% for total belimumab versus for 0.7% placebo), lupus nephritis (0.5% for total belimumab versus for 0.4% for placebo), neutropenia (0.5% for total belimumab versus 0.2% for placebo), leukopenia (0.5% for total belimumab versus 0.1% for placebo) and myalgia (0.5% for total belimumab versus 0.1% for placebo). No safety signals were identified on review of severity data from the other studies included in the belimumab safety database.

Table 74 – Tabular Summary of Number (%) of Subjects with Severe Adverse Reactions Reported by ≥ 3 Belimumab-Treated Patients in the Pooled Studies 1056, 1057 and LBSL02

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
Headache	6 (0.9%)	5 (0.7%)	4 (3.6%)	8 (1.2%)	17 (1.2%)
Pneumonia	3 (0.4%)	6 (0.9%)	1 (0.9%)	3 (0.4%)	10 (0.7%)
Abdominal Pain	6 (0.9%)	3 (0.4%)	0	3 (0.4%)	6 (0.4%)
Anemia	5 (0.7%)	2 (0.3%)	2 (1.8%)	3 (0.4%)	7 (0.5%)
Lupus Nephritis	3 (0.4%)	4 (0.6%)	0	3 (0.4%)	7 (0.5%)
Proteinuria	6 (0.9%)	1 (0.1%)	1 (0.9%)	2 (0.3%)	4 (0.3%)
Neutropenia	2 (0.3%)	2 (0.3%)	1 (0.9%)	4 (0.6%)	7 (0.5%)
Urinary Tract Infection	4 (0.6%)	3 (0.4%)	0	2 (0.3%)	5 (0.3%)
Arthralgia	2 (0.3%)	1 (0.1%)	1 (0.9%)	4 (0.6%)	6 (0.4%)
Fatigue	4 (0.6%)	1 (0.1%)	1 (0.9%)	2 (0.3%)	4 (0.3%)
Leukopenia	1 (0.1%)	2 (0.3%)	2 (1.8%)	3 (0.4%)	7 (0.5%)
Myalgia	1 (0.1%)	4 (0.6%)	0	3 (0.4%)	7 (0.5%)
Thrombocytopenia	2 (0.3%)	3 (0.4%)	0	3 (0.4%)	6 (0.4%)
Vomiting	3 (0.4%)	3 (0.4%)	1 (0.9%)	1 (0.1%)	5 (0.3%)
Back Pain	1 (0.1%)	2 (0.3%)	1 (0.9%)	0	3 (0.2%)
Dyspnea	1 (0.1%)	1 (0.1%)	1 (0.9%)	1 (0.1%)	3 (0.2%)
Pyrexia	2 (0.3%)	0	0	6 (0.9%)	6 (0.4%)
SLE Arthritis	3 (0.4%)	3 (0.4%)	0	2 (0.3%)	5 (0.3%)
Bronchitis	4 (0.6%)	0	1 (0.9%)	3 (0.4%)	4 (0.3%)
Dehydration	5 (0.7%)	2 (0.3%)	0	2 (0.3%)	4 (0.3%)
Infusion Related Reaction	1 (0.1%)	2 (0.3%)	0	3 (0.4%)	5 (0.3%)
Cholethiasis	2 (0.3%)	1 (0.1%)	0	2 (0.3%)	3 (0.2%)
Depression	0	3 (0.4%)	0	2 (0.3%)	5 (0.3%)
Herpes Zoster	2 (0.3%)	1 (0.1%)	0	2 (0.3%)	3 (0.2%)
Migraine	2 (0.3%)	1 (0.1%)	0	2 (0.3%)	3 (0.2%)
Mouth Ulceration	0	3 (0.4%)	0	2 (0.3%)	5 (0.3%)
Nausea	1 (0.1%)	2 (0.3%)	1 (0.9%)	1 (0.1%)	4 (0.3%)
Skin Ulcer	1 (0.1%)	2 (0.3%)	0	2 (0.3%)	4 (0.3%)
Abdominal Pain Upper	0	3 (0.4%)	1 (0.9%)	0	4 (0.3%)
Cellulitis	1 (0.1%)	2 (0.3%)	1 (0.9%)	0	3 (0.2%)
Deep Vein Thrombosis	1 (0.1%)	0	0	3 (0.4%)	3 (0.2%)
Lymphopenia	0	0	0	3 (0.4%)	3 (0.3%)

Modified Sponsor's Table T37; p. 1047.

### 7.3.5 Submission Specific Primary Safety Concerns

#### a. Serious Infections

Because of its mechanism of action, belimumab would also be anticipated to increase the risk of infections, including serious infection. In fact, as shown in Table 75 below, infections were the most common system-organ-class (SOC) reported, and the exposure-adjusted-incidence of serious infection was higher in the combined

belimumab groups compared to placebo (5.2 vs. 6.0 infections per 100 patient-years for placebo and belimumab groups, respectively).

Table 75 - 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
<b>Serious Infections Totals, n (%)</b>	35 (5)	46 (7)	7 (6)	35 (5)	88 (6)
<b>Exposure-Adjusted Incidence (per 100 patient-years)</b>	5.2				6.0
<b>Cases of Sepsis Most Common Preferred Terms</b>	3 (0.4)	4 (0.6)	1 (0.9)	5 (0.7)	10 (0.7)
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

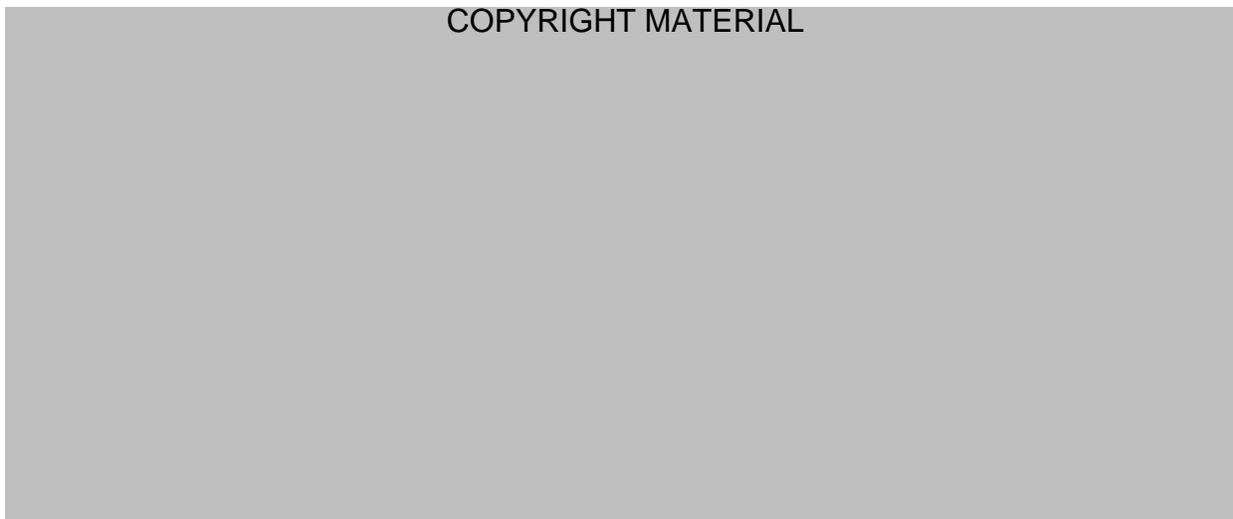
Unusual infections included: 1 case of West Nile virus infection occurring in a patient treated with belimumab 4 mg/kg; 1 case of disseminated herpes zoster occurring in a patient on belimumab 10 mg/kg; 1 case of disseminated cytomegaloviral infection occurring in a patient on belimumab 10 mg/kg, 1 case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

**b. Infusion Reactions, Hypersensitivity, and Anaphylaxis**

Because belimumab is a protein for infusion that contains foreign sequences, a certain level of infusion reactions, hypersensitivity, and anaphylaxis would be expected. Describing these events is difficult to do with accuracy, and no consistent methodology was used in the belimumab clinical development program for capturing and classifying these events. FDA asked the Applicant to retrospectively assess adverse events to

determine whether they met clinical criteria for diagnosing anaphylaxis, as agreed upon at the Second Symposium on the Definition and Management of Anaphylaxis sponsored by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN). These criteria are summarized in Table 76, below.

**Table 76- Clinical Criteria for Diagnosing Anaphylaxis**  
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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 77, below. These data raise some concerns, as follows:

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

- Patients inconsistently received prophylaxis for infusion reactions, which included antihistamines and corticosteroids, at the discretion of the investigator. This may have blunted or obscured hypersensitivity responses.

Table 77 - 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 (%)
<b>BLA Original Analysis</b>				
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)
<b>FDA-Requested Additional Analyses</b>				
<b>Leading to discontinuation/interruption (regardless of day of occurrence)</b>				
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)
<b>Serious and/or severe</b>				
Serious and/or severe Infusion and hypersensitivity rxns (HGS definition)	40 (5.9)	10 (9.0)	46 (6.8)	37 (5.5)
<b>FDA terms</b>				
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. Table courtesy of Dr. Susan Limb.

### c. Neuropsychiatric Adverse Events

#### *Neuropsychiatric Adverse Events*

Neuropsychiatric manifestations are a not uncommon complication of SLE, although the actual incidence of neuropsychiatric involvement appears to range widely depending on the population studied and the specific manifestation in question. Some sort of cognitive dysfunction is reported in the majority of patients (from 55% to 80%). Headache (24 to 72%) and mood disorders (14 to 57%) are also commonly reported. Depression and anxiety are common in SLE patients and have been reported to occur in 24 to 57% of SLE patients. Frank psychosis is relatively uncommon (up to 8% of patients)<sup>5</sup>. Not unexpectedly, these adverse events have been reported in the

<sup>5</sup> Hanly, et al Rheum Dis Clin N Am (2005) 31:273-298

belimumab SLE clinical development program; however once again, there was a numerical imbalance against belimumab, with more belimumab-treated patients reporting neurologic and psychiatric adverse events, SAEs, and suicides. Ascertaining the role of belimumab in this imbalance is again difficult, as patients were exposed to placebo-treatment for shorter durations and there was unequal randomization. However a promoting or permissive role of belimumab cannot be ruled out.

#### *Narratives on Completed Suicides*

1. Study LBSL02: Subject US034-002 was a 43-year-old white female with SLE. She received 2 doses of belimumab 1.0 mg/kg IV, on 23Oct03 and 07Nov03. Medical history included peptic ulcer, candidiasis, Raynaud's phenomenon, ileus, cutaneous vasculitis, uterine hemorrhage, pelvic pain, migraine, uterine leiomyoma, hemangioma of liver, tremor, nausea, nervous system disorder, hepatic cyst, hypokalemia, tinnitus, diplopia, reduced visual acuity, vertigo, gastroesophageal reflux disease, pyrexia, dehydration, anorexia, joint dislocation, connective tissue disorder, ovarian cyst, tobacco abuse, family stress, fractured coccyx, pelvic fracture, photosensitivity reaction, mouth ulceration, and stomatitis. Past medical and surgical procedures included abdominal hysterectomy, bilateral salpingo-oophorectomy, myomectomy, appendectomy, tonsillectomy and adenoidectomy. Ongoing medical conditions included fibromyalgia, osteoporosis, chronic sinusitis, hypertension, esophageal dyskinesia, depression, chronic fatigue syndrome, aptyalism, synovitis, insomnia, Sjogren's syndrome, intervertebral disc degeneration, contusion, amnesia, anxiety, intervertebral disc protrusion, arthritis, alopecia, and cerebral disorder. The screening physical examination on 01Oct03 revealed malar facial rash, thin hair, discoid patches on the arms, and synovitis of both hands. Concomitant medications included prednisone, citalopram, acetaminophen with hydrocodone, dextroamphetamine, carisoprodol, diazepam, metoclopramide, sucralfate, rabeprazole, propranolol, alendronate, celecoxib, and esomeprazole. On (b) (6), the subject was considered to have worsening depression and committed suicide by a self-inflicted gunshot. No action was taken with regard to the study agent prior to the suicide.

2. Study 1057: Subject KR008-001 was a 23-year-old Asian female with SLE. She received her 1<sup>st</sup> dose of 10.0 mg/kg belimumab on 07Jan08 and received 11 doses. The subject discontinued belimumab on 05Oct08 because of this SAE; her last dose was on 22Sep08. Medical history included autoimmune thyroiditis, hepatitis (drug-induced), bronchitis, cystitis, herpes zoster, upper respiratory tract infection, depressed mood, and psychotic disorder due to general medical condition. Ongoing conditions included, drug hypersensitivity (penicillin and cephalosporins), and osteopenia. Concomitant medications included hydroxychloroquine, levothyroxine, acetylsalicylic acid, calcium carbonate, rebamipide, azathioprine, meloxicam, and methylprednisolone. On (b) (6) (b) (6) days after her 11<sup>th</sup> dose of belimumab, the subject committed suicide. Her condition was improving during the trial and her steroid dose had been tapered. When she missed her Week (b) (6) visit, the study coordinator contacted the subject's family. The

subject's mother informed the coordinator that the subject had committed suicide on (b) (6) because of a conflict with her father. The subject did not have any mental illness as diagnosed by a psychiatrist; however, she had a period of a depressive mood in 2006. She had not been in a depressive state during the period that the suicide occurred. An autopsy was not performed.

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

#### *Narratives on Suicide Attempts/Ideation*

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

On (b) (6) days after her most recent dose of belimumab, the subject's husband found her sleepy and unresponsive and called the paramedics. She was transported via ambulance to the local hospital. Upon arrival, she was unresponsive and an ammonia capsule to the left nare resulted in a combative response. Her blood pressure was 145/87 mmHg, respirations 20 per minute, heart rate (HR) 109 beats per minute (bpm), temperature 98 degrees Fahrenheit, and oxygen saturation 94%. During her examination, she was anxious and uncooperative, but otherwise her exam was

unremarkable. She reportedly took a drug overdose while intoxicated and was subsequently admitted for suicide gesture. Her hematology and chemistry laboratory results were normal except for potassium 3.5 mmol/L. Urinalysis and urine drug screen were normal. Her Tylenol level was normal at 12 and alcohol level was 68 mg/dL. A CT scan revealed no acute concerns. Arterial blood gas showed a pCO<sub>2</sub> of 50. She was transferred to another hospital for psychiatric follow-up. The subject reported being lonely, discouraged, and upset with her sister. In addition, she reported stress secondary to family problems. She did not seek out help, but started drinking alcohol (unknown type) and took some pills (not identified and amount not provided by subject). She reported her plan was to hurt herself, although she was vague about a suicidal attempt. She reported not being suicidal, just reaching out for help. She had no delusions and repeatedly denied plans to kill herself. She was not considered psychotic. The evaluation indicated she had partial insight and questionable judgment when she is under the influence of alcohol. No gross abnormality was noted for short and long term memory. No action was taken with regard to belimumab.

2. Subject US003-0013 in ongoing long-term extension study LBSL99, receiving 10 mg/kg belimumab, reported depression and suicide attempt on (b) (6) days after first dose of belimumab. No further details provided.

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

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

For a few weeks prior to 16Jul08, the subject had been experiencing increased anger and outbursts. On (b) (6) days after her 5<sup>th</sup> dose of placebo, after being questioned and scolded by her father for poor performance on exams, the subject consumed 10 to 15 mL of phenyl with the intention of self harm. She was admitted to a local hospital on (b) (6) and managed conservatively until discharge on (b) (6). On 21Jul08, she was evaluated by psychiatrists and on (b) (6) she was hospitalized for treatment of adjustment disorder, personality disorder, and intentional self injury. Laboratory tests of cerebrospinal fluid an MRI of the brain, and cerebrospinal fluid analysis results were all normal. She was treated with alprazolam and fluoxetine. The subject was discharged on (b) (6). No action was taken with regard to placebo.

An internal consultant, Dr. Gregory Dubitsky, from the Agency's Division of Psychiatry Products also reviewed these data. Based on the two suicides that occurred in patients treated with belimumab he could not conclude that treatment with the product plays a significant etiologic role in suicide. However, he did recommend that future studies conducted with belimumab rate patients using the Columbia Suicide-Severity Rating Scale (C-SSRS) at baseline and at each visit to improve the timely ascertainment of suicidality-related events. A retrospective assessment of suicidality according to the Columbia Algorithm for Suicide (C-CASA) conducted by an expert consultant in this area, (b) (4), was submitted as an amendment to the application by the Applicant. Although (b) (4) acknowledged methodological limitations in conducting a retrospective analysis of attribution in causality due to ascertainment bias, she concluded there was no difference seen in the primary safety population with regard to suicidal behaviors (completed suicide and suicide attempt) since the rate of suicide/suicide attempt reported in the primary safety population for belimumab (0.13/100 subject years) is similar to the rate reported for placebo patients (0.14/100 subject years). Based on a retrospective assessment of suicide and suicide attempt in the first 300 patients with SLE attending a lupus clinic over 20-years of follow-up by Karassa et al<sup>6</sup>, (b) (4) estimated that if all the patients in the primary safety database were followed for 20 years the rate of suicide/suicide attempts would be 0.12 (95% CI 0.05, 0.24)/100 patient years, which is consistent with the rate seen in the long-term belimumab experience of 0.18 (95% CI 0.07, 0.36)/100 patient years.

#### d. Neurologic and Psychiatric Adverse Events

Neurologic and Psychiatric SAE and common AE are listed in Table 78 and below:

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<sup>6</sup> Karassa FB, Magliano M, Isenberg DA. Suicide attempts in patients with Systemic Lupus Erythematosus. *Ann Rheum Dis* 2003;62:58-60.

Table 78 - 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
<b>Nervous System Disorders</b>	<b>8 (1.2)</b>	<b>10 (1.5)</b>	<b>1 (0.9)</b>	<b>16 (2.4)</b>
<b>Exposure-Adjusted Incidence<sup>1</sup> per 100 pt-yrs</b>	<b>1.2</b>	<b>Combined: 1.8</b>		
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)			
<b>Psychiatric Disorders</b>	<b>3 (0.4)</b>	<b>4 (0.6)</b>	<b>0</b>	<b>8 (1.2)</b>
<b>Exposure-Adjusted Incidence<sup>1</sup> per 100 pt-yrs</b>	<b>0.4</b>	<b>Combined: 0.8</b>		
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

<sup>1</sup>Exposure is 672.3 subject-years for placebo and 1472.9 subject-years for combined belimumab groups

Table 79 - 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
<b>Nervous System Disorders</b>	<b>241 (35.7)</b>	<b>231 (34.3)</b>	<b>58 (52.3)</b>	<b>249 (36.9)</b>
<b>Exposure-Adjusted Incidence<sup>1</sup> per 100 pt-yrs</b>	<b>35.8</b>	<b>Combined: 36.5</b>		
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)
<b>Psychiatric Disorders</b>	<b>82 (12.1)</b>	<b>103 (15.3)</b>	<b>25 (22.5)</b>	<b>100 (14.8)</b>
<b>Exposure-Adjusted Incidence<sup>1</sup> per 100 pt-yrs</b>	<b>12.2</b>	<b>Combined: 15.5</b>		
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

<sup>1</sup>Exposure is 672.3 subject-years for placebo and 1472.9 subject-years for combined belimumab groups

As noted in Table 78 and Table 79 above, there is a consistent overall numeric and exposure-adjusted imbalance against belimumab in reported neurologic and psychiatric serious AE and common AE. Although the Agency's internal consultant found no convincing evidence of a signal for belimumab-related psychiatric experiences based on the presented reporting rates for psychiatric adverse events in the three placebo

controlled SLE studies conducted with belimumab, he recommended the Applicant recalculate the reporting rates for anxiety-related and depression-related adverse events after combining similar preferred terms in an effort to elucidate a more distinct signal. Review of this new analysis did not identify a more distinct signal for belimumab associated psychiatric events in the SLE population studied.

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

Most patients (>92%) experienced an adverse event during the controlled IV SLE trials. Table 80 lists the frequency of the adverse events observed in these studies by system organ class and treatment group. Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, Gastrointestinal Disorders, Skin and Subcutaneous Tissue Disorders and Nervous System Disorders were the most common types of adverse events observed. Overall, the types and incidences of common adverse events were consistent with what would be expected for patients with active SLE who had been exposed to immunosuppressive therapies. The incidences for these adverse event categories were similar for the placebo and belimumab 1 mg/kg and 10 mg/kg groups; however, they were frequently higher in the belimumab 4 mg/kg group, which was much smaller in size (thus small numeric changes resulted in larger proportional changes).

Table 80: Common Adverse Events in Studies LBSL02, 1056, and 1057

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

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

Table 81 lists common adverse event preferred terms reported by 5% or more patients in any treatment group during the controlled IV SLE trials. The adverse events most commonly reported by belimumab treated patients were: headache, upper respiratory tract infection, arthralgia, nausea, urinary tract infection, and diarrhea. Overall, the incidences for individual adverse events were similar across the placebo and

belimumab 1 mg/kg and 10 mg/kg treatment groups but were again frequently higher in the 4 mg/kg group. No dose-dependent phenomena are apparent on the basis of these data. No other safety issues were identified on review of adverse event data generated from the other belimumab studies included in the application's safety database.

Table 81 - Common AEs Occurring at >5% Frequency in Any Treatment Group in Studies LBSL02, 1056, and 1057, by Preferred Term

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

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

#### 7.4.2 Laboratory Findings

Laboratory data from the randomized controlled Phase 3 trials, 1056 and 1057, and from the Phase 2 study, LBSL02, were presented as follows: serial changes from baseline at each study visit, serial shifts from baseline to final study visit, and worst grade observed. The Applicant provided normal ranges of values for each lab parameter assessed. These were reviewed and the clinically acceptable range for normal appeared appropriate. The findings from these analyses for the Week 52 time point are as follows:

##### a. Hematology:

Since belimumab is a lymphocyte modulating agent and SLE can also affect the hematological system (e.g., hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia, etc...), the hematological lab data results were examined for possible signs of toxicity. As shown in Table 82 mean hematology parameter values were generally similar across the four treatment groups and appeared to remain stable over the course of study treatment.

Table 82 – Mean Change in Hematology Parameters in Studies 1056, 1057 and LBSL02

Indices	Placebo N=675		Belimumab 1mg/kg N=673		Belimumab 4 mg/kg N=111		Belimumab 10 mg/kg N= 674	
	Baseline	Wk 52	Baseline	Wk 52	Baseline	Wk 52	Baseline	Wk 52
<b>Hematocrit (%)</b>								
<i>N</i>	645	513	631	530	111	95	635	532
<i>Mean (SD)</i>	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (.1)	0.4 (0.0)	0.4 (0.0)	0.4 (0.1)	0.4 (0.0)
<i>Median</i>	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
<i>(Min, Max)</i>	(0.2, 0.6)	(0.2, 0.6)	(0.2, 0.5)	(0.2, 0.5)	(0.3, 0.5)	(0.3, 0.5)	(0.2, 0.5)	(0.2, 0.5)
<b>WBC (x10<sup>3</sup>/mcl)</b>								
<i>N</i>	645	513	630	528	111	95	630	532
<i>Mean (SD)</i>	6.2 (2.7)	6.0 (2.6)	6.2 (2.8)	6.1 (2.8)	5.9 (2.8)	5.6 (2.6)	6.1 (2.6)	6.1 (2.5)
<i>Median</i>	5.7	5.6	5.6	5.5	5.2	5.1	5.6	5.7
<i>(Min, Max)</i>	(1.7, 19)	(1.7, 21)	(1.2, 21)	(1.3, 20)	(2.3, 20)	(1.4, 16)	(1.2, 21)	(1.9, 14)
<b>Basophils (%)</b>								
<i>N</i>	656	515	656	530	111	97	644	533
<i>Mean (SD)</i>	0.2 (0.2)	0.3 (0.3)	0.2 (0.2)	0.3 (0.3)	0.3 (0.2)	0.3 (0.3)	0.2 (0.3)	0.3 (0.3)
<i>Median</i>	0.2	0.2	0.2	0.2	0.2	0.0	0.2	0.2
<i>(Min, Max)</i>	(0.0, 2.1)	(0.0, 2.1)	(0.0, 2.1)	(0.0, 3.0)	(0.0, 2.3)	(0.0, 1.1)	(0.0, 3.0)	(0.0, 2.4)
<b>Eosinophils (%)</b>								
<i>N</i>	656	515	653	530	111	97	644	533
<i>Mean (SD)</i>	2.2 (2.3)	2.0 (2.1)	2.2 (2.5)	2.4 (2.8)	2.2 (2.0)	2.6 (2.3)	2.1 (2.2)	2.1 (2.4)
<i>Median</i>	1.5	1.4	1.5	1.8	1.6	1.9	1.5	1.4
<i>(Min, Max)</i>	(0.0, 16)	(0.0, 15)	(0.0, 22)	(0.0, 22)	(0.0, 15)	(0.0, 10)	(0.0, 14)	(0.0, 20)
<b>Lymphocytes (%)</b>								
<i>N</i>	656	515	653	530	111	97	644	533
<i>Mean (SD)</i>	23 (12)	23 (11)	22 (10)	23 (10)	23 (11)	22 (9.7)	23 (11)	23 (11)
<i>Median</i>	21	22	21	22	21	22	23	22
<i>(Min, Max)</i>	(1.0, 72)	(2.4, 64)	(2.8, 52)	(2.0, 61)	(3.6, 46)	(2.9, 52)	(2.1, 61)	(2.0, 56)
<b>Monocytes (%)</b>								
<i>N</i>	656	515	653	530	111	97	644	533
<i>Mean (SD)</i>	5.1 (3.3)	5.6 (3.4)	5.1 (3.3)	6.0 (3.4)	5.6 (3.2)	6.4 (3.3)	5.0 (3.1)	5.8 (3.8)
<i>Median</i>	4.7	5.1	4.6	5.3	5.3	5.8	4.7	5.1
<i>(Min, Max)</i>	(0.0, 22)	(0.0, 20)	(0.0, 24)	(0.0, 18)	(0.0, 18)	(0.1, 16)	(0.0, 25)	(0.0, 37)
<b>Neutrophils (%)</b>								
<i>N</i>	656	515	653	530	111	97	644	533
<i>Mean (SD)</i>	70 (14)	69 (13)	70 (13)	67 (12)	69 (12)	68 (11)	70 (13)	69 (13)
<i>Median</i>	70	69	71	68	69	68	70	70
<i>(Min, Max)</i>	(14, 97)	(26, 95)	(29, 96)	(26, 97)	(44, 93)	(40, 95)	(29, 95)	(26, 95)
<b>Platelets (x10<sup>3</sup>/mcl)</b>								
<i>N</i>	628	505	616	522	106	94	618	526
<i>Mean (SD)</i>	261 (81)	252 (80)	260 (82)	255 (77)	241 (63)	254 (72)	257 (81)	257 (76)
<i>Median</i>	253	241	255	250	233	244	251	246
<i>(Min, Max)</i>	(52, 685)	(24, 624)	(8.0, 590)	(6.0, 587)	(71, 404)	(107, 464)	(53, 622)	(65, 537)

Modified Sponsor's Table T184; p. 3780-3893.

As displayed in Table 83, reference range shifts from baseline are observed for a number of hematological indices, however, these shifts were generally similar on cross comparison of the four treatment groups. The shifts from normal/low to high prothrombin time can be attributed to the 25% of patients who were taking concomitant anticoagulant therapy while participating in these trials.

Table 83 – Tabular Summary of Hematology Reference Range Shifts from Baseline for Studies 1056, 1057 and LBSL02

Indices	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10 mg/kg N= 674
<b>Hematocrit</b>				
Shift from Normal/High to Low	181 (27%)	167 (25%)	33 (31%)	175 (26%)
Shift from Normal/Low to High	35 (5%)	36 (5%)	3 (3%)	41 (6%)
<b>Red Blood Cells</b>				
Shift from Normal/High to Low	155 (23%)	141 (21%)	23 (21%)	144 (22%)
Shift from Normal/Low to High	20 (3%)	28 (4%)	4 (4%)	26 (4%)
<b>Basophils</b>				
Shift from Normal/High to Low	0	0	0	0
Shift from Normal/Low to High	8 (1%)	6 (1%)	0	6 (1%)
<b>Eosinophils</b>				
Shift from Normal/High to Low	0	1 (0.2%)	0	0
Shift from Normal/Low to High	104 (16%)	131 (20%)	17 (16%)	114 (17%)
<b>Lymphocytes</b>				
Shift from Normal/High to Low	281 (42%)	292 (44%)	33 (31%)	245 (37%)
Shift from Normal/Low to High	90 (13%)	81 (12%)	22 (20%)	89 (13%)
<b>Monocytes</b>				
Shift from Normal/High to Low	0	0	0	0
Shift from Normal/Low to High	125 (19%)	158 (24%)	20 (19%)	143 (21%)
<b>Neutrophils</b>				
Shift from Normal/High to Low	56 (8%)	61 (9%)	20 (19%)	71 (11%)
Shift from Normal/Low to High	293 (44%)	296 (45%)	34 (32%)	243 (36%)
<b>Prothrombin Time</b>				
Shift from Normal/High to Low	0	0	--	0
Shift from Normal/Low to High	12 (2%)	16 (3%)	--	19 (3%)

Modified Sponsor's table T183; p. 3773-3779

Prothrombin Time not assessed in Study LBSL02

Since both belimumab and underlying SLE disease activity may account for some of the shift changes observed in Table 83, the Applicant also analyzed the hematological lab results by toxicity grades. Table 84 summarizes these parameters for which Grade 3 and 4 toxicities were observed in the controlled SLE studies. The incidence of hematological Grade 3 and 4 toxicities were again similar on comparison of the four treatment groups. Not surprisingly, lymphopenia and prolonged prothrombin time were the hematological indices with the highest frequencies of Grade 3 and 4 abnormalities observed in these studies. No dose-response phenomena were noted on examination of these data.

Table 84 – Tabular Summary of Hematology Parameters by Worst Toxicity Grade for Studies LBSL02, 1056, and 1057

Worst Grade Observed	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Hemoglobin	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	30 (4.5%)	21 (3.1%)	4 (3.6%)	9 (1.3%)
Grade 4	2 (0.3%)	3 (0.4%)	1 (0.9%)	1 (0.1%)
Lymphocyte Count	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	155 (23.0%)	175 (26.2%)	22 (20.0%)	160 (23.8%)
Grade 4	19 (2.8%)	12 (1.8%)	2 (1.8%)	20 (3.0%)
Neutrophil Count	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	25 (3.7%)	29 (4.3%)	9 (8.2%)	28 (4.2%)
Grade 4	7 (1.0%)	4 (0.6%)	1 (0.9%)	7 (1.0%)
Platelet	(n=673)	(n=668)	(n=110)	(n=671)
Grade 3	6 (0.9%)	6 (0.9%)	--	5 (0.7%)
Grade 4	4 (0.6%)	5 (0.7%)	--	--
Prothrombin Time (PT)	(n=664)	(n=663)	(n=110)	(n=664)
Grade 3	32 (4.8%)	39 (5.9%)	13 (11.8%)	36 (5.4%)
Grade 4	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 (0.3%)	1 (0.2%)	--	--
Grade 4	--	3 (0.5%)	--	--
White Blood Cells (WBC)	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	20 (3.0%)	18 (2.7%)	5 (4.5%)	26 (3.9%)
Grade 4	--	--	--	1 (0.1%)

Sponsor's Table 2.7.4-37; p. 132 Summary of Clinical Safety

Review of the hematological lab data from the ongoing long term SLE studies, the Phase 1 SLE trials, and studies conducted in RA showed similar findings for lymphopenia and prolonged prothrombin time, the latter of which was again attributed to the use of warfarin.

b. Chemistry:

Since SLE can affect the renal system and also cause an autoimmune hepatitis, test results of renal and hepatic function were also examined (Table 85). Mean liver and renal parameter values were generally similar across the four treatment groups and

appeared to remain stable over the course of study treatment. For completeness, mean serum electrolyte values were also reviewed and were also found to be generally similar and without clinically meaningful patterns of change on cross comparison of treatment groups (data not shown).

Table 85 – Mean Change in Liver and Renal Function Tests for Studies LBSL02, 1056, and 1057

Liver Function Test	Placebo N=675 Belimumab		1mg/kg N=673 Belimumab		4 mg/kg N=111 Belimumab		10 mg/kg N= 674	
	Baseline	Wk 52	Baseline	Wk 52	Baseline	Wk 52	Baseline	Wk 52
<b>Alk phos (U/L)</b>								
<i>N</i>	670	514	669	536	108	97	661	534
<i>Mean (SD)</i>	70 (31)	73 (30)	70 (30)	73 (26)	73 (26)	72 (25)	69 (27)	74 (31)
<i>Median</i>	65	67	66	69	69	68	64	69
<i>(Min, Max)</i>	(24, 462)	(29, 425)	(23, 542)	(29, 203)	(34, 144)	(36, 176)	(27, 298)	(28, 344)
<b>AST/SGPT (U/L)</b>								
<i>N</i>	670	514	669	536	108	97	661	534
<i>Mean (SD)</i>	21 (17)	20 (17)	19 (17)	19 (15)	18 (13)	18 (13)	20 (14)	19 (13)
<i>Median</i>	16	16	15	15	15	16	16	16
<i>(Min, Max)</i>	(4.0, 195)	(4.0, 167)	(4.0, 243)	(4.0, 177)	(5.0, 108)	(5.0, 121)	(4.0, 173)	(4.0, 176)
<b>AST/SGOT (U/L)</b>								
<i>N</i>	665	512	669	535	108	97	656	532
<i>Mean (SD)</i>	24 (14)	24 (15)	23 (19)	22 (9.7)	21 (8.2)	20 (6.8)	24 (18)	22 (12)
<i>Median</i>	20	20	20	20	20	19	20	20
<i>(Min, Max)</i>	(7.0, 177)	(10, 242)	(7.0, 296)	(9.0, 141)	(12, 72)	(10, 55)	(10, 316)	(7.0, 154)
<b>GGT (U/L)</b>								
<i>N</i>	670	514	669	536	108	97	661	534
<i>Mean (SD)</i>	36 (39)	39 (106)	34 (39)	34 (36)	33 (36)	31 (936)	34 (42)	35 (45)
<i>Median</i>	23	23	23	24	23	22	23	22
<i>(Min, Max)</i>	(5.0, 375)	(8.0, 2211)	(3.0, 510)	(4.0, 359)	(8.0, 232)	(8.0, 249)	(4.0, 590)	(9.0, 571)
<b>LDH</b>								
<i>N</i>	665	512	669	535	108	97	656	532
<i>Mean (SD)</i>	178 (54)	177 (52)	178 (94)	172 (43)	165 (43)	164 (43)	178 (60)	172 (44)
<i>Median</i>	167	168	165	165	152	156	170	163
<i>(Min, Max)</i>	(60, 522)	(57, 721)	(52, 2118)	(67, 347)	(94, 329)	(91, 347)	(49, 963)	(49, 473)
<b>Total bili (mg/dl)</b>								
<i>N</i>	670	514	669	536	108	97	661	534
<i>Mean (SD)</i>	7.5 (3.8)	7.6 (3.3)	7.5 (3.4)	7.9 (3.80)	6.89 (2.5)	7.4 (3.0)	7.6 (3.7)	7.9 (3.5)
<i>Median</i>	6.0	6.0	6.0	6.0	6.8	6.8	6.0	6.8
<i>(Min, Max)</i>	(2.0, 55)	(2.0, 34)	(3.0, 38)	(2.0, 30)	(3.4, 15)	(1.7, 17)	(2.0, 42)	(3.4, 30)
<b>Albumin (g/L)</b>								
<i>N</i>	670	514	669	536	108	97	661	534
<i>Mean (SD)</i>	40 (4.5)	40 (4.4)	40 (4.7)	41 (4.4)	39 (3.4)	40 (4.0)	40 (4.6)	41 (3.4)
<i>Median</i>	40	40	40	41	40	40	40	42
<i>(Min, Max)</i>	(20, 52)	(24, 55)	(20, 54)	(15, 54)	(29, 48)	(23, 49)	(19, 55)	(27, 51)
<b>BUN/Creat Ratio</b>								
<i>N</i>	670	514	669	536	108	97	661	534
<i>Mean (SD)</i>	64 (31)	64 (31)	64 (30)	63 (30)	16 (5.5)	16 (4.8)	64 (31)	61 (928)
<i>Median</i>	65	65	66	63	15	16	65	62
<i>(Min, Max)</i>	(6.0, 186)	(8.0, 190)	(8.0, 205)	(9.0, 179)	(4.0, 38)	(7.0, 28)	(3.0, 182)	(5.0, 179)
<b>BUN (mmol/L)</b>								
<i>N</i>	670	514	669	536	108	97	661	534
<i>Mean (SD)</i>	5.2 (2.2)	5.4 (2.7)	5.2 (2.1)	5.3 (2.2)	5.4 (2.2)	5.3 (2.5)	5.3 (2.6)	5.1 (928)
<i>Median</i>	4.6	4.9	5.0	5.0	5.0	5.0	4.6	4.5
<i>(Min, Max)</i>	(1.5, 16)	(1.5, 43)	(1.9, 18)	(1.8, 26)	(1.1, 14)	(2.1, 17)	(1.1, 41)	(1.0, 48)
<b>Creat. Cl (ml/min)</b>								
<i>N</i>	670	513	667	536	108	97	661	534
<i>Mean (SD)</i>	107 (33)	103 (32)	105 (34)	102 (31)	104 (34)	99 (34)	104 (34)	103 (33)
<i>Median</i>	105	100	102	99	100	99	100	99
<i>(Min, Max)</i>	(24, 282)	(7.0, 270)	(19, 300)	(11, 209)	(31, 204)	(30, 204)	(17, 284)	(25, 299)

Modified Sponsor's Tables T190 and T199; p.3904-3939 and p.4005 – 4052.

Table 86 lists chemistry parameters that were remarkable for shifts in baseline values. Overall, these shifts were similar on cross group comparison with the highest frequency occurring in serum chloride, carbon dioxide and total protein and were not indicative of a dose-response relationship or suggestive of belimumab-related toxicity. Shifts from normal/low to high in BUN and BUN/creatinine may be attributed to those patients who either developed or had worsening of underlying lupus nephritis during these trials.

Table 86 - Tabular Summary of Chemistry Reference Range Shifts from Baseline for Studies 1056, 1057 and LBSL02

Chemistry Parameters	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10 mg/kg N= 674
<b>Lactate Dehydrogenase</b>				
Shift from Normal/High to Low	0	0	0	0
Shift from Normal/Low to High	103 (15%)	101 (15%)	12 (11%)	85 (13%)
<b>Chloride</b>				
Shift from Normal/High to Low	13 (2%)	11 (2%)	2 (2%)	7 (1%)
Shift from Normal/Low to High	262 (39%)	275 (41%)	49 (45%)	281 (42%)
<b>Carbon Dioxide</b>				
Shift from Normal/High to Low	266 (47%)	261 (47%)	--	272 (49%)
Shift from Normal/Low to High	3 (1%)	8 (1%)	--	1 (0%)
<b>BUN/Creatinine Ratio</b>				
Shift from Normal/High to Low	6 (1%)	5 (1%)	--	5 (1%)
Shift from Normal/Low to High	167 (25%)	167 (25%)	21 (19%)	180 (27%)
<b>BUN</b>				
Shift from Normal/High to Low	58 (9%)	66 (10%)	12 (11%)	64 (10%)
Shift from Normal/Low to High	59 (9%)	65 (10%)	11 (10%)	66 (10%)
<b>Total Protein</b>				
Shift from Normal/High to Low	57 (9%)	90 (14%)	19 (17%)	84 (13%)
Shift from Normal/Low to High	31 (5%)	10 (2%)	1 (1%)	24 (4%)

Modified Sponsor's Tables T194 and T189; Appendix 15.

The Applicant also analyzed liver and renal function as well as electrolyte results by toxicity grades. Table 87 summarizes these parameters for which Grade 3 and 4 toxicities were observed in the controlled SLE studies. The incidence of Grade 3 and 4 toxicities for these laboratory parameters were again similar on cross comparison of the four treatment groups and were very low overall. Gamma-glutamyl-transferase, albumin and hyperglycemia were the parameters with the highest frequency of Grade 3 and 4 abnormalities observed in these trials. Since many of the patients who participated in these studies were taking concomitant systemic corticosteroids, the hyperglycemia observed in these trials may be a result of corticosteroid-induced glucose intolerance. Definitive dose-response effects were not observed on examination of these data. Review of the chemistry, renal and liver function data from the ongoing long term SLE studies, the Phase 1 SLE trials, and studies conducted in RA also did not reveal any new safety signals.

Table 87 – Chemistry, Liver and Renal Function Worst Toxicity Grade for Studies 1056, 1057 and LBSL02

Lab Test Worst Grade Observed	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10 mg/kg N= 674
<b>Hypocalcemia</b>	(n=562)	(n=554)	(n=110)	(n=561)
Grade 3	--	1 (0.2%)	--	1 (0.2%)
Grade 4	--	--	--	--
<b>Hypomagnesemia</b>	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	1 (0.1%)	--	--	--
Grade 4	--	--	--	--
<b>Hypophosphatemia</b>	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	6 (0.9%)	8 (1.2%)	1(0.9%)	8 (1.2%)
Grade 4	--	--	--	--
<b>Hyperkalemia</b>	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	1 (0.3%)	1 (0.1%)	--	1 (0.1%)
Grade 4	3 (0.4%)	1 (0.1%)	--	1 (0.1%)
<b>Hypernatremia</b>	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	1 (0.1%)	2 (0.3%)	--	--
Grade 4	--	--	--	1 (0.1%)
<b>Hyponatremia</b>	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	--	1 (0.1%)	--	--
Grade 4	--	1 (0.1%)	--	--
<b>Alkaline Phosphatase</b>				
Grade 3	--	--	--	1 (0.1%)
Grade 4	1 (0.1%)	--	--	--
<b>ALT (SGPT)</b>				
Grade 3	2 (0.3%)	3(0.4%)	--	1 (0.1%)
Grade 4	2 (0.3%)	--	--	--
<b>AST (SGOT)</b>				
Grade 3	2 (0.3%)	1 (0.1%)	--	3 (0.4%)
Grade 4	1 (0.1%)	3 (0.4%)	1 (0.9%)	1 (0.1%)
<b>Gamma-glutamyl-transferase</b>				
Grade 3	18 (2.7%)	16(2.4%)	2 (1.8%)	21 (3.1%)
Grade 4	10 (1.5%)	3 (0.4%)	3 (2.7%)	4 (0.6%)
<b>Total Bilirubin</b>				
Grade 3	--	--	--	1 (0.1%)
Grade 4	1 (0.1%)	--	--	--
<b>Albumin</b>				
Grade 3	10 (1.5%)	6 (0.9%)	1 (0.9%)	9 (1.3%)
Grade 4	3 (0.4%)	5 (0.7%)	--	--
<b>Creatinine</b>				
Grade 3	1 (0.1%)	2 (0.3%)	--	1 (0.1%)
Grade 4	2 (0.3%)	--	--	--
<b>Hyperglycemia</b>				
Grade 3	11 (1.6%)	7 (1.0%)	1 (0.9%)	10 (1.5%)
Grade 4	1 (0.1%)	1 (0.1%)	--	1 (0.1%)
<b>Hypoglycemia</b>				
Grade 3	3 (0.4%)	1 (0.1%)	--	1 (0.1%)
Grade 4	--	1 (0.1%)	--	--

Modified Sponsor's Tables T186, T191 and T196; Appendix 15.

c. Urinalysis

Although the protocols for the controlled SLE trials prohibited the entry of patients with severe lupus nephritis, some of the participating patients had disease activity in this organ system. Table 88 lists selected mean urinalysis parameter values. These data were generally similar across the four treatment groups and appear to be without clinically meaningful changes particularly for the protein/creatinine ratio.

Table 88 – Mean Change in Selected Urinalysis Parameters for Studies 1056, 1057, LBSL02

Urinalysis Parameter	Placebo N=675		Belimumab 1mg/kg N=673		Belimumab 4 mg/kg N=111		Belimumab 10 mg/kg N= 674	
	Baseline	Wk 52	Baseline	Wk 52	Baseline	Wk 52	Baseline	Wk 52
<b>Protein/Creatinine Ratio (mg/mg)</b>								
<i>N</i>	662	507	660	525	108	91	649	532
<i>Mean (SD)</i>	0.47 (0.94)	0.38 (0.90)	0.46 (0.90)	0.35 (0.86)	0.23 (0.39)	0.26 (0.35)	0.45 (0.79)	0.31 (0.59)
<i>Median</i>	0.14	0.13	0.14	0.12	0.12	0.14	0.15	0.12
<i>(Min, Max)</i>	(0.01, 8.33)	(0.02, 12.3)	(0.04, 6.55)	(0.03, 10.4)	(0.04, 2.38)	(0.05, 1.96)	(0.03, 6.13)	(0.03, 3.98)
<b>Creatinine</b>								
<i>N</i>	660	506	657	525	107	91	648	531
<i>Mean (SD)</i>	9.98 (6.49)	10.2 (6.84)	9.59 (6.35)	10.6 (7.62)	9.01 (5.17)	9.2 (6.0)	9.58 (6.61)	10.2 (7.32)
<i>Median</i>	8.59	8.68	8.18	8.55	7.70	7.42	8.27	8.56
<i>(Min, Max)</i>	(0.86, 37.7)	(0.99, 39.9)	(0.80, 36.1)	(0.98, 47.6)	(1.79, 26.1)	(2.61, 36.9)	(0.61, 42.7)	(0.59, 59.2)
<b>Protein (mg/L)</b>								
<i>N</i>	576	479	582	509	32	80	563	510
<i>Mean (SD)</i>	523 (1239)	399 (986)	468 (1047)	423 (1730)	233 (350)	193 (238)	485 (1096)	315 (718)
<i>Median</i>	140	122	130	120	100	95	140	113
<i>(Min, Max)</i>	(49, 16520)	(49, 9450)	(49, 9300)	(49, 30630)	(50, 1620)	(50, 1280)	(49, 13280)	(49, 7770)

Modified Sponsor's Table T204; p. 4060-4075

As displayed in Table 89, reference range shifts from baseline were observed for urinary protein concentration and white blood cells. A higher incidence in shifts from normal/low to high urinary protein concentration occurred in both placebo patients (12%) and in the belimumab 4 mg/kg treatment group (35%) in these studies as compared to the belimumab 1mg/kg (2%) and 10 mg/kg (0.1%) treatment groups. The higher incidence observed in the 4 mg/kg belimumab group may have been impacted by the small number of patients who underwent this evaluation. The incidence shifts in urinary white blood cell counts were similar on cross group comparison and may be related to the number of urinary tract infections observed in patients during these trials.

Table 89 - Tabular Summary of Urinalysis Parameter Reference Range Shifts from Baseline for Studies 1056, 1057 and LBSL02

Urinalysis Parameter	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10 mg/kg N= 674
<b>Protein Concentration</b>				
N	580	584	26	581
Shift from Normal/High to Low	0	0	0	0
Shift from Normal/Low to High	11(12%)	14 (2%)	9 (35%)	4 (0.1%)
<b>White Blood Cells</b>				
n	111	114	109	110
Shift from Normal/High to Low	0	0	0	0
Shift from Normal/Low to High	49 (44%)	56 (49%)	44 (40%)	46 (42%)

Modified Sponsor's Table T203; p. 4059.

The Applicant also analyzed urinalysis results by toxicity grades. Table 90 summarizes these parameters for which Grade 3 and 4 toxicities were observed in the controlled SLE studies. Overall, the incidence of Grade 3 and 4 toxicities for these laboratory parameters were low with the lowest incidence occurring in the belimumab 4 mg/kg group and similar rates observed on cross comparison of the placebo and belimumab 1 mg/kg and 10 mg/kg treatment groups. Review of urinalysis data from the long term ongoing SLE, Phase 1 studies and RA studies did not reveal any safety issues.

Table 90 – Urinalysis Worst Toxicity Grade for Studies 1056, 1057 and LBSL02

Lab Test Worst Grade Observed	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10 mg/kg N= 674
<b>Protein/Creatinine Ratio</b>	(n=668)	(n=665)	(n=109)	(n=668)
Grade 3	49 (7.3%)	41 (6.2%)	5 (4.6%)	44 (6.6%)
Grade 4	31 (4.6%)	34 (5.1%)	2 (1.8%)	34 (5.1%)
<b>Protein</b>	(n=669)	(n=666)	(n=110)	(n=671)
Grade 3	20 (3.0%)	10 (1.5%)	--	18 (2.7%)
Grade 4	--	--	--	--
<b>Red Blood Cells</b>	(n=669)	(n=666)	(n=110)	(n=671)
Grade 3	12 (1.8%)	11 (1.7%)	9 (8.2%)	11 (1.6%)
Grade 4	--	--	--	--

Modified Sponsor's Table T200; Appendix 15

#### d. Immunoglobulins

As shown in Table 91 below, there does appear to be a generally dose-related trend toward a higher proportion of patients experiencing low immunoglobulin levels of each isotype with exposure to higher dose regimens of belimumab. As might be expected, the largest impact appeared to be on IgM levels, which have the ability to change the most acutely. With increasing duration of exposure to belimumab, the proportion of

patients with IgG less than the lower limit of normal increased over time from 8% to 14% (as per section 2.7.4.3.6.1.2 and the LBSL99 clinical study report). The proportion of patients with IgM less than the lower limit of normal increased from 33% to 63% over time and levels of IgA were stable. As per the applicant, there was not a corresponding increase in infections or serious infections.

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

Table 91 - Immunoglobulin Shifts from Baseline in Studies LBSL02, 1056, and 1057

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
<b>IgA</b>				
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)
<b>IgG</b>				
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)
<b>IgM</b>				
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

### 7.4.3 Vital Signs

According to the common protocol for the Phase 3 studies 1056 and 1057 and the protocol for the Phase 2 study LBS02, patients were mandated to undergo measurement of sitting blood pressure (BP) at each study visit. Since the common protocol for these studies did not require assessment of oral temperature, heart rate or respiratory rate which were collected in the Phase 2 study LBSL02 and its OLE study LBSL99, the review of these data was limited by the incomplete collection of data.

Vital signs from the pooled safety databases for the three multidose Phase 3 postsurgical pain trials were presented as follows: baseline values and change from baseline by parameter, the incidence of shifts from normal range relative to baseline, and any significant observations (i.e., values meeting pre-specified criteria for possible

clinical significance and/or reported as AEs such as tachycardia, bradycardia, hypertension and hypotension). The Applicant's listing of normal ranges of values for each vital sign parameter was reviewed and the clinically acceptable range for normal appeared appropriate. Examination of the vital sign data revealed no clinically meaningful trends on change from baseline or on analyses of shift tables for any of the assessed parameters except for slightly lower proportions of subjects in all three treatment groups (placebo: 15%; belimumab 1mg/kg: 12%; and belimumab 10mg/kg: 13%) who had hypertension as compared to baseline (placebo: 19%; belimumab 1mg/kg: 14%; and belimumab 10 mg/kg: 17%) that may be a result of the predefined use of antihypertensive medications over the course of these trials. (Note: The Applicant did not do shift analyses for temperature or respiratory rate.)

Overall, no new safety signal associated with the use of belimumab was identified on review of the vital sign data collected during the controlled and open label Phase 1, 2 and 3 SLE and RA trials.

#### 7.4.4 Electrocardiograms (ECGs)

Since belimumab is a therapeutic biological protein that is not expected to interact with cardiac ion channels, the Applicant was not required to do QT prolongation studies as part of their pre-clinical and clinical development program. Serial ECGs were also not performed on subjects who participated in the trials conducted in support of the safety profile of this product.

#### 7.4.5 Special Safety Studies/Clinical Trials

In view of its mechanism of action, the Applicant conducted a small substudy as part of Study 1056 that evaluated the effect of belimumab on vaccinations. Functional antibodies levels in patients previously immunized to tetanus, streptococcus pneumoniae and influenza vaccines were assayed at the Day 0 and Week 52 visits. Data from this substudy suggests that treatment with belimumab did not alter the levels of pre-existing antibody titers nor did it appear to impact on subjects' ability to maintain a protective immune response to immunizations received prior to the study. Since the number of patients who received tetanus (n=4) or pneumococcus (n=7) vaccine while participating in this study was low, an assessment of the ability to mount an antibody response to these vaccines administered while receiving belimumab treatment could not be performed. Due to the presence of the same influenza strains in consecutive seasonal flu vaccines, most of the 76 subjects who received seasonal influenza vaccine during the trial had pre-existing antibody titers in the protective range for the majority of antigens. Thus, it is impossible to draw any conclusions regarding the immune system's ability to mount antibody response to influenza vaccine administered while receiving belimumab therapy. As a result of these findings, the Applicant has stated they will be evaluating the impact of belimumab on response to vaccines in a postmarketing study.

## 7.4.6 Immunogenicity

Immunogenicity assay results for the two pivotal studies are summarized in Table 92 below. The highest rate of immunogenicity appears to be associated with the lower (1 mg/kg) dose of belimumab, which may be due to less immunosuppression at this dose. The apparently higher rate of persistent immunogenicity with exposure to placebo raises questions regarding how many placebo-treated patients were errantly exposed to belimumab. The dose proposed for marketing, 10 mg/kg, is associated with the lowest immunogenic response. There did not appear to be an association of anti-product antibody positivity and risk for adverse events, but it is difficult to draw definitive conclusions with so few patients being anti-product antibody positive.

Table 92 - Immunogenicity Results in Studies C1056 and C1057

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

Source: Table T216 in Summary of Clinical Safety Appendices

<sup>1</sup>Persistently positive is a positive result at 2 or more assessments or the final assessment

<sup>2</sup>Transiently positive is a positive results at only 1 assessment and negative at the final

<sup>3</sup>Neutralizing any time post-baseline among subjects with neutralization assay results

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Examination of the safety data collected from the randomized, double-blind, placebo controlled, parallel group, dose comparison Phase 3 trials (1056 and 1057) and from the Phase 2 multiple, repeat-dose, dose-ranging studies (LBSL02 and LBRA01) failed to

identify any trends suggestive of a possible dose-dependent relationship associated with exposure to belimumab.

### 7.5.2 Time Dependency for Adverse Events

In support of belimumab's safety profile, the Applicant performed a time dependency analysis for the occurrence of adverse events. This analysis entailed calculating the incidence rate of adverse events for 6-month intervals of the three randomized controlled studies adjusted for subject-years of exposure to study medication within each interval. Since two of the three studies were 52 weeks in duration, only comparisons of 0 – 0.5 year and 0.5 – 1.0 year were reviewed. The incidence rates for the four treatment groups during each time interval were generally comparable except for lower rate of serious adverse events occurring in the 4 mg/kg belimumab group during both time intervals (0-0.5yrs: 17 per 100-subject-years; 0.5-1.0yrs:10 per 100-subject-years) as compared to the other treatment groups (placebo group: 0-0.5 yrs: 19 per 100-subject-years; 0.5-1.0 yrs: 17 per 100-subject years); 10 mg/kg belimumab ( 0-0.5 yrs: 23 per 100-subject-years; 0.5-1.0 yrs:16 per 100-subject years); and 1mg/kg belimumab (0-0.5 yrs: 25 per 100-subject-years; 0.5-1.0yrs:15 per 100-subject years). However, the incidence of deaths during the first time interval was highest in the 1mg/kg belimumab group (0.5-1.0 yrs: 1.2 per 100-subject years) as compared to the other three treatment groups which had similar rates [placebo (0.5-1.0 yrs: 0.6 per 100-subject years); 10mg/kg belimumab (0.5-1.0 yrs: 0.6 per 100-subject years); and 4 mg/kg belimumab (0-0.5 yrs: 0 per 100-subject years)]. During the second time interval the incidence rate for death remained unchanged for the 4 mg/kg belimumab group (0.5-1.0 yrs: 0 per 100-subject years) but decreased in the 1mg/kg belimumab (0.5-1.0yrs: 0.3 per 100-subject years) and placebo (0.5-1.0yrs: 0.3 per 100-subject years) groups but increased in the 10 mg/kg belimumab group (0.5-1.0yrs: 1.3 per 100-subject years). No other time dependent safety signals were observed on examination of these data.

### 7.5.3 Drug-Demographic Interactions

Subgroup analyses of AEs were conducted on pooled data generated from the Phase 3 studies 1056 and 1057 and from the Phase 2 study LBSL02 in order to determine if there were any drug-demographic interactions. In general, subgroup analysis was limited by small sample sizes particularly for gender and age. Since SLE is a disease that primarily affects young females, it is not surprising that these studies were overwhelmingly comprised of female patients (2004/2133; 94%) with few subjects > 65 years of age (35/2133; < 2%). Due to the paucity of male patients (n=129) and geriatric patients (n=35) who participated in these trials, no definitive conclusions regarding the risk for developing AEs associated with belimumab treatment can be made for either of these demographic groups.

Table 93 shows the race based analysis of adverse events for the six racial groups represented in these trials. The number of Native Hawaiian/Pacific Islander subjects is too small to draw any definitive safety conclusions about this subgroup. Of the remaining subgroups, no overall comparative safety differences due to race is observed for White/Caucasian, Asian, Black/African American, Alaska Native/American Indian, and African/indigenous American. In terms of the types of AEs, the highest incidence of AEs experienced by White/Caucasians, Asians, Black African/Americans and Alaska Native/American Indian occurred in the Infections and Infestations SOC. Slight imbalances in other SOC were noted on cross group comparison for Black/African American who had higher incidence rates for AEs in the Musculoskeletal and Connective Tissue disorders, Eye disorders, GI disorders, and Skin disorders compared to the other subgroups.

**Table 93 – Tabular Summary of the Number (%) of Subjects with ≥ 1 AE by Race while Participating in Studies 1056, 1057, and LBSL02**

Race	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=674	Total Belimumab N=1458
White/Caucasian with ≥ 1 AE	(n=350) 323 (92%)	(n=350) 328 (94%)	(n=76) 75 (99%)	(n=338) 316 (94%)	(n=764) 719 (94%)
Asian with ≥ 1 AE	(n=120) 114 (95%)	(n=115) 108 (94%)	(n=1) 1 (100%)	(n=131) 123 (94%)	(n=247) 232 (94%)
Black/African American with ≥ 1 AE	(n=74) 69 (93%)	(n=72) 70 (97%)	(n=31) 28 (90%)	(n=78) 73 (94%)	(n=181) 171 (94%)
Alaska Native/American Indian with ≥ 1 AE	(n=128) 115 (90%)	(n=135) 119 (88%)	(n=3) 3 (100%)	(n=126) 112 (93%)	(n=264) 234 (89%)
Native Hawaiian/Pacific Islander with ≥ 1 AE	(n=3) 3 (100%)	(n=1) 1 (100%)	(n=0) 0 (0%)	(n=1) 1 (100%)	(n=2) 2 (100%)
African/Indigenous American with ≥ 1 AE	(n=174) 157 (90%)	(n=180) 163 (91%)	(n=0) 0 (0%)	(n=175) 158 (90%)	(n=355) 321 (90%)

Modified Sponsor's Tables: T219, T220, T221, T222, and T223.

#### 7.5.4 Drug-Disease Interactions

No drug-disease interactions were noted during the review of the safety data submitted in support of this application.

#### 7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were conducted by the Applicant in support of belimumab's safety. Belimumab is a therapeutic biologic protein and is not expected to interact with CYP450 enzymes or p-glycoproteins. Review of the database did not identify any adverse events that appeared related to an interaction with concomitant medications.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

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

Table 94 - 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
<b>Subjects with ≥ 1 Malignancy</b>	<b>3 (0.4%)</b>	<b>3 (0.4%)<sup>1</sup></b>	<b>0</b>	<b>3 (0.4%)</b>	<b>6 (0.4%)</b>
Basal cell carcinoma	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Squamous cell carcinoma	0	0	0	2 (0.3%)	2 (0.1%)
Breast cancer	1 (0.1%)	1 (0.1%)	0	0	1 (0.1%)
Carcinoid tumor of the stomach	1 (0.1%)	0	0	0	0
Cervical carcinoma (stage 0)	0	1 (0.1%)	0	0	1 (0.1%)
Ovarian cancer	0	1 (0.1%)	0	0	1 (0.1%)

<sup>1</sup>Excludes Subject US052-000009 diagnosed with a thyroid neoplasm

The controlled trials were not designed to determine the risk for developing a malignancy due to exposure to belimumab. Nonetheless, the exposure-adjusted incidence rate for malignancies including and excluding non-melanoma skin cancers was calculated based on the number of cases observed in these studies based on the limited exposure data available. As shown in Table 95, the exposure-adjusted incidence rates for malignancies in both the placebo and combined belimumab treatment groups were low with rate ratios <1 for both analyses, and did not appear to be increased in the combined belimumab treatment group.

Table 95 - Rate of Malignancy in the Studies LBSL02, 1056, and 1057

	Placebo	Belimumab	Rate Ratio
<b>Number of Subjects</b>	675	1458	
<b>Subject-Years</b>	672 subject-years	1473 subject-years	
<b>Number of Malignancies<sup>1</sup></b>	3 (0.4%)	6 (0.4%)	
<b>Malignancies/100 Subject-Yrs</b>	0.45	0.41	0.91
<b>95% Confidence Interval</b>	(0.09, 1.30)	(0.15, 0.89)	(0.19, 5.64)
<b>Number of Subjects</b>	675	1458	
<b>Subject-Years</b>	672 subject-years	1475 subject-years	
<b>Number of Malignancies</b>	2 (0.3%)	3 (0.2%)	
<b>Malignancies (excl. NMSC<sup>2</sup>)/100 Subject-Yrs</b>	0.30	0.20	0.68
<b>95% Confidence Interval</b>	(0.04, 1.07)	(0.04, 0.60)	(0.08, 8.20)

<sup>1</sup>Includes Subject TW005-002 diagnosed with breast cancer after 2 months S/P completing study.

<sup>2</sup>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 96 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 96 -Malignancy Rates Excluding Non-Melanoma Skin Cancers for all Belimumab SLE Trials as of data cut-off date of July 9, 2010

	Background Rate <sup>1</sup>	Belimumab	Rate Ratio
<b>Number of Subjects</b>	9547	1955	
<b>Subject-Years</b>	76,948 subject-years	3507 subject-years	
<b>Subjects with Events<sup>2</sup></b>	410 (4.3%)	17 (0.9%)	0.91
<b>Malignancy Rate/100 Subject-Yrs (95% CI)</b>	0.53 (0.48, 0.59)	0.48 (0.28, 0.78)	(0.52, 1.47)

<sup>1</sup>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.

<sup>2</sup>Includes the following subjects with events unspecified as benign or malignant: LBSL99-US040-010 with hepatic and lung neoplasm, LBSL99-US046-029 with lung neoplasm, LBSL99-US007-002 with thyroid and lung neoplasm. Does not include the following subjects with events unspecified as benign or malignant LBSL02-US052-009, LBSL99-US028-001, LBSL99-US031-007 and LBSL99-US045-003 with thyroid neoplasms and LBSL99-US029-001 with soft tissue tumor.

Adapted Sponsor's Table 6-4; Appendix 6 of the Summary of Clinical Safety.

Table 97 below is a tabular summary of all cases of malignancy and neoplasms observed in the belimumab SLE safety database as of the cut-off date of December 31, 2009. The most common malignancies observed in SLE patients exposed to belimumab were squamous cell cancer (4 cases), basal cell cancer (3 cases), breast cancer (3 cases), colon cancer (2 cases), and B-cell lymphoma (2 cases). Of note, there were a total of 5 cases of thyroid neoplasms reported either singly (4 case) or associated with hepatic neoplasm (1 case) in patients treated with belimumab. One out of these 5 cases

of thyroid neoplasms (Subject US052-009) occurred during the controlled studies, while the remainder were observed in the open-label studies following prolonged exposure to belimumab. Cases of non-malignant thyroid neoplasm are not unexpected, given the reported increased prevalence of thyroid disorders associated with SLE (ranging from 11.5% to 24%) in the worldwide literature.<sup>7</sup> However there was a numeric imbalance, with more cases occurring in the belimumab treatment arms.

Table 97: Neoplasms in the Belimumab SLE Trials (data cut-off December 31, 2009)

	Placebo	Belimumab 1mg/kg	Belimumab 4 mg/kg	Belimumab 10mg/kg	Total Belimumab
<b>Total Subjects with ≥ 1 Malignancy/Neoplasm</b>	<b>3</b>	<b>5</b>	<b>1</b>	<b>24</b>	<b>30</b>
<b>Solid Tumors :</b>					
Breast Cancer	1	1	0	2	3
Colon Cancer	0	0	0	2	2
Malignant Melanoma	0	0	0	1	1
Carcinoid Tumor of the Stomach	1	0	0	0	0
Cervical Carcinoma (Stage 0)	0	1	0	0	1
Rectal Cancer	0	0	0	1	1
Renal Cell Carcinoma	0	0	0	1	1
Ovarian Cancer	0	1	0	0	1
Malig. Lung Neoplasm w/Mets (Bone/Marrow)	0	0	0	1	1
<b>Hematologic/Lymphatic:</b>					
B-cell Lymphoma	0	0	1	0	1
Nodal Marginal Zone B-cell Lymphoma	0	0	0	1*	1*
Multiple Myeloma	0	0	0	1	1
<b>Non-Melanoma Skin Cancer:</b>					
Basal Cell Carcinoma	1	0	0	3	3
Squamous Cell Carcinoma	0	0	0	4	4
<b>Solid Tumors of Unspecified Classification:</b>					
Hepatic and Lung Neoplasm	0	0	0	1	1
Lung and Thyroid Neoplasm	0	0	0	1	1
Lung Neoplasm	0	0	0	1	1
Thyroid Neoplasm	0	1	0	3	4
Soft Tissue Neoplasm	0	0	0	1	1
Breast Neoplasm	0	1	0	0	1

Reviewer's table based on Sponsor's Table 6-1; Appendix 6 of Summary of Clinical Safety Appendices  
 Per 120-day safety update, follow-up evaluation revealed this event to be non-malignant lymphadenopathy.

<sup>7</sup> 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 Disease 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.

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

### 7.6.2 Human Reproduction and Pregnancy Data

All of the study protocols that evaluated belimumab as a treatment for SLE or RA prohibited pregnant and breast feeding females from participating in these trials. Although these studies' entry criteria required women of reproductive potential to practice effective forms of contraception for the duration of the trials, there were a total of 47 pregnancies that occurred in the one Phase 2 and two Phase 3 SLE trials as of the data cut-off date of December 31, 2009. (Note: No pregnancies were reported to have occurred in the RA clinical development program or in the Phase 1 studies.) As shown in Table 98 below, 41 out of the 47 pregnancies occurred in patients who received belimumab while the remaining 6 pregnancies occurred in placebo-treated patients. Based on the outcome data collected by the Applicant on 38 completed pregnancies, similar rates for spontaneous abortion and stillbirth were observed for the placebo and total belimumab treatment groups, however, total fetal loss rates for both the placebo (3/6 subjects; 50%) and total belimumab (10/32; 31%) treatment groups were higher than that reported in the literature (range: 15-25%). Since the presence of anti-cardiolipin antibodies is associated with an increase in risk for fetal loss in SLE patients, serology data collected from subjects who became pregnant while participating in these studies was also examined for the presence of this antibody. Three out of the 6 placebo patients (50%) and 12 out of the 41 belimumab treated patients who became pregnant were positive for anti-cardiolipin antibodies. Additional review of these 38 completed pregnancies revealed 2 out of the 3 (50%) placebo patients and 7 out of 10 (70%) belimumab treated patients who had either a spontaneous abortion or stillbirth were positive for anti-cardiolipin antibodies.

Table 98 – Tabular Summary of Pregnancies During Phase 2 and 3 IV SLE Studies (cutoff date Dec. 31, 2009)

	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=1158	Total Belimumab N=1942
<b>Total Pregnancies</b>	6	13	2	26	41
<b>Ongoing</b>	0	3	0	4	7
<b>Unknown Outcome</b>	0	1	0	1	2
<b>Pregnancies with Known Outcomes</b>	6	9	2	21	32
<b>Live Birth without Congenital Anomaly</b>	0	4 (44%)	0	8 (38%) <sup>2</sup>	12 (38%)
<b>Live Birth with Congenital Anomaly</b>	0	0	0	1 (5%) <sup>1</sup>	1 (3%)
<b>Elective Termination</b>	3 (50%)	3 (33%)	1 (50%)	5 (24%) <sup>2</sup>	9 (28%)
<b>Spontaneous Abortion</b>	2 (33%)	2 (22%)	1 (50%)	6 (27%) <sup>1</sup>	9 (28%)
<b>Stillbirth</b>	1 (17%)	0	0	1 (5%)	1 (3%)
<b>Anti-Cardiolipin Positive</b>	3 (50%)	6 (46%)	2 (100%)	4 (15%)	12 (29%)
<b>  In subjects with live birth</b>	0	1/4 (25%)	0	0/9 (0%)	1/13 (8%)
<b>  In subjects with fetal loss</b>	2/3 (67%)	2/2 (100%)	1/1 (100%)	4/7 (57%)	7/10 (70%)

Adapted Sponsor's Table 2.7.4-44; p. 171 Summary of Clinical Safety

<sup>1</sup>Subject US011-001 in Study LBS02 had two pregnancies while in the trial: the first pregnancy ended in a spontaneous abortion while the second pregnancy resulted in the live birth of an infant with translocation of chromosomes 11 and 13 (microcephaly and atrioventricular septal defect). This chromosomal defect was also present in the mother (Subject). This infant died a few days post birth.

<sup>2</sup>Subject US020-002 in Study LBSL99 had two pregnancies while in the trial: the first pregnancy was electively terminated while the second pregnancy resulted in the live birth of a premature infant without congenital abnormalities or complications approximately more than ten weeks after the last dose of belimumab.

Further examination of the data displayed in Table 98 was remarkable for the occurrence of one live birth of an infant with a congenital anomaly (e.g., chromosomal translocation of 11 and 13 resulting in microcephaly and atrioventricular septal defect) to a 24 year-old female treated with 10 mg/kg of belimumab in LBSL02. This infant died a few days after birth as a result of its congenital abnormalities. The subject, who had the same congenital chromosomal abnormality as her infant, had an earlier pregnancy during the trial that resulted in a spontaneous abortion. Additionally, there were two premature live births without congenital abnormalities to patients treated with 10 mg/kg of belimumab (Subject US020-002 and Subject CO001-008). The premature infant born to Subject CO001-008 had multiple serious adverse events as a result of its prematurity but survived and was reportedly in good condition at four months except for low weight.

The safety database also contained information regarding three pregnancies in partners of subjects treated with placebo, 1 mg/kg and 10mg/kg of belimumab during these trials that resulted in one live birth without congenital abnormalities (placebo), one unknown outcome (1 mg/kg), and one spontaneous abortion (10mg/kg).

Since SLE typically affects young women of childbearing potential, the sponsor is proposing to conduct a pregnancy registry to further explore the potential effects of belimumab during pregnancy.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

This application did not contain any data generated from assessments of belimumab's effect on growth since the Applicant has not conducted a study in children or adolescents.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant stated in their submission that no overdoses occurred with belimumab during its clinical development. Since belimumab is a monoclonal antibody which has to be administered via intravenous infusion and is associated with serious adverse events such as infections and anaphylaxis, it is unlikely that this product will be abused. No evidence of withdrawal effects or increases in disease severity following treatment with belimumab were noted on review of follow-up data collected from patients who participated in the multidose, long term studies post-withdrawal of belimumab therapy.

## 7.7 Additional Submissions / Safety Issues

On November 23, 2010, the Applicant submitted a major amendment to this BLA consisting of a post hoc assessment of suicidality according to the Columbia Algorithm for the Assessment of Suicide (C-CASA) by [REDACTED] (b) (4) of suicides observed in patients exposed to belimumab in the application's safety database. The results of this analysis and a discussion of these findings can be found in the preceding Section 7.3.5c. Additional safety information that was contained in the Applicant's 120-day safety update submitted on October 6, 2010 has been incorporated into the appropriate preceding subsections of this review.

## 8 Postmarket Experience

Belimumab is a new molecular entity that has not been approved for marketing in any country.

## 9 Appendices

### 9.1 Literature Review/References

The Applicant conducted a review of the worldwide literature of the following databases: EMBASE and MEDLINE. A total of 4 publications were thus identified that described the

safety and tolerability of belimumab in SLE studies submitted in support of this application. These publications were examined for clinical content and no new safety issues related to the use of belimumab as a treatment for SLE were identified.

An updated literature search was conducted by this medical officer in early February 2011 using the search engine PubMed. A total of 19 citations in English were identified out of which 4 were included in the original literature review by the Applicant. Examination of the remaining 15 citations did not reveal any new potential safety signals associated with the use of belimumab.

**References:**

1. Abrahamowicz et al. The Relationship Between Disease Activity and Expert Physician's Decision to Start Major Treatment in Active Systemic Lupus Erythematosus: A Decision Aid for Development of Entry Criteria for Clinical Trials. *J Rheumatol* 1998; 25(2):277-284
2. ACR Ad Hoc Committee on SLE Response Criteria. The American College of Rheumatology Response Criteria for Systemic Lupus Erythematosus Clinical Trials: Measures of Overall Disease Activity. *Arthritis & Rheum*, November 2004, 50(11):3418-3426
3. Appenzeller S, Pallone AT, Natalin RA, Costallat LT. Prevalance of Thyroid Dysfunction in Systemic Lupus Erythematosus. *J Clin Rheumatol*. 2009; 15:117-119.
4. Bernatsky S, Boivin JF, Joseph L, et al. Mortality in Systemic Lupus Erythmetosus. *Arth Rheu* 2006;54(8):2550-7.
5. Furie RA, et al., Novel Evidence-Based Systemic Lupus Erythematous Responder Index, *Arthritis & Rheum* 2009, 61(9):1143-1151.
7. Gladman et al. The Development and Initial Validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus. *Arthritis & Rheum*, March 1996, 39(3):363-369.
8. Hanly JG. Neuropsychiatric Lupus. *Rheum Dis Clin N Am* (2005) 31:273-298
9. Karassa FB, Magliano M. Isenberg DA. Suicide attempts in patients with Systemic Lupus Erythematosus. *Ann Rheum Dis* 2003;62:58-60.
10. Lazurova I, Benhatchi K, Rovensky J, Kozakova D, et al. Autoimmune Thyroid Disease and Autoimmune Rheumatic Disorders: A Two-sided Analysis. *Ann NY Acad Sci* 2009; 1173:211-216.
11. 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.
12. Petri M, J Buyon, M Kim. Classification and Definition of Major Flares in SLE Clinical Trials. *Lupus* (1999) 8, 685-691
13. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, et al., *J Allergy Clin Immunol*, 2006, 117(2):391-397

## 9.2 Labeling Recommendations

Proposed package labeling was included in this submission, however, a line-by-line labeling review is not included since negotiations with the Applicant are on-going. The following are general recommendations for the product label based on review of the data submitted in support of this application:

1. The tradename Benlysta® is acceptable. It has been deemed acceptable by both DMETS and the Division
2. Benlysta® should have a Medication Guide. A MedGuide has been proposed by the Applicant and has been deemed acceptable by both DRISC and the Division

3. The Warnings and Precautions section should include information regarding the increase in risk for deaths
4. Section 2.2 Premedication Recommendations needs to be revised to state that prescribers should consider administering premedication prophylaxis for hypersensitivity and infusion reactions
5. Sections 5.4 Hypersensitivity/Anaphylactic Reactions and 5.5 Infusion Reactions need to be revised to reflect the information generated from the pivotal Phase 3 trials based on the Division's analysis of these data
6. Under Section 8 Use in Specific Populations information regarding the lower response rates observed in black subjects needs to be added
7. Under Section 12.2 Pharmacodynamics (b) (4)  
  - a. Summary table for clinical response rates needs to be revised to include the results from the 1mg/kg belimumab dose group for both trials
  - b. Add information regarding the lack of efficacy in black patients
  - c. Include information regarding belimumab's effect on corticosteroid tapering
  - d. Add information regarding belimumab's effect in preventing severe flares

### 9.3 Advisory Committee Meeting

On November 16, 2010, an Arthritis Advisory Committee (AAC) meeting was convened to discuss the risks and benefits associated with the use of belimumab based on the efficacy and safety issues identified during the agency's review of the data submitted in support of this application. In addition to formal presentations from the Applicant and the Division's clinical and statistical reviewers, the meeting included personal testimonies from SLE patients and patient advocates that highlighted the paucity of effective treatments for this life-threatening and disabling condition. The 6 questions posed to the Committee and a tabulation of votes are shown below in Table 99:

**Table 99 – Questions and Voting Results for November 16, 2020 Arthritis Advisory Committee Meeting on Belimumab**

Questions	Votes		
	Yes	No	Abstain
Q1. Discuss the efficacy data of belimumab consider the following: a. Efficacy driven by contribution of musculoskeletal and mucocutaneous organ systems results b. Lack of demonstrated efficacy in organ systems associated with poor outcome and mortality in SLE c. Lack of demonstrated efficacy in patients of African American or African heritage d. Numerically smaller efficacy results for patients from US and Canada compared to some other regions	Non-voting question		
Q2. Discuss the overall safety profile of belimumab considering the following: a. Safety signals of infection, malignancy suicidality and mortality b. Potential risk of using belimumab when combined with other immunosuppressive agents, which may be needed to treat more serious manifestations of SLE that are associated with poor outcome and mortality	Non-voting question		
Q3. Discuss the suicidality data and provide recommendations for further evaluation, if necessary.	Non-voting question		
Q4. Considering the totality of the data, has belimumab at a dose of 10mg/kg at-week intervals for the first 3 doses and at 4-week intervals thereafter demonstrated substantial evidence of efficacy (b) (4) in adult patients with active, autoantibody-positive, SLE who are receiving standard therapy? a. If not, what further efficacy data should be obtained?	10	5	0
Q5. Is the safety profile of belimumab sufficient for approval (b) (4) in adult patients with active, autoantibody-positive SLE who are receiving standard therapy? a. If not, what further efficacy data should be obtained?	14	10	0
Q6. Do the efficacy and safety data provide substantial evidence in support of approval of belimumab at a dose of 10mg/kg at 2-week intervals for the first 3 doses and at 4 week intervals thereafter (b) (4) in adult patients with active, autoantibody-positive SLE who are receiving standard therapy?	13	2	0

In general, the AAC acknowledged the limitations of the efficacy and safety data particularly in patients of African-American or African heritage, and patients with severe renal lupus and central nervous system disease. Additionally, there were concerns raised that Study 1057, which had the more robust efficacy results of the two pivotal studies submitted in support of this application, did not closely reflect the demographics of the lupus population in this country. The AAC did know that belimumab's safety profile appears to be favorable compared to the other medicines that are currently used to treat SLE but they did recognize a number of safety issues including depression and suicidality and the lack of information regarding the potential risk of using belimumab in combination with other immunosuppressive agents that would need to be addressed in post-marketing studies. Based on the weighing of evidence presented to them, the AAC voted overwhelmingly to recommend approval of belimumab and recommended that the product's label should clearly state that patients with severe renal and central nervous system disease were not evaluated.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**BLA Number: 125370**

**Applicant: Human Genome Sciences**      **Stamp Date: June 9, 2010**

**Drug Name: Benlysta®  
(Belimumab)**

**BLA Type: Priority**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: LBSL01 Study Title: A Phase 1, multicenter, DB, single and double dose escalation study to evaluate the safety, tolerability, immunogenicity, PK and PD of belimumab in patients with SLE Sample Size: 28 subjects Arms: 4 cohorts (1mg, 4 mg, 10 mg and 20 mg/kg) Location in submission: Module 5.3.3.2	X			
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and	X			

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1: C1056 – 76 week, Phase 3, multicenter, DB, RCT to evaluate the efficacy and safety of belimumab. Indication: Treatment of SLE Pivotal Study #2: C1057: 52 week, Phase 3, multicenter, DB, RCT to evaluate the efficacy and safety of belimumab. Indication: Treatment of SLE				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Refer to Oct. 2006 SPA agreement filed under IND 9970
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

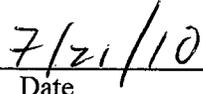
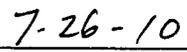
**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?     X**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No potential clinical review issues have been identified at this time.

 _____ Reviewing Medical Officer	 _____ Date
 _____ Clinical Team Leader	 _____ Date