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APPLICATION NUMBER:

761043Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number	761043
Priority or Standard	Standard
Submit Date	September 22, 2016
Received Date	September 22, 2016
PDUFA Goal Date	July 22, 2017
Division / Office	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)/ODEII
Reviewer Name	Rosemarie Neuner, MD, MPH
Review Completion Date	June 20, 2017
Established Name	Belimumab
(Proposed) Trade Name	Benlysta® (b) (4)
Therapeutic Class	Monoclonal Anti-BLyS Antibody
Applicant	Human Genome Sciences, Inc.(GSK)
Formulation	Subcutaneous Injection
Dosing Regimen	200 mg subcutaneously (SC) once weekly
Indication	Treatment of patients with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard of care
Intended Population	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends approval of this biological licensing application for the subcutaneous formulation of 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 when coupled with data reviewed in support of the IV formulation under BLA 125370, is sufficient to support a finding of efficacy and safety for belimumab administered as a fixed dosing regimen of 200 mg subcutaneously via prefilled syringe or autoinjector once weekly.

1.2 Risk Benefit Assessment

The efficacy of the subcutaneous formulation of belimumab as a treatment for (b) (4) in adult patients with active, autoantibody-positive SLE on standard therapy was assessed in a single, adequate and well-controlled study, C1115, that evaluated a single fixed dosing regimen of 200 mg of belimumab administered subcutaneously (SC) via prefilled syringe (PFS) once weekly compared to placebo in 836 subjects with active, antibody-positive SLE on stable immunosuppressive medications. Other than requiring a higher SELENA SLEDAI disease score at baseline (i.e., ≥ 8 instead of ≥ 6), the protocol for study C1115 was similar in design to the common protocol utilized by the two pivotal phase 3 trials, 1056 and 1057, reviewed in support of the licensing approval of the intravenous formulation of belimumab under BLA 125370. In study C1115, patients treated with belimumab SC had a modest but statistically higher rate of response than placebo patients as assessed by the composite endpoint, the SLE Responder Index (SRI). The proportions of subjects achieving success for each of the subcomponents of the SRI were numerically higher in the belimumab group than the placebo group in this study and also reached statistical significance generating support for the robustness of the modest findings from the primary analysis. Additional support was provided by the results from the four prespecified sensitivity analyses which were consistent overall with those of the primary efficacy analysis as well as consistently positive results from other secondary analyses that employed higher reductions in SELENA SLEDAI thresholds (e.g. SELENA SLEDAI ≥ 5 through ≥ 8) for the SRI responder analysis and the EMA-modified SRI response rate. These results were consistent with the results from the studies supporting the intravenous formulation of belimumab under BLA 125370.

Although a consistent reduction in the risk for SLE disease flares was not observed in the two clinical trials reviewed in support of the IV belimumab BLA, the Applicant is

interested in obtaining a marketing claim for this clinical finding for belimumab SC based on the results from the analysis of the first major secondary endpoint in study C1115. A significant reduction in risk for severe disease flare over 52 weeks as assessed by the SELENA SLEDAI Flare Index (SFI) in favor of the belimumab SC group was noted for this assessment. This reduction in flare risk was associated with a prolongation in the median time to first severe flare of 171 days in the belimumab SC group versus 118 days in the placebo group. Results from the other ancillary secondary disease flare assessments such as any SFI flare, severe SFI flare, and median time to first SFI flare as well as SFI flare rates from Week 24 to Week 52 following implementation of background medication restrictions were all robust and supportive of those for this first major secondary endpoint. In view of these findings, consideration should be given in granting the Applicant's request for a marketing claim for reduction in SLE disease flares with belimumab SC.

A numerically higher proportion of belimumab SC patients were able to reduce their baseline corticosteroids by at least 25% to ≤ 7.5 mg/day during Weeks 40 through 52, but the results from this clinically relevant second major secondary endpoint were not significant on comparison to placebo which was consistent with the data reviewed in support of the IV formulation of the product.

(b) (4)
Although a greater improvement over baseline FACIT-Fatigue score was observed in favor of the belimumab SC group as compared to placebo, and a higher proportion of subjects in the belimumab SC group achieved an improvement in their FACIT-Fatigue score exceeding the Applicant-proposed minimally important clinical difference (MCID) of ≥ 4 points versus the placebo group, these improvements were not consistently maintained over the course of the study. (b) (4)

Unlike what was observed in the pivotal studies for IV belimumab, results from various subgroups analyses involving patients of African American or Black race suggest a favorable treatment effect for belimumab SC. However, the results from these analyses should be interpreted cautiously given the small number of subjects involved. Determination of efficacy in this population who is at risk for more aggressive disease and worse disease outcomes will have to be delayed until results from the ongoing, randomized, controlled, post-marketing commitment study BEL11547 in SLE patients of African American or Black race become available.

Specific safety concerns raised during the review of safety in support of the IV formulation of belimumab were noted again for belimumab SC. These include deaths, a higher rate of serious infections including sepsis and an increase in psychiatric events that included depression and suicidality in patients treated with belimumab SC. The

types of deaths associated with belimumab SC 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. Although an increase in the risk for serious infections is an expected finding for an immunosuppressive agent such as belimumab that targets B cells, the exposure-adjusted incidence rates for serious infections in study C1115 suggest no difference in the rates for serious infections for the two treatment groups. However, the exposure-adjusted incidence rate for sepsis was higher for the belimumab SC treatment group. Two out of the three deaths in the belimumab SC group were due to sepsis and both of these subjects had body weights in the lowest weight quartile (e.g., < 55 kg). Given the very small number of events, definitive conclusions could not be drawn about a potential association between an increase in risk for fatal infections (sepsis) and higher exposure to belimumab. Further, a weight-based quartile analysis for serious adverse events including infections did not support such an association and there was no increase in infections or serious infections observed in belimumab SC patients who had treatment-related reductions in immunoglobulins. Although the protocol for study C1115 prohibited the enrollment of potential subjects with evidence of serious suicide risk and/or any suicidal ideation on the Columbia Suicide Severity Rating Scale (C-SSRS) and required a suicidality assessment at each visit, there were two cases of suicide/self-injury which occurred in belimumab SC treated patients versus none in the placebo group. Not unexpectedly, a higher proportion of subjects in the belimumab SC group had injection site reactions as compared to placebo patients, an observation which warrants inclusion in product labeling. Since many patients who participated in this trial were taking concomitant corticosteroids, this may have resulted in an underestimation of the risk for injection site reactions as well as for hypersensitivity spectrum reactions including anaphylaxis to occur with belimumab SC.

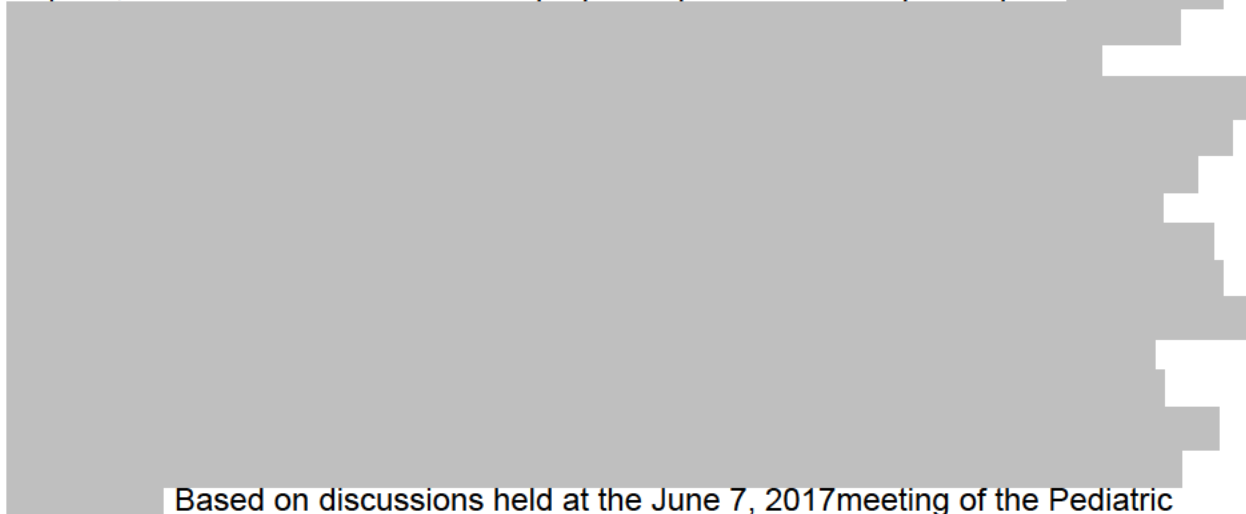
Examination of long-term safety data generated from the ongoing open-label extension of study C1115, the numerous ongoing open-label extensions and postmarketing required and commitment studies in Asian patients, Black race patients, BLyS activity signature test, pregnancy and adverse events of interest registries that are being conducted with the IV formulation of belimumab as well as of the postmarketing worldwide literature also did not reveal any new safety signals.

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 for potential treatments for this disease. The SRI represents both a statistically and clinically rigorous endpoint to achieve. Based on the totality of data generated from the adequate and well-controlled study C1115, when coupled with the efficacy and safety results from the two well-controlled studies 1056 and 1057 conducted with IV belimumab reviewed previously under BLA 125370, the risk/benefit

assessment favors approval of the 200 mg once weekly dose of belimumab SC as add-on treatment for patients with active, sero-positive SLE despite standard of care

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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 ≥ 5 through ≤ 18 years old with SLE pending the submission of the safety, efficacy and PK/PD data from their ongoing phase 3 pediatric SLE study BEL114055 evaluating weight-based dosing with the IV formulation of belimumab has been completed, in order to ensure that the SC formulation's risk/benefit profile warrants further evaluation in the pediatric population. Pursuant to the latter request, this submission contained a proposed pediatric development plan (b) (4)



Based on discussions held at the June 7, 2017 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 ≥ 5 through ≤ 17 years of age was acceptable.

In addition to their ongoing pediatric SLE study BEL114055, the Applicant has a number of ongoing postmarketing required studies with the IV formulation of belimumab under BLA 125370. These include a 1-year safety study BEL115467 in 4,000 SLE patients evaluating adverse events of interest (e.g., mortality, serious infection, malignancy, depression/suicidality and hypersensitivity spectrum reactions including anaphylaxis) and a pregnancy registry (BEL114256) that the Applicant is proposing to amend to include SLE patients exposed to belimumab SC. Additionally, there are ongoing postmarketing commitment studies evaluating the safety and efficacy of IV belimumab in patients of Black race (study BEL11547) and lupus nephritis (study BEL 115471) as

well as studies evaluating treatment holiday (BEL116027) and BLyS activity signature (Study 201509) that hopefully should provide much needed data to answer longstanding questions regarding belimumab's safety and efficacy profile. Additionally, the Applicant is proposing to conduct a B-cell modulation study evaluating the efficacy and safety of co-administration of belimumab SC with rituximab in SLE patients with refractory disease. In view of these ongoing trials, no additional postmarketing required studies or commitments should be required for belimumab SC other than the proposed pediatric study.

1.4 Recommendations for Postmarket Requirements and Commitments

A Risk Evaluation Minimization Strategy (REMS) is not necessary for belimumab SC since its safety profile appears to be similar to that of the marketed IV formulation. However, this requirement may be reconsidered if future postmarketing evidence identifies a safety risk that cannot be managed by labeling.

2 Introduction and Regulatory Background

2.1 Product Information

The established name of the subject product of this application is belimumab subcutaneous (SC) liquid formulation and the proposed trade name is Benlysta (b) (4)®. The established name will be used in this review to refer to the product. Belimumab SC liquid formulation is supplied as 200 mg belimumab in 1 mL as a single-use, sterile liquid drug product in two presentations: a prefilled syringe and a prefilled syringe contained within an autoinjector. Both formats use the same prefilled syringe container closure which consists of a 1mL long, Type (b) (4) glass syringe with a half-inch 27 gauge, staked (b) (4) needle, (b) (4) rubber plunger stopper, and a rigid needle shield (b) (4). Each presentation contains 1.0mL (deliverable) of 200 mg/mL of belimumab in .65 mg/mL L histidine, 1.2 mg/mL L-histidine monohydrochloride, 6.7 mg/mL sodium chloride, 5.3 mg/mL L-arginine hydrochloride, 0.1 mg/mL polysorbate 80, with a pH of 6.0 for single use administration.

Belimumab is a recombinant human IgG1λ therapeutic monoclonal antibody specific for B lymphocyte stimulator (BLyS: BAFF) that binds to soluble BLyS with high affinity (b) (4)

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 (b) (4)

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 currently that are approved and available for the treatment of SLE:

Table 1 – Currently Available Treatments for SLE

Product	Year of Approval	Indication
Aspirin	1948	Treatment of arthritis and pleurisy of SLE
Prednisone	1955	During an exacerbation or as maintenance therapy in selected cases of SLE
Hydroxychloroquine	1955	Treatment of discoid and systemic lupus erythematosus
Belimumab IV (Benlysta)	2011	Treatment of active, autoantibody positive systemic SLE despite standard of care

The effectiveness of the first three oral 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 particularly for major organ involvement. The

currently approved USPI for belimumab contains a limitations of use for off-label biologics (e.g., rituximab) and intravenous cyclophosphamide as well as for patients with severe lupus nephritis and severe central nervous system lupus since all of the phase 3 studies conducted in support of the product excluded patients receiving concurrent treatment with these agents or with these disease manifestations.

2.3 Availability of Proposed Active Ingredient in the United States

Belimumab is an approved therapeutic biologic product that is available and marketed in the U.S. (since 2011) and in over 60 countries worldwide (as of October 2017) as an intravenous (IV) formulation at a dose of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

2.4 Important Safety Issues With Consideration to Related Drugs

A number of safety concerns have been identified with the use of belimumab. These are listed under the Warnings and Precautions section of the product's label and include: increased risk for mortality, increased susceptibility for serious and fatal infections, increased risk for progressive multifocal leukoencephalopathy (PML), hypersensitivity reactions including anaphylaxis and infusion reactions, as well as depression including suicidality. Due to belimumab's mechanism of action, patients should not be administered immunizations with live vaccines concurrently while receiving the product.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following are highlights of the regulatory activity that occurred during the development program for belimumab SC under IND 9970.

An End-of-Phase 2 meeting with the Applicant was held on July 7, 2011. Agreements and discussion of key clinical and regulatory issues at that time include:

- Agreement reached on CMC tests including analytical procedures and acceptance criteria for adequacy for release and stability testing of belimumab bulk drug substance
- Agreement reached that no additional non-clinical studies were required to support the phase 3 SC program
- Agreement reached that positive results from a single, placebo-controlled, phase 3 pivotal study of similar design to the prior pivotal IV studies should be adequate to support the filing of the new formulation and route of administration and on the acceptability of the proposed adverse events of special interest (mortality, infections, malignancy, depression/suicidality, and anaphylactic/hypersensitivity reactions)

- Agreement for the Applicant to perform population PK analysis using a nonlinear mixed effect modeling approach based on a pooled PK dataset

At a Type C meeting held on January 26, 2013, the following items summarize the agreements reached between the Applicant and the Division as well as the key clinical and regulatory issues that were discussed at that time.

- Agreement reached on the bridging plan for commercial prefilled syringe (PFS) from the phase 3 PFS product (including human factor validation plan)
- Concerns raised regarding the adequacy of the bridging plan for the autoinjector (AI) and the adequacy of testing of commercial AI to provide data on reliability of the device with real-life use
- The Applicant was told that they would have to submit a separate original BLA for the PFS and AI belimumab SC products since the proposed products are not quantitatively and qualitatively identical or alike biological products in composition to the approved IV belimumab product and they require a change in composition (i.e., formulation) from the approved belimumab to support the change in the route of administration

On April 8, 2013, January 24, 2014 and May 1, 2014, the following understandings and agreements were reached between the Applicant and the Division regarding the belimumab SC bridging program

- A single dose study in SLE subjects was inadequate for device bridging and the AI drug product had to be tested in SLE patients with chronic real-life use
- Agreement reached on the acceptability of the AI PK study in healthy volunteers (Protocol BEL 117100)
- The inadequacy of the real life use Protocol 200339 in terms of size and duration and the unlikelihood of accurate assessment and interpretation of the PK trough concentrations from this study because of the study's short duration and potential nonequilibrium conditions
- Agreement was reached regarding the bridging program after changes were made to the real life use Protocol 200339 (i.e., 100 SLE patients for 8 weeks)

A pre-BLA meeting was held on September 8, 2015. The following items summarized the understandings reached between the Applicant and the Division and the key clinical and regulatory issues that were discussed at that time.

- The single phase 3 belimumab SC study was sufficient to support the filing of a BLA for belimumab SC when supported by the belimumab IV clinical studies and the device bridging program. Final determination of adequacy would be a review issue.
- No additional clinical pharmacology studies were needed and the proposed clinical pharmacology package including the population PK and PD analysis were sufficient to support filing and review of the BLA for 200 mg of belimumab SC

once weekly administered either by AI or PFS. Final determination of the adequacy would be a review issue.

- Agreements were reached regarding conducting additional analyses of the primary and first major secondary endpoints (i.e., tipping point analysis), cross referencing data previously submitted to support the licensure of IV belimumab, the content and format of the application as well as the approach and cut-off date for the 120-day safety update
- Agreement on (b) (4) a distinguishing proprietary name. Alternatively, a unified USPI would be acceptable.

On May 10, 2016, the Applicant informed the Division of a delay in the submission of the BLA application for belimumab SC. The following items summarized the understanding reached between the Applicant and the Division on May 31, 2016 as a result of this delay:

- Agreement on the revised cut-off date of March 8, 2016 for safety data
- Submission of the 120-day safety update in December 2016
- Submission of bulk drug substance and drug product stability data during the BLA review

2.6 Other Relevant Background Information

According to the Applicant, similar agreements regarding the pivotal phase 3 study protocol and statistical analysis plan for the primary and major secondary endpoints of this trial were reached with the European Medicines Agency (EMA). However, the EMA additionally requested a modification of the primary endpoint, the SRI response rate at Week 52, which involved replacing the “No New BILAG 1A/2B domain score” component of the SRI with “No BILAG 1A/2B domain score.” (Note: For completeness, the results of this modified analysis of the SRI endpoint at Week 52 are shown in Table 43 located in Section 6.)

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 report for the pivotal trial BEL112341, the Applicant certified that this study 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).

3.3 Financial Disclosures

The financial disclosure information for this application is discussed under Section 10.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Sean Fitzsimmons from OPQ/OBP/DBRRI reviewed the CMC data submitted in support of belimumab SC. He is recommending approval pending the results from a drug product inspection at Glaxo scheduled to occur between June 29th and July 7th 2017 with a PMC to re-evaluate belimumab drug product lot release acceptance criteria for osmolality, potency and protein concentration assays after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods with corresponding data, analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications submitted by HGS.

4.2 Clinical Microbiology

Dr. Jessica Hankins from OPQ/OPF/DMAMABIV is reviewing the microbial control, CMC sterility assurance and microbiology product quality data for this application. She will be recommending approval with PMCs that are still being determined.

4.3 Preclinical Pharmacology/Toxicology

Dr. Brett Jones reviewed the preclinical pharmacology/toxicology data contained in this application. Dr. Jones recommends approval of this application based on the following:

- Non-clinical information cross-referenced by the Applicant from the IV formulation of belimumab (BLA 125370)

- The results from a 4-week subcutaneous local tolerance study conducted in cynomolgus monkeys did not raise any nonclinical safety concerns for the administration of belimumab by the subcutaneous route

4.4 Clinical Pharmacology

The Clinical Pharmacology data in this application was reviewed by Dr. Sury Sista who recommends approval of this application based on the following:

- Absolute bioavailability of belimumab from the SC formulation 06-D (200 mg/mL) administered via prefilled syringe (PFS) ranged from 74-82%. The overall estimate of SC bioavailability from a population PK analysis was 74%.
- Dose of 200 mg/week via SC administration led to comparable belimumab average study-state concentrations as the approved IV 10 mg/kg every 4 weeks dose regimen
- Comparable pharmacokinetics (PK) was established between the PFS and autoinjector (AI) presentations for belimumab SC
- No apparent effect was found on belimumab's PK in four subjects who tested positive for anti-belimumab antibodies, supporting the conclusion that the anti-belimumab antibodies were non-neutralizing. None of the subjects in the other studies tested positive for immunogenicity

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 IV and SC trials. Additionally, these changes were seen as early as Weeks 8 or 12 of treatment and were sustained through Week 52. The changes in C3, C4 and naïve B-cells were correlated with response to belimumab IV and SC but did not adequately predict responses to treatment with the product.

4.4.3 Pharmacokinetics

The pharmacokinetic (PK) profile of the to-be-marketed 06-D formulation of belimumab SC was assessed in the phase 2 bioavailability studies BEL11448 and BEL116119 that were conducted in healthy volunteer adults and Japanese subjects, respectively, and in the phase 3 efficacy and safety study BEL112341 conducted in subjects with SLE. In order to establish comparability between the PFS and AI presentations, the Applicant conducted an additional phase 2, relative bioavailability bridging study, BEL117100, in subjects with SLE.

Based on a population PK analysis using a nonlinear mixed effect model of pooled PK data from the above listed studies, a total of 688 subjects (544 SLE patients and 107 healthy volunteers who received belimumab SC, and 27 healthy volunteers subjects who received belimumab IV), belimumab SC's C_{max} was 108 µg/mL, $AUC_{0-\infty}$ was 726 day·µg/mL, half-life was 1.1 days and systemic clearance was 204 mL/day. Belimumab SC's volume of distribution was 5L. Similarity in C_{max} and $AUC_{0-\infty}$ between abdomen and thigh injection sites was also observed. Bioequivalence between the belimumab AI and PFS presentations was established based on comparable PK. Systemic exposure to belimumab in the Population PK analyses demonstrated that a dose adjustment is not required for age, gender, or race. Subjects in higher body weight quartiles or body mass index (BMI) categories had lower systemic belimumab exposure but the effects of body weight and BMI on exposure to belimumab SC were not considered clinically relevant. As no clinically relevant effect on efficacy or safety was noted on review of weight and BMI analyses for the efficacy and safety of belimumab, no dose adjustment is required based on these parameters. Studies in renal and hepatic impairment have not been conducted with the product.

Clinical and pharmacokinetic data (e.g., belimumab trough concentrations when patients were switched from IV to SC administration in study 200399) suggest an

interval of 1 to 4 weeks when switching from the last IV administration to the first SC dose of belimumab.

No formal drug-drug interaction studies have been 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, four subjects in the belimumab SC clinical development program tested positive for anti-belimumab antibodies. None of these four subjects participated in the 52-week phase 3 study BEL112341 (study C1115). The clinical pharmacology reviewer concluded these anti-belimumab antibodies were non-neutralizing as they did not have an apparent effect on belimumab SC's PK profile.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

As part of their clinical development program for belimumab SC as a treatment for SLE, the Applicant conducted a total of seven clinical trials: four phase 1 trials (HGS1006-C11105/BEL114448, BEL116119, BEL117100 and HGS1006-C1058), two phase 2 trials (BEL112232/HGS1005-C1070 and 200339), and 1 phase 3 trial (BEL112341/HGS1006-C1115). Key design features of these trials are summarized in Table 2. Five of the studies in Table 2 (HGS-C11105/BEL114448, BEL116119, BEL117100, 200339 and BEL112341/HGS1006-C1115) evaluated the proposed to-be-marketed formulation of belimumab SC (06-D). The two remaining studies (HGS1006-C1058 and BEL112232/HGS1006/C1070) are listed for completeness since they evaluated another liquid formulation of belimumab for subcutaneous administration (06-C) that is no longer under clinical development by the Applicant.

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

Study/ Objectives	Study Design; Duration; No. of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 1					
Protocol HGS-C1105/BEL114448 Objectives: Determine the absolute bioavailability, PK, tolerability and safety of a single dose or multiple doses of belimumab administered via subcutaneous (SC) injection	Multi- center, randomized, parallel group, open label, single and multidose study 4 sites in USA	Single Dose: Groups 1-4: 120 mg belimumab x 2 sequential SC injections; 200 mg or 240 mg belimumab x 1 SC injection; or 240 mg belimumab x 1 IV infusion Multiple Dose: Groups 5-6: 120 mg belimumab x 2 sequential SC injections; or 200 mg belimumab x 1 SC injection on Days 0, 7, 14, and 21	N=108 Groups 1-4: 78 Single dose: SC Belimumab 2x120 mg: 20 1x200 mg: 19 1x 240 mg:20 IV Belimuamb 240 mg: 19 Groups 5 and 6 N=40 Multiple dose: SC Belimuamb every 4 wks: 2x120: 20 1x200: 20	Healthy volunteer adults	PK parameters (AUC _{0-t} , AUC _{0-∞} , C _{max} , t _{max} , t _{1/2}) Adverse events, vital signs, electrocardiograms, clinical lab tests, local tolerance evaluation (injection site), biomarkers and immunogenicity
BEL116119 Objectives: Evaluate the safety, tolerability, and PK following IV administration and SC administration of belimumab	Single center, open label, randomized, parallel group, single dose study 1 Japanese site	Belimumab 200 mg single dose via IV infusion or SC injection	N=16	Healthy Japanese males	PK parameters (AUC _{0-t} , AUC _{0-∞} , C _{max} , t _{max} , t _{1/2}) Adverse events, vital signs, electrocardiograms, clinical lab tests, local tolerance evaluation (injection site), biomarkers and immunogenicity
BEL117100 Objectives: Determine the relative bioavailability, safety, and tolerability of belimumab administered via SC injection	Single center, randomized, open-label, parallel group, single dose study 1 site in USA	Belimuamb 200 mg single dose via prefilled syringe (PFS) SC injection or autoinjector (AI) SC injection in thigh or abdomen	N=81 Abdomen PFS: 20 AI: 20 Thigh PFS: 20 AI: 21	Healthy volunteer subjects	PK parameters (AUC _{0-t} , AUC _{0-∞} , C _{max})

Table 2 (cont.) – Key Design Features of the Belimuamb SC SLE Clinical Development Program Trials

Study/ Objectives	Study Design; Duration; No. of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 1					
HGS1006-C1058 Objectives: Determine the absolute bioavailability of belimumab administered via subcutaneous injection; 2. Assess the safety of SC vs IV belimumab	Multicenter, randomized, open label, parallel group, absolute bioavailability trial 3 sites USA	Single dose of belimumab 100 mg via IV infusion over 1 hour Single dose of belimumab 100 mg via SC injection (Note: Evaluated belimumab formulation 06-C which is not proposed for marketing)	N=36 17 subjects in belimumab IV group 19 subjects in belimumab SC group	Healthy volunteer adults	PK parameters (AUC _{0-t} , AUC _{0-∞} , C _{max}) Adverse events, vital signs, electrocardiograms, clinical lab tests, biomarkers and immunogenicity
Phase 2					
BEL112232/HGS1006/C1070 Objectives: Assess safety, tolerability and biological activity of two dosing schedules of belimumab administered SC via subcutaneous injection	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 (Note: Evaluated belimumab formulation 06-C which is not proposed for marketing)	N=56 28 subjects every two weeks 28 subjects three times/week	Adults age ≥ 18 years with SLE as defined by ACR criteria that is active as per SELENA SLEDAI disease activity score ≥ 4 at screening with positive autoantibodies	Safety and tolerability, absolute and % change from baseline in B cells and B cell subsets at Weeks 12 and 24
200339 Objectives: Assess the safety and PK of SC belimumab; 2. Evaluate the suitability of an AI for self-administration in real-life conditions in subjects with SLE	Open label, single arm, multi-dose, real-life use study for 8 weeks	Belimumab 200 mg weekly SC injection via Autoinjector (AI)	N=95	Adults age ≥ 18 years with SLE as defined by ACR criteria that is active as defined by the presence of ANA or anti-dsDNA autoantibodies (at screening or historically)	Proportion of subjects successfully able to self-administer their observed first and second doses in Weeks 1 and 2.

Table 2 (cont.) – Key Design Features of the Belimuamb SC SLE Clinical Development Program Trials (cont.)

Phase 3					
BEL112341/HGS1006-C1115 Objectives: Assess the safety, tolerability, and efficacy of belimumab administered via SC injection	Multicenter, randomized, double-blind, placebo-controlled, 52-week comparative parallel group trial Total 177 sites in North America (67 sites), Europe (53 sites), Latin America (25 sites) and Asia (34 sites)	Belimumab 200 mg or placebo via weekly SC injection All subjects received concomitant SLE standard therapy	N=836 556 subjects belimumab 200 mg SC 280 subjects placebo SC	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	SRI Response 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)

5.2 Review Strategy

The Applicant conducted one adequate and well controlled phase 3 trial, BEL11234/HGS1006-C1115, in support of this application which provided the evidence of efficacy and placebo-controlled safety data. Therefore, this study was the primary focus of my review. Additionally, the Applicant submitted the completed results from three phase 1 trials (HGS1006-C11105/BEL114448, BEL116119, BEL117100) and one phase 2 trial (200339) which were not reviewed in support of the proposed belimumab liquid formulation's efficacy (b) (4) in patients with active, autoantibody-positive SLE on standard therapy for the following reasons: HGS1006-C11105/BEL114448, BEL116119, BEL117100 and 200339 were open label trials and were not designed to evaluate the efficacy (i.e., the primary objective was either pharmacokinetics or safety) of the product, evaluated doses of the liquid formulation of belimumab that were not studied in the pivotal phase 3 study (HGS1006-C11105/BEL114448), or was conducted in a population different from the patient population (e.g., healthy adult volunteers or healthy Japanese males) evaluated in the pivotal phase 3 study (BEL11448, BEL117100, and BEL116119).

The safety database included all subjects who participated in the pivotal phase 3 trial (BEL11234/HGS1006-C1115) as well as safety data collected from the phase 1 and phase 2 studies. These data will be discussed in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

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 pivotal studies reviewed in support of the marketing approval of the IV formulation of belimumab as well as in the pivotal phase 3 study, BEL11234/HGS1006-C1115, conducted in support of the belimumab liquid SC formulation the subject of this review.

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.¹ A clinically meaningful difference has been reported to be improvement of 6 points or worsening of 8 points.² The SLEDAI was modified in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial; this

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

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

modification, known as the SELENA-SLEDAI, added clarity to some of the definitions of activity in the individual items but did not change the basic scoring system. The SELENA-SLEDAI was the index used in the belimumab pivotal trials.

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

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

The 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 primary endpoint utilized in the pivotal phase 3 study for belimumab SC (BEL11234/HGS1006-C1115) was the SLE Responder Index (SRI). This was the same endpoint used by the pivotal phase 3 studies reviewed in support of IV belimumab. This novel, three-component endpoint was created based on exploratory analyses of a failed phase 2 study conducted as part of the clinical development program for IV belimumab with the intention of capturing clinically meaningful change while ensuring there would not be significant worsening in overall disease activity.³ It is comprised of the 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:

- ≥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.

Minimal clinically important differences have been defined for both the SELENA SLEDAI and PGA, while the BILAG was created on the principle of clinically important

³ Furie et al., Arthritis & Rheum, 2009, 61(9):1143-1151

differences. Based on the results from the pivotal phase 3 studies for IV belimumab, a SRI responder rate $\geq 10\%$ is considered to be a clinically important difference between treatments. 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.

A study report for the randomized controlled trial BEL11234/HGS1006-C1115 that evaluated the prefilled syringe presentation of belimumab SC will be presented below. A study report for the phase 2 actual use study 200339 evaluating the autoinjector presentation of belimumab SC may be found in Section 10.

Study Number and Title: BEL112341 (HGS1006-C1115) - A Phase 3, Multicenter, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab, (HGS1006) Administered Subcutaneously (SC) to Subjects with Systemic Lupus Erythematosus (SLE) –Double-Blind Endpoint Analysis

Study Centers: 177 sites in 30 countries in North America, South America, Europe and Asia

Dates Conducted: This trial was started on November 16, 2011 and the last subject visit for the double-blind endpoint analysis was February 13, 2015.

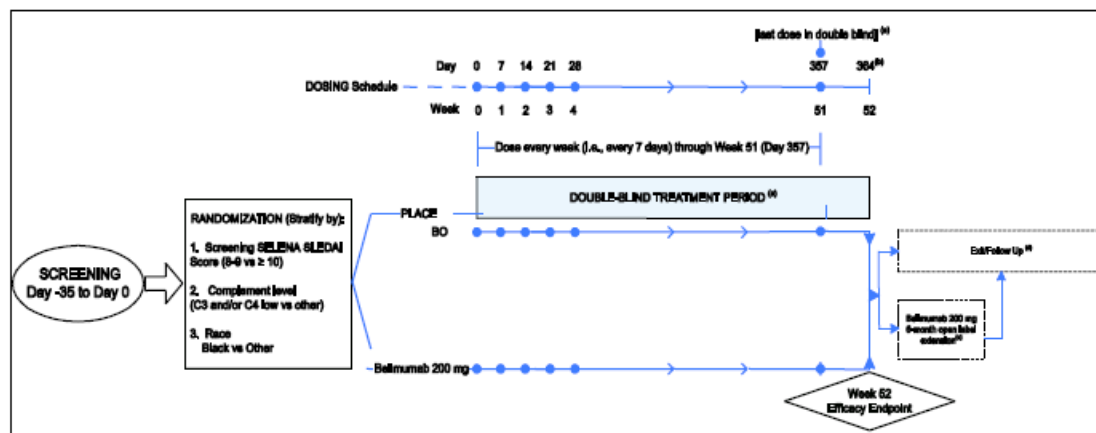
Objectives:

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

Study Design:

Study C1115 was a multicenter, double-blind, placebo-controlled, randomized study in adult patients with active seropositive SLE on stable standard of care immunosuppressive medications for their disease. Eligible candidates were to have been randomized via a 2:1 ratio to the following 2 treatment groups: 200 mg belimumab SC weekly or placebo SC weekly. Randomization was to have been stratified by subjects' screening SELENA SLEDAI score (8-9 vs ≥ 10), complement level (C3 and/or C4 low vs other) and race (Black 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 1 week post-administration of the last study injection. Upon completion of the 52-week study, participants were to have had the option of participating in a 6-month, open label continuation study. Those who did not wish to participate in continuation study were to have returned for an additional follow-up visit 8 weeks post-administration of their final study infusion. Figure 1 is a schema of the proposed study.

Figure 1 - Study Schematic for C1115



- The last dose of study agent was given on the Day 357 (Week 51) visit to subjects NOT participating in the 6-month open-label extension phase of the study.
- Subjects participating in the 6-month open-label extension phase of the study were dosed on the Day 364 (Week 52) visit. This Day 364 (Week 52) represented the 1st dose (i.e., Day 0) of the 6-month open-label extension phase. The visit window is ± 1 day. For subjects not participating in the 6-month open-label extension phase of the study, the Day 364 (Week 52) visit served as the Exit visit with follow-up visits occurring 8 weeks after the last dose of study agent.
- The primary treatment period included 51 weeks of study agent administration (Day 0 to the Day 357 visit) and a final visit for the primary endpoint assessment at Week 52 which was 1 week after the last dose of the study agent.
- An Exit visit (1-4 weeks after the last dose of study agent) and a follow-up visit 8 weeks after the last dose of study agent was performed for subjects withdrawing at any time during the study and at the time of completion for subjects in the open-label extension phase. The 8 week follow-up visit was not required in subjects entering the separate continuation protocol.
- At the end of the 6 month extension period, subjects who wished to continue treatment could do so by being prescribed the commercially available IV belimumab. If IV belimumab was not licensed and able to be prescribed in a subject's country of participation, subjects could continue to receive belimumab administered IV every 4 weeks under a separate continuation protocol until belimumab became commercially available. The target window for the first dose of IV belimumab is 2-3 weeks after the last dose of SC belimumab.

Source: Sponsor's Fig. 1; p. 34.

Major Inclusion Criteria:

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

- Diagnosis of SLE as per the American College of Rheumatology (ACR) criteria
- A diagnosis of active SLE defined as a SELENA SLEDAI score ≥ 8 at screening
- 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 (≥ 30 IU/mL) serum antibody) or
 - One positive historical test result and 1 positive test result during the screening period
- 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):
 - Subjects on SLE combination therapy, must be on a stable steroid dose fixed within the range of 0-40 mg/d (prednisone or prednisone equivalent)
 - Subjects who are only taking steroids as treatment for their SLE must be on a stable steroid dose fixed within the range of 7.5 to 40 mg/d (prednisone or prednisone equivalent)
 - Subjects on alternating day doses of steroids, the average of 2 daily doses will be used to calculate the average daily steroid dose
 - 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. 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 starting 2 weeks prior to administration of the first dose of the study agent until 16 weeks after the last dose of the study agent

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 90 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, or NSAID 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 ratio, 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 (≤ 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.
20. Subjects who have evidence of serious suicide risk including any H/O suicidal behavior in the last 6 months and/or any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) in the last 2 months or who pose a significant suicide risk in the opinion of the investigator.
21. Unable to administer study agent by SC injection and has no other reliable resource to administer the injection

Treatment:

All study medications were to have been self-administered via subcutaneous injection starting on Days 0 and 7 and then weekly through 51 weeks of treatment. Patients were to have been instructed on self-injection administration techniques by study personnel. The first and second administrations of study meds were to have been done under supervision at the trial site following which subjects were required to remain for 3 hours of observation. Trained caregivers were also permitted to administer study treatments.

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, or became pregnant.

Concomitant Medications:

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 (≤ 40 mg/day of prednisone or equivalent), antimalarials, NSAIDs, MTX, azathioprine, leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide, 6-mercaptopurine, mizoribine or thalidomide. Changes in background immunosuppressive agents were permitted due to toxicity or shortages as were adjustments in concurrent medications as clinically needed post-administration of the first study injection 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. Patients who receive IA steroids during the 8 weeks prior to the Week 52 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
- NSAIDs and Aspirin: Initiation of new treatment used for ≥ 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 3 and Table 4 are tabular flow charts of the scheduled study observations and procedures: _

Table 3 – Schedule of Procedures and Evaluations for Study C1115

Procedures	52-week Treatment Period Days 0 – 364 (Weeks 0 – 52)																Post-Treatment Follow-up Period
	Day 0 Visit	Day 28 Visit ± 7 day	Day 56 Visit ± 7 day	Day 84 Visit ± 7 day	Day 112 Visit ± 7 day	Day 140 Visit ± 7 day	Day 168 Visit ± 7 day	Day 196 Visit ± 7 day	Day 224 Visit ± 7 day	Day 252 Visit ± 7 day	Day 280 Visit ± 7 day	Day 308 Visit ± 7 day	Day 336 Visit ± 7 day	Day 364/Exit Visit for complete non- completers ^a ± 7 day	Day 364/for non- completers ± 7 day	8 wk Follow-up Visit (8-wks post last dose) ^b ± 7 day ^c	Unscheduled Visit ^c
SC administration of study agent ^a	X																
Clinical Assessments:																	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom-driven PE	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
C-SSRS Baseline/Screening																	
C-SSRS Since Last Visit ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Collect self-injection logs; record dosing in CRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Record All Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
SLE Disease Activity Scales ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
SLICC/ACR Damage Index	X													X			
FACIT-Fatigue Scale ^c	X	X	X	X			X			X				X			
Survival assessment ^d															X		
Laboratory Assessments:																	
Pregnancy Test ^e	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 Creatinine Ratio	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hematology & Modified Chem 20 (non fasting) ^f	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Complement (C3/C4) and anti-dsDNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pharmacokinetics ^g	X	X	X		X		X							X		X	X
Immunogenicity ^h	X		X				X							X		X	X
B cells	X		X				X							X			
ANA	X																
Extractable nuclear antigens (ENAs) ⁱ	X		X				X							X			
Antiphospholipid antibodies (aCL, lupus anticoagulant, +/- beta-2-glycoprotein-1)	X		X				X							X		X	
Serum Immunoglobulin (IgA, IgM, IgG)	X		X		X		X		X		X			X		X	

Source: Sponsor's Table 6-1; p. 52-54 of Protocol C1116.

Table 4 - Schedule of Procedures and Evaluations for Study C1115 (cont.)

Procedures	52-week Treatment Period Days 0 – 364 (Weeks 0 – 52)															Post-Treatment Follow-up Period
	Day 0 Visit Day 28 Visit ± 7 day	Day 56 Visit ± 7 day	Day 84 Visit ± 7 day	Day 112 Visit ± 7 day	Day 140 Visit ± 7 day	Day 168 Visit ± 7 day	Day 196 Visit ± 7 day	Day 224 Visit ± 7 day	Day 252 Visit ± 7 day	Day 280 Visit ± 7 day	Day 308 Visit ± 7 day	Day 336 Visit ± 7 day	Day 364 Exit Visit for completers/ non-completers ^a ± 7 day	Day 364 for non-completers ± 7 day	8 wk Follow-up Visit (8-wks post last dose) ^b ± 7 day	Unscheduled Visit ^c
BLyS Protein	X															
Pharmacogenetic Sampling ^d	X															

^a The 1st (Day 0) and 2nd (Day 7 ± 1) day administration will be under supervision at the study site.

^b Final Assessment will occur at Week 52, approximately 7 days after the last injection of study agent. This is Exit visit for subjects not entering the extension phase of the protocol and Day 0 for subjects entering the extension phase of the protocol. This is also an exit visit (which should happen 1-4 weeks after last study dose) for subjects who discontinue treatment at any time prior to Week 52 and therefore not receiving the study agent

^c For subjects not entering the extension phase or withdrawing from the study at any time.

^d Perform other assessments as clinically indicated.

^e SLE Disease Activity Scales: SELENA SLEDAI, SLE Flare Index, BILAG, PGA.

^f Must be completed by the subject prior to any study-related discussion with the investigator or study coordinator. The FACIT-Fatigue Scale will only be completed by subjects for whom a survey exists in the subject's language.

^g Assessed only for subjects who withdraw from treatment prior to Week 52. Attempt should be made to follow subjects who have lost to follow-up.

^h Serum pregnancy test is required at screening. The results of urine pregnancy test at subsequent visits, if required. See Section 6.1 (Screening Procedures) for definition of those exempted from subsequent pregnancy testing.

ⁱ Refer to Appendix 8 for a listing of laboratory assessments to be completed.

^j Pharmacokinetic sampling: prior to the injection on Day 0, and at any time at Weeks 4, 8, 16, 24 and 52 and anytime during the 8-week follow-up and unscheduled visit.

^k For subjects not entering the extension portion of the 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, or upon completion and/or unblinding of the study whichever is later (see Section 6.9).

^l 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.

^m Pharmacogenetic sampling informed consent must be obtained prior to any blood being taken for PGx research. Sample should be drawn prior to dosing.

ⁿ C-SSRS Since Last Visit (see Appendix 12) will be used at Day 0 and all subsequent visits. The C-SSRS Baseline/Screening form (see Appendix 11) is only used at Screening.

Source: Sponsor's Table 6-1; p. 52-54 of Protocol C1116

Primary efficacy endpoint:

Primary efficacy variable is the SLE Responder Index (SRI) response rate at Week 52 which was 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:

- Time to first severe flare (as measured by the modified SLE Flare Index [SFI])
- Percentage of subjects whose average prednisone dose has been reduced by $\geq 25\%$ from baseline to ≤ 7.5 mg/day during Weeks 40 through 52

Ancillary secondary variables:

- SRI by visit
- Percentage of patients with ≥ 4 point reduction from baseline in SELENA SLEDAI score at Week 52 and by visit
- Percent of patients with not new BILAG A organ domain score or new 2 BILAG B organ domain scores compared with baseline at Week 52 and by visit
- Percent of patients with no worsening (increase of <0.30 points from baseline) in PGA at Week 52 and by visit
- Percent of patients with durable SRI from Week 44-52
- Time to the first SRI that is maintained through Week 52

- Duration of longest response among subjects with at least 1 SRI response
- SRI5-8 at Week 52 and by visit

Disease Activity:

- Mean percent change and mean change in PGA at Week 24
- Mean percent change and mean change in SELENA SLEDAI score by visit

Organ Specific:

- Percent of patients with organ improvement by SELENA SLEDAI by visit
- Percent of patients with organ worsening by SELENA SLEDAI by visit
- Percent of patients with organ improvement by BILAG visit
- Percent of patients with organ worsening by BILAG visit
- Mean/median percent (in patients with proteinuria at baseline) and mean/median absolute in all patients) change in proteinuria by visit
- Time to renal flare over 52 weeks
- Percent of patients developing at least 1 renal flare over 52 weeks
- Percent of patients with doubling of serum creatinine

SFI Flare:

- Time to flare over 52 weeks
- Time to flare after Week 24
- Time to severe flare after Week 24
- Rate of flare per 100 subject years
- Rate of severe flare per 100 subject years

Steroids (Based on average steroid dose between visits)

- Percent of patients with daily prednisone dose reduced ≤ 7.5 mg/day from > 7.5 mg /day at baseline by visit
- Percent of patients with daily steroid dose increased to >7.5 mg/day from ≤ 7.5 mg/day at baseline over time
- Percent of patients with any increase in steroid use by visit
- Percent of patients with a 50% decrease in steroid dose by visit
- Percent of subjects with a 50% increase in steroid dose by a minimum of ≥ 5 mg/day by visit
- Mean/median changes in steroid dose (mg/day) by visit

SLICC/ACR Damage Index (SDI):

- Mean change from baseline in SDI at Week 52
- Percent of subjects with any SDI worsening (change >0) at Week 52 compared with baseline

Patient Reported Outcomes:

- Mean change in FACIT-Fatigue Scale score at Week 52 and by visit
- Percent of subjects with improvement in FACIT-fatigue score exceeding the Minimally Important Clinical Difference (MCID) (≥ 4) at Week 52 and by visit

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

- Mean and percent change from baseline in: total serum Ig, lupus anticoagulant anti-dsDNA, ENAs, aCL, C3, C4, and beta-2-glycoprotein interferon
- Percent of patients with normalized serological activity at Week 52 and over time: total serum Ig, lupus anticoagulant anti-dsDNA, ENAs, aCL, C3, C4, and beta-2-glycoprotein interferon

Statistical Design, Definitions of Analyzed Populations and Analyses Plan:

Sample size calculations were based on data generated from the two pivotal phase 3 SLE studies (1056 and 1057) conducted by the sponsor in support of IV belimumab. The proposed study had approximately 90% power at a significance level of 5% to show an absolute difference in improvement of 12% in the response rate of the 200 mg belimumab group as compared to the placebo group at Week 52. The assumptions used in the statistical power calculations included:

- 44% placebo response rate
- 56% belimumab response rate
- 50% population standard deviation

Efficacy and safety analyses were to have been conducted using the intention-to-treat (ITT) population which was defined as all subjects who were randomized and treated with at least 1 dose of study agent.

The primary efficacy endpoint (the SRI response rate at Week 52) and the major secondary endpoint (prednisone reduction) were to have been analyzed via logistic regression. The remaining major secondary endpoint (time to first severe SLE flare over 52 weeks) was to have been analyzed via the Cox proportional hazard model. A step-down sequential testing procedure controlling for type 1 error was to have been employed in calculating the primary and the major secondary endpoints. For purposes of the primary analysis as well as the analysis of the second major endpoint time to flare, any patient who missed or withdrew from the study before the Week 52 visit and/or started a prohibited medication or had a change in the dose of a restricted medication prior to that time point was to have been considered a nonresponder or as having had a severe SLE flare at the time the prohibited medication was started.

Safety Evaluation:

Descriptive statistics were used to summarize data describing AEs, SAEs, deaths, abnormal lab tests, vital signs, and antibodies to belimumab.

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 48 and at the 8-week follow-up visit for all subjects and for those who withdrew prior to study completion.

Study Conduct

Protocol Amendments:

Listed below are the 4 protocol amendments that were made to Study C1115.

- a. Amendment 1 (implemented on August 30, 2011)
 - Description of the DMC was revised to indicate that it was to be composed of at least 3 physicians without specifying their specialty areas
 - Frequency of PT and PTT assessments was reduced from every visit to be performed at screening, Day 0, Weeks 8, 24, and 52 and at Week 24 in the 6-month open label extension period. (Note: The tables for the schedule of study events and procedures were also updated to reflect these changes.)
 - Dosing schedule for subjects who decided not to participate in the long term extension study was modified so that the last dose was administered at the Week 23 visit of the 6-month open label extension
 - ANA titer and anti-Sm testing was replaced with extractable nuclear antigens (ENAs) testing
 - Deletion of CRP testing with a corresponding updating of the schedule of study events and procedures tables
 - Clarification that alcohol and drug screening, HIV-1/2 antibody, hepatitis C antibody, hepatitis B surface antigen and serum pregnancy testing will only be performed at study screening
- b. Amendment 2 (implemented October 4, 2011)
 - Modification of the efficacy analysis section to state that if the Week 52 visit is missing, data collected at a visit within +/- 28 days of the Week 52 visit may be used for analysis of the primary and secondary efficacy endpoints
 - The amount of time for subjects to be monitored following self-administration of study medication on the first (Day 0) and second (Day 7) injections was modified from 1 to 3 hours in the double-blind treatment period and 6-month open label extension
 - Clarification that subjects who had completed the double blind treatment period and continued in the 6-month open label extension would not have to return to study site for study medication administration training
- c. Amendment 3 (implemented November 17, 2011)
 - Deletion of the long-term extension phase after the 6-month open-label extension in order to allow subjects who were benefitting to continue to receive SC belimumab if IV belimumab was not commercially available in their country at the time they completed the study. A separate continuation protocol was to have been offered that would provide IV belimumab to patients who benefited and resided in countries where the product was not commercially available

- Revision of the monitoring schedule for the DMC from approximately every 4 months after the first meeting to every 6 months in order to align it with the monitoring schedules for other ongoing belimumab SLE trials
- d. Amendment 4 (implemented February 4, 2011)
- Modification of Inclusion Criterion 6 to recommend that females receiving mycophenolate mofetil (MMF) who rely on oral contraceptives for birth control should employ an additional method (e.g., barrier method)
 - Modification of the statistical analysis for the major secondary endpoint of time to first severe flare which will be adjusted for baseline randomization factors if “<10 events (severe flares)” are observed with deletion of the other category of “<10 non-events” which is not applicable in a time to event analysis
 - Clarification regarding the risk of hypersensitivity reactions, with increased emphasis on patient education about the signs and symptoms of hypersensitivity reactions, and a recommendation for an extended period of monitoring (greater than the protocol-specified 3 hours after the first 2 injections) if symptoms of acute hypersensitivity are apparent. In the event that a subject misses 3 or more consecutive doses, the next dose should be administered at the site and the subject should remain at the clinic for 3 hours following the injection for observation
 - Clarification that although pharmacogenetic samples should be drawn prior to the first dose they can be drawn at any time
 - Clarification of Section 7 regarding the collection of SAEs occurs from the time a subject consents to participate in the study and prior to treatment provided that the SAEs have been deemed to be related to study participation. As per recommendations in ICH guideline E2A, only unexpected SAEs considered by the sponsor to be related to belimumab treatment will be reported. Additionally, the sponsor or designee will follow all applicable local and national regulatory requirements regarding safety reporting

RESULTS:

Disposition of Subjects:

A total of 839 subjects were randomized to the two treatment groups as follows: 280 patients to the placebo group and 556 to the belimumab 200 mg SC 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 5.

Table 5 – Subject Disposition for Study C1115

	Placebo	Belimumab	Total
Number of Patients Randomized	280	559	839
Number of Patients Treated (ITT)	280	556	836
Number of Patients Who Completed Week 52	214 (76%)	463 (83%)	677 (81%)
Number of Patients Withdrawn Prior to Week 52:	66 (24%)	93 (17%)	159 (19%)
Subject Request	15 (5%)	12 (2%)	27 (3%)
Adverse Event	25 (9%)	40 (7%)	65 (8%)
Disease Progression/Lack of Efficacy	10 (4%)	15 (3%)	25 (3%)
Non-Compliance	2 (1%)	1 (0%)	3 (0%)
Lost to Follow-Up	2 (1%)	6 (1%)	8 (1%)
Protocol Violation	3 (1%)	4 (1%)	7 (1%)
Investigator Decision	5 (2%)	1 (0%)	6 (1%)
Other¹	4 (1%)	14 (3%)	18 (2%)

¹Includes one subject in the placebo group (0.4%) and six subjects in the belimumab 200 mg SC group who withdrew due to pregnancy.

Source: Sponsor's Tables 1.2 and 1.4; p. 398 and 400.

Protocol Deviations/Violations:

Protocol deviations that were deemed to be “important” as defined by the ICH E3 guidance (e.g., events related to study inclusion or exclusion criteria, adherence to the protocol, conduct of the study, subject management or subject assessment that were likely to affect the interpretation of the results and/or lead to exclusion of any subject data from an analysis) are summarized in Table 6. There were a total of 131 important protocol violations incurred by 131 subjects reported in this study as follows: 60 subjects were as having a variety of important protocol deviations classified as other (accidental unblinding by CRO or sponsor's staff [4 subjects], missed doses, dose which could not be verified due to insufficient source data or incomplete dosing logs in the subject diary, and wrong treatment due to the wrong kit number dispensed [3 subjects]); 47 subjects did not meet study entry criteria; and 36 subjects developed withdrawal criteria but were not withdrawn. The two treatment groups were balanced for the overall number of protocol deviations despite a higher proportion of placebo treated subjects (9%) having been classified as having “other” important protocol deviations compared to belimumab SC subjects (6%) and more belimumab SC subjects (7%) who did not meet study entry criteria as compared to placebo subjects (4%).

Table 6 – Summary of Protocol Violations for Study C1115

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Any Important Protocol Deviation	41 (15%)	90 (16%)	131 (16%)
Other^{1, 2}	25 (9%)	35 (6%)	60 (7%)
Entered Study But Did Not Meet Entry Criteria	10 (4%)	37 (7%)	47 (6%)
Developed Withdrawal Criteria But Was Not Withdrawn	13(5%)	23 (4%)	36 (4%)

Source: Sponsor's Table 1.7; p. 404

¹"Other": Four subjects from 4 different sites were accidentally unblinded. In 2 of these cases, the study treatment kit was sent to the site with the unblinded packaging information (Subjects (b) (6) and (b) (6) which was discovered by the local clinical research associated at each site. The remaining 2 subjects (Subjects (b) (6) and (b) (6)) were appropriately unblinded by site personal who sent the information forward to the local medical monitor and clinical research associate.

²"Other": Three subjects received the wrong medication kit but only subject (b) (6) received the wrong treatment (1 placebo injection instead of belimumab).

Treatment Compliance and Drug Exposure:

The protocol specified that patients' compliance was to have been monitored via a monthly review of the subjects' self-injection log book and assessed by the number of used study medication syringes returned at each visit. Overall mean compliance was high for both treatment groups ($\geq 96\%$) with 57% of the subjects receiving > 51 injections over the 52 weeks of the study (Table 7). Mean duration of exposure to study medication was similar for both treatment groups (319 days for placebo group and 330 days for the belimumab group).

Table 7 – Study Compliance and Subject Exposure

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Percent Compliance¹:			
Mean (SD)	96.4 (9.7)	96.4 (9.4)	96.4 (9.5)
Median	100.0	100.0	100.0
(Min, Max)	(25.0, 100.0)	(25.0, 100.0)	(25.9, 100.0)
Number (%) of Subjects Receiving:			
1-12 injections	15 (5%)	28 (5%)	43 (5%)
13-24 injections	21 (8%)	24 (4%)	45 (5%)
25-36 injections	14 (5%)	26 (5%)	40 (5%)
25-36	14 (5%)	26 (5%)	40 (5%)
37-51 injections	75 (27%)	156 (28%)	231 (28%)
>51 injections	155 (55%)	322 (58%)	477 (57%)
Duration of Exposure² (days)			
Mean (SD)	319 (95)	330 (85)	326 (88)
Median	364	364	364
(Min, Max)	(7, 391)	(7, 378)	(7, 391)

¹Percent compliance = 100 (number of injections prescribed – number of injections missed)/number of injections prescribed

²Duration was calculated as last injection date – first injection date + 7

Source: Sponsor's Table 1.29; p. 659.

Demographics:

As summarized in the following tables (Table 8 and Table 9), the treatment groups within Study C1115 were generally well balanced with respect to baseline demographics, region, disease characteristics and activity.

The subjects who participated in this trial were predominantly Caucasian (60%) and female (94%). Ten percent (10%) of the patients were of African American/African in origin and 29% identified their ethnicity as Hispanic or Latino. The majority of the subjects were from the USA/Canada (28%) and Eastern Europe (23%). The mean age of subjects was 39 years and their mean BMI was 26 kg/m². No important imbalances in these demographic factors across the treatment groups were noted within Study C1115.

Table 8 - Demographic Characteristics of Subjects Enrolled in Study C1115

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Gender:			
Female	268 (96%)	521 (94%)	789 (94%)
Male	12 (4%)	35 (6%)	47 (6%)
Race¹:			
Caucasian	166 (59%)	336 (60%)	502 (60%)
Asian	63 (23%)	119 (21%)	182 (23%)
African American	30 (11%)	56 (10%)	86 (10%)
Alaskan Native/American Indian	21 (8%)	43 (8%)	64 (8%)
Native Hawaiian/Pacific Islander	0	2 (0%)	2 (0%)
Multiracial	3 (1%)	6 (1%)	9 (1%)
Hispanic Origin:	80 (29%)	160 (29%)	240 (29%)
Age (years):			
Mean (SD)	40 (13)	38 (12)	39 (12)
≤ 45	193 (69%)	403 (73%)	596 (71%)
> 45 to <65	80 (29%)	141 (25%)	221 (26%)
≥ 65	7 (3%)	12 (2%)	19 (2%)
> 65 to <75	7 (3%)	11 (2%)	18 (2%)
≥ 75	0	1 (0%)	1 (0%)
BMI (kg/m²)			
Mean (SD)	26 (7.2)	26 (6.3)	26 (6.6)
(Min, Max)	(16, 60)	(15, 51)	(15, 60)
Region and Country			
USA/Canada	84 (30%)	153 (28%)	237 (28%)
Americas (excluding USA/Canada)	57 (20%)	115 (21%)	172 (21%)
Western Europe/Israel	19 (7%)	48 (9%)	67 (8%)
Eastern Europe	59 (21%)	129 (23%)	188 (23%)
Asia	61 (22%)	111 (20%)	172 (21%)

¹Subjects who checked more than one race category are counted under individual race category according to the minority rule as well as multiracial category.
Source: Sponsor's Table 1.8; p. 405-406

As shown in Table 9 below, the overall mean duration of SLE disease was 7 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 10 with 58% 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, at least 1 flare measured by the SLE flare index, and proteinuria > 2 g/24 hours. (Note: Patients with a baseline SELENA SLEDAI score category 0 to 3 were unable to achieve a response of ≥ 4 points necessary for a positive response as assessed by the primary endpoint, the SRI.)

Table 9 – Tabular Summary of Subject’s Baseline Disease Characteristics for Study C1115

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
SLE Disease Duration (yr): Mean (SD)	7 (7)	6 (7)	7 (7)
BILAG Organ Domain Involvement¹:			
At least 1A or 2B	210 (75%)	388 (70%)	598 (72%)
At Least 1A	51 (18%)	87 (16%)	138 (17%)
At Least 1A or 1B	258 (92%)	499 (90%)	757 (91%)
No A or B	13 (5%)	29 (5%)	42 (5%)
SELENA SLEDAI Category:			
0 to 3	0 (0%)	4 (1%)	4 (1%)
≤9	112 (40%)	200 (36%)	312 (37%)
10 to 11	74 (26%)	161 (29%)	235 (28%)
> 12	94 (34%)	191 (34%)	285 (34%)
SELENA SLEDAI Score: Mean (SD)	10.3 (3.0)	10.5 (3.2)	10.4 (3.1)
SLE Flare Index¹:			
At Least 1 Flare	57 (20%)	92 (17%)	149 (18%)
At Least 1 Severe Flare	4 (1%)	8 (1%)	12 (1%)
PGA Category:			
0 to 1	19 (7%)	40 (7%)	59 (7%)
>1 to 2.5	255 (91%)	507 (91%)	762 (91%)
>2.5	5 (2%)	7 (1%)	12 (1%)
Missing	1 (0%)	2 (0%)	3 (0%)
PGA Scale: Mean (SD)	1.54 (0.45)	1.58 (0.43)	1.57 (0.44)
SLICC Damage Index Score Mean (SD)	0.7 (1.27)	0.6 (0.99)	0.6 (1.05)
Proteinuria Category (g/24 hr): ≥ 2	20 (7%)	19 (3%)	39 (5%)
Proteinuria Level (g/24 hr) Mean (SD)	0.44 (0.84)	0.39 (0.71)	0.40 (0.75)

¹Subjects may be included in more than one category
Source: Sponsor’s Table 1.14; p.470-472.

As shown in Table 10 below, the majority of subjects who participated in study C1115 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 two treatment groups.

Table 10 – Summary of Baseline SELENA SLEDDAI Organ Involvement for Subjects Who Participated in Study C1115 (ITT Population)

Organ System	Number (%) of Patients		
	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Mucocutaneous	248 (89%)	487 (88%)	735 (88%)
Musculoskeletal	218 (78%)	438 (79%)	656 (79%)
Immunologic	210 (75%)	423 (76%)	633 (76%)
Renal	41 (15%)	58 (10%)	99 (12%)
Vascular	18 (6%)	46 (8%)	64 (8%)
Hematologic	23 (8%)	40 (7%)	63 (8%)
Cardiovascular and Respiratory	18 (6%)	29 (5%)	47 (6%)
Constitutional	3 (1%)	7 (1%)	10 (1%)
CNS	2 (1%)	7 (1%)	9 (1%)

Source: Sponsor's Table 1.16; p. 475-476.

A summary of moderate to severe BILAG organ system involvement (A or B score) at baseline is displayed in Table 11 below. The most common organ systems involved in subjects participating in study C1115 were musculoskeletal (65%), mucocutaneous (62%), and hematology (17%). Both treatment groups in this trial were generally well balanced for baseline organ involvement.

Table 11 – Baseline BILAG Organ Domain Grade A and B for Subjects Who Participated in Study C1115 (ITT Population)

BILAG Organ Domain ¹ / Grade	Number (%) of Patients		
	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
General			
A	0	1 (0%)	1 (0%)
B	29 (10%)	38 (7%)	67 (8%)
Mucocutaneous			
A	19 (7%)	30 (5%)	49 (6%)
B	182 (65%)	333 (60%)	515 (62%)
Neurological			
A	0	1 (0%)	1 (0%)
B	0	3 (1%)	3 (0%)
Musculoskeletal			
A	29 (10%)	54 (10%)	83 (10%)
B	180 (64%)	359 (65%)	539 (65%)
Cardiovascular and Respiratory			
A	2 (1%)	0	2 (0%)
B	5 (2%)	13 (2%)	18 (2%)
Vasculitis			
A	4 (1%)	9 (2%)	13 (2%)
B	20 (7%)	38 (7%)	58 (7%)
Renal			
A	3 (1%)	4 (1%)	7 (1%)
B	27 (10%)	49 (9%)	76 (9%)
Hematology			
A	0	1 (0%)	1 (0%)
B	48 (17%)	90 (16%)	138 (17%)

¹Organ Domain Categories: A= requires disease modifying treatment; B=mild reversible problems requiring only symptomatic therapy; C=stable mild disease; D=previously affected but currently inactive; and E=system never involved.

Source: Sponsor's Table 1.7; p. 477-478.

The majority (96%) of patients in this trial were overwhelmingly seropositive for ANA and/or anti-dsDNA as shown in Table 12 below. The treatment groups within the trial were also generally well balanced with respect to baseline biomarkers of disease activity with the following exceptions. Slightly lower proportions of patients in the placebo group were positive for the presence in aCL, had serum IgG levels that were below the lower limits of normal (LLN), or had had low levels of C3.

Table 12 - Tabular Summary of Subject's Baseline Serologies, Immunoglobulins, Complement and Other Biomarkers for Study C1115

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Anti-dsDNA:			
Positive (≥ 30 IU/mL)	193 (69%)	404 (73%)	597 (71%)
Mean (SD)	516 (977)	629 (1588)	593 (1420)
ANA:			
Positive (≥ 80 Titer)	254 (91%)	492 (89%)	746 (89%)
Mean (SD)	622 (507)	644 (501)	636 (502)
ANA and/or Anti-dsDNA			
Positive:	270 (96.4%)	531 (96%)	801 (96%)
aCL:			
Positive¹	38 (14%)	94 (17%)	132 (16%)
IgG:			
Mean (SD)	15.3 (5.3)	15.6 (5.6)	15.5 (5.6)
>ULN (16.18 g/L)	3 (1%)	10 (2%)	13 (2%)
<LLN 6.94 g/L	97 (35%)	223 (40%)	320 (38%)
IgA:			
Mean (SD)	3.2 (1.5)	3.3 (1.7)	3.3 (1.6)
>ULN (4.63 g/L)	4 (1%)	7 (1%)	11 (1%)
<LLN (0.81 g/L)	34 (12%)	91 (16%)	125 (15%)
IgM:			
Mean (SD)	1.2 (0.8)	1.1 (0.8)	1.1 (0.8)
>ULN (2.71 g/L)	39 (14%)	74 (13%)	113 (14%)
<LLN (0.48 g/L)	12 (4%)	21 (4%)	33 (4%)
C3:			
Mean (SD)	99 (33)	98 (31)	98 (32)
Low (<90 mg/L)	111 (40%)	245 (44%)	356 (43%)
C4:			
Mean (SD)	16 (9)	16 (9)	16 (9)
Low (<10 mg/dL)	71 (25%)	146 (26%)	217 (26%)
BLyS:			
Above LOQ	259 (93%)	504 (91%)	763 (92%)
Mean (SD)	1.8 (1.3)	1.8 (1.4)	1.8 (1.4)

¹aCL was positive if any of the three aCL parameters (IgG, IgA, or IGM) were positive

Source: Sponsor's Tables 1.18, 1.19, 1.20; p. 479-485.

The following Table 13 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 two treatment groups in this trial, however, with a higher proportion of patients in the placebo group taking other immunosuppressives (49%) and NSAIDs (26%) as compared to the belimumab SC group (44% and 22%), respectively).

Table 13 – Tabular Summary of Concomitant SLE Medications Used by >10% of Subjects in Study C1115

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Total Glucocorticoid Use:	241 (86%)	481 (87%)	722 (86%)
Methylprednisolone	44 (16%)	103 (19%)	147 (18%)
Prednisolone	51 (18%)	96 (17%)	147 (18%)
Prednisone	136 (49%)	258 (46%)	394 (47%)
Prednisone or Equivalent Dose at Baseline:			
0 mg/day	39 (14%)	75 (14%)	114 (14%)
>0 - ≤ 7.5 mg/day	73 (26%)	146 (26%)	219 (26%)
>7.5 mg/day	168 (60%)	335 (60%)	503 (60%)
Average Prednisone or Equivalent Dose at Baseline:			
Mean (SD)	11.2 (9.1)	10.8 (8.2)	10.9 (8.5)
Antimalarials:	189 (68%)	391 (70%)	580 (69%)
Other Immunosuppressives:	137 (49%)	244 (44%)	381 (46%)
Azathioprine	58 (21%)	107 (19%)	165 (20%)
Methotrexate	38 (14%)	52 (9%)	90 (11%)
Mycophenolate Mofetil	22 (8%)	46 (8%)	68 (8%)
NSAIDs	72 (26%)	124 (22%)	196 (23%)

Source: Sponsor's Table 1.24; p. 493-495.

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 14, patients treated with belimumab 20 mg SC had a statistically higher rate of response than placebo patients in Study C1115. The results from the analyses of the subcomponents of the SRI were 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 group than the placebo group in the study and reached statistical significance.

Table 14 – Week 52 Primary Endpoint and Subcomponent Results for Study C1115 (ITT Population)

	Placebo (N=280)	Belimumab (N=556)
Response:	135/279 (48%)	340/554 (61%)
Observed Difference vs Placebo		13%
OR (95% CI)¹ vs Placebo		1.68 (1.25, 2.25)
P-value		0.0006
Subcomponents		
4-Point Reduction in SELENA SLEDAI:	137/279 (49%)	345/554 (62%)
OR (95% CI)¹ vs Placebo		1.69 (1.26, 2.27)
P-value		0.0005
No Worsening in PGA:	203/279 (73%)	450/554 (81%)
OR (95% CI)² vs Placebo		1.61 (1.15, 2.27)
P-value		0.0061
No New 1A/2B BILAG Domain Scores:	207/279 (74%)	448/554 (81%)
OR (95% CI)³ vs Placebo		1.46 (1.04, 2.07)
P-value		0.0305

Three ITT subjects did not have a baseline PGA assessment and were not included in the SRI/subcomponent analyses

OR=Odds Ratio; CI =Confidence Interval

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

²OR (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

³OR (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 15 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. Imbalances in disposition of response are noted not in favor of the placebo group for having less than a 4-point reduction in SELENA SLEDAI and “dropout not a medication failure”.

Table 15 - Summary of Disposition of Response at Week 52 for Study C1115

	Placebo (N=280)	Belimumab (N=556)
n	279	554
Response¹	135 (48%)	340 (61%)
No Response:	144 (52%)	214 (39%)
Dropout² – Not a Medication Failure	42 (15%)	55 (10%)
Medication Failure³	27 (10%)	42 (8%)
<4 Point Reduction in SELENA SLEDAI (SS)⁴	73 (26%)	112 (20%)
≥4 Point Reduction in SS with the following⁴:	2 (1%)	5 (1%)
Worsening in PGA only⁴	0	1 (0%)
New 1A/2B BILAG only⁴	1 (0%)	4 (1%)
Both Worsening in PGA and New 1A/2B BILAG⁴	1 (0%)	0

¹Three ITT subjects did not have a baseline PGA assessment and did not contribute to SRI/component analyses

²Subjects who withdrew early and had no data in the Day 364 +/- 28 day window

³Includes 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

⁴In subjects who did not dropout and were not medication failures.

Source: Sponsor's Table 2.4; p. 931

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 consistent with the primary efficacy analysis and are shown in Table 16.

Table 16 - Summary of Sensitivity Analyses for Primary Endpoint Response at Week 52 for Study C1115

	Placebo (N=280)	Belimumab (N=556)
Unadjusted Response (ITT Population)¹:	135/279 (48%)	340/554 (61%)
Observed Difference vs Placebo		13
OR (95% CI)² vs Placebo		1.69 (2.27, 2.27)
P-value		0.0004
LOCF Response (adjusted) (ITT Population)¹:	152/279 (55%)	362/554 (65%)
Observed Difference vs Placebo		11
OR (95% CI)³ vs Placebo		1.56 (1.15, 2.10)
P-value		0.0039
Completer Response (adjusted) (Completers Population)⁴:	135/214 (63%)	337/462 (73%)
Observed Difference vs Placebo		10
OR (95% CI)³ vs Placebo		1.54 (1.07, 2.20)
P-value		0.0185
Per Protocol Response (adjusted) (Per Protocol Population)⁵:	129/267 (48%)	322/520 (62%)
Observed Difference vs Placebo		14
OR (95% CI)³ vs Placebo		1.75 (1.29, 2.37)
P-value		0.0003

¹Three ITT subjects did not have a baseline PGA assessment and did not contribute to SRI/component analyses

²Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo without adjustment for any covariates

³Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELINA SLEDA (≤ 9 vs ≥ 10), baseline proteinuria level (<2 g/24 hr vs ≥ 2 g/24 hr equivalent) and race (African descent or indigenous-American descent vs other).

⁴One placebo subject did not have a baseline PGA assessment and did not contribute to this SRI analysis

⁵One belimumab subject did not have a baseline PGA assessment and did not contribute to this SRI analysis

Source: Sponsor's Tables 2.5, 2.6, 2.7 and 2.8; p. 932-935.

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 two major and numerous ancillary secondary endpoints for this trial. The major secondary endpoints will be presented with the secondary ancillary endpoints by corresponding assessment area. As per the statistical analysis plan, a step-down sequential testing procedure controlling for type 1 error was to have been employed in calculating the primary and two major secondary endpoints. However, no multiplicity correction was implemented for the non-major secondary endpoints. Declaring statistical significance of the non-major secondary and ancillary endpoints using unadjusted p-values therefore may be inappropriate due to multiplicity concerns.

SLE Flares:

The first major secondary endpoint in this study was the time to the first severe flare over 52 weeks assessed via the SLE Flare Index (SFI). Subjects in the belimumab SC group had a 49% decrease in the risk of experiencing a severe SFI flare that was significantly different on comparison to the placebo group (hazard ratio: 0.51; 95%

confidence interval [CI] (0.35, 0.74); $p=0.0004$). The median time to first severe flare was 171 days for patients who flared in the belimumab group versus 118 days for those who flared in the placebo group. Results from the ancillary secondary endpoints for SLE flare were all positive and supported the results of this analysis and are listed below.

- Time to first SFI flare (i.e., any flare, mild/moderate or severe) over 52 weeks: The median time to any first flare for the belimumab SC group (190 days) was longer as compared to the placebo group (141 days). A 22% decrease in the risk of experiencing a first SFI flare over 52 weeks was observed for the belimumab SC group that was significantly different on comparison to the placebo group (hazard ratio: 0.78; 95% CI (0.65, 0.93); $p=0.0061$).
- Time to first SFI flare (any or severe) from Week 24 to Week 52: A 20% decrease in the risk of experiencing any SFI flare from Week 24 to Week 52 was observed for the belimumab SC group that was significantly different on comparison to the placebo group (hazard ratio: 0.80; 95% CI (0.65, 0.99); $p=0.0415$). Additionally, the belimumab SC group subjects had a 44% lower risk of having a severe SFI flare from Week 24 to Week 52 (hazard ratio: 0.56; 95% CI (0.34, 0.92); $p=0.0215$).
- Rate of SFI flare (any or severe) per 100 subject years over 52 weeks: The adjusted rate ratio for SFI flares per subject-year from Day 0 to Week 52 was 19% lower for the belimumab 200 mg SC group compared to the placebo group ($p=0.0186$). For severe flares, the adjusted rate ratio per subject-year from Day 0 to Week 52 was 46% lower for the belimumab group compared to the placebo group ($p=0.0128$).
- Percent of subjects with at least one SFI flare (any or severe) by visit: Numerical increases in the percent of subjects with at least one SFI flare increased over time in both treatment groups from 17% at baseline to 61% by week 52 for subjects in the belimumab SC group versus 20% at baseline to 69% by Week 52 for the placebo group. Similar numerical increases in the percent of subjects who had experienced at least one severe flare from Day 0 to Week 52 were observed in both treatment groups (belimumab SC: 18% versus placebo group: 11%).

Steroid Use:

The second major secondary endpoint was the percentage of subjects whose average prednisone dose was reduced by $\geq 25\%$ for baseline to ≤ 7.5 mg/day during Weeks 40 through 52 in subjects who were receiving >7.5 mg/day prednisone at baseline. A total of 60% of the subjects who participated in this trial were eligible for this analysis. Numerically more patients in the belimumab SC group (18%) were able to reduce prednisone use by $\geq 25\%$ as compared to placebo (12%) which was significantly different on comparative analysis (odds ratio: 1.65, 95% CI (0.95, 2.84); $p=0.0732$).

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

- Change in prednisone from baseline by visit: A numerically higher mean decrease in prednisone was observed for the belimumab SC group which was

not sustained at all visits and was not significantly different from the placebo at Week 52 ($p=0.4888$, observed population).

- Prednisone reduction or increase by $\geq 50\%$ from baseline by visit among subjects using prednisone at baseline: The percentage of subjects who had prednisone reduction $\geq 50\%$ from baseline was small and similar for both treatment groups over the course of the 52-week study (range: belimumab SC 0.2-15.2% versus placebo: 0-14.1% where range indicates minimum and maximum percentage of subjects at any time during the study's 52 weeks). A significantly lower percentage of belimumab SC subjects required increases in their prednisone $\geq 50\%$ from baseline by a minimum of ≥ 5 mg/day starting at Week 40 (4.9%) as compared to placebo (8.2%) that was maintained through Week 52 (belimumab SC: 4.9% versus placebo: 7.9%; odds ratio: 0.56; 95% CI [0.31, 1.02]; $p=0.0574$).
- Any decrease or increase in prednisone from baseline: The percentage of subjects who achieved a decrease in prednisone from baseline was similar for both treatment groups at each visit (belimumab SC range: 1.9-25%; placebo range: 2.1-22%) over the course of the study. A lower percentage of subjects in the belimumab SC group as compared to the placebo group had any increases in prednisone over the study's 52 weeks that was significantly different by Week 20 that was sustained through Week 52 with the exception of Week 32 (Week 52: 8.1% belimumab SC versus 13.2% placebo group; odds ratio 0.55; 95% CI [0.34, 0.87]; $p=0.0117$).
- Daily prednisone dose reduction or increase: The percentage of subjects who had prednisone dose reduced to ≤ 7.5 mg/day among subjects with baseline prednisone dose was similar for both treatment groups over the 52 weeks of the study (belimumab SC range: 0-20% versus placebo range: 0-14%). The percentage of subjects whose prednisone was increased to > 7.5 mg/day from ≤ 7.5 mg/day was also similar between the two groups over the 52 weeks of the study (belimumab SC range: 2.3-8.6% versus placebo range: 1.8-9.8%).
- Cumulative prednisone dose: The mean ($\pm$ SD) cumulative prednisone dose was 3934 mg ($\pm$ 3661mg) over 52 weeks in the belimumab SC group versus 4567 mg ($\pm$ 5982 mg) over 52 weeks in the placebo group.

Disease Activity:

- SRI by visit: Numeric improvements in response rates were observed in both treatment groups starting at Week 4. A separation in the response rate curves was observed starting at Week 8 with significantly higher response rates for the belimumab SC group occurring at Week 12 compared to placebo which were sustained through Week 52 ($p<0.05$).
- Percent of patients with durable SRI from Week 44-52: A significantly higher percentage of subjects in the belimumab SC group (54.3%) achieved a durable SRI response compared to placebo subjects (40.9%) (Odds ratio: 1.71; 95% CI [1.27, 2.30]; $p=0.0004$).
- Time to the first SRI maintained through Week 52: The median number of days to first SRI response maintained through Week 52 was 235 days for the

belimumab SC group versus 338 days for the placebo group. A significantly higher proportion of subjects in the belimumab SC group (61%) were responders for this endpoint as compared to the placebo group (48%) (Hazard ratio: 1.48; 95% CI [1.21, 1.81]; $p=0.0001$).

- Duration of longest response among subjects with at least 1 SRI response: A significantly longer duration of SRI response was observed for subjects in the belimumab SC group (194 days) as compared to the placebo group (169 days) (95% CI [7.46, 41.84]; $p=0.0050$).
- Duration of Week 52 SRI response: A higher proportion of subjects in the belimumab SC group had a SRI response of ≥ 1 month duration post-baseline through ≥ 10 month duration post baseline that was sustained through Week 52 versus placebo ($p \leq 0.05$).
- Percentage of patients with ≥ 4 point reduction from baseline in SELENA SLEDAI score at Week 52 and by visit: The results of the Week 52 analysis (Table 14 above) for this endpoint demonstrated a significantly higher proportion of subjects in the belimumab SC group were able to achieve this reduction compared to placebo. The by-visit analysis of this endpoint showed the response curves for the two treatment groups initially separating at Week 8 with a significantly higher proportion of subjects in the belimumab SC group (63%) achieving a ≥ 4 point reduction from baseline in SELENA SLEDAI as compared to the placebo group (55%) by Week 28 ($p=0.0294$) that was maintained through Week 52.
- Mean percent change from baseline in SELENA SLEDAI score: Numeric improvements were observed in both treatment groups that were significantly different at Weeks 20, 24, and 36 through 52 time points for the belimumab SC group compared to placebo (Week 52: belimumab SC (-40%) versus placebo (-33%), 95% CI [-13.9, 0.34]; $p=0.0660$).
- Mean change from baseline in SELENA SLEDAI score: Numeric improvements were observed in both treatment groups that were significantly different at Weeks 16, 20, 24, and 32 through 52 time points for the belimumab SC group compared to placebo (Week 52: belimumab SC (-4.4%) versus placebo (-3.6%), 95% CI [-1.5, -0.23]; $p=0.0069$).
- Percent of patients with organ improvement by SELENA SLEDAI: Improvement over baseline SELENA SLEDAI scores at Week 52 was observed in the following organ systems in the belimumab SC group compared to the placebo group: mucocutaneous ($p=0.0132$), musculoskeletal ($p=0.0007$), immunologic ($p=0.0002$) and vascular organ systems ($p=0.0138$). Numerical trends suggestive of improvement with belimumab SC were observed in the other organ systems (e.g., renal, hematologic, cardiovascular and respiratory, and CNS).
- Percent of patients with organ worsening by SELENA SLEDAI: The rates for new organ involvement were comparable for the two treatment groups with the following exceptions: 5% of subjects in the belimumab SC group versus 0% in the placebo group had new involvement in the musculoskeletal organ system

and 10% belimumab SC subjects versus 15% placebo subjects had new involvement in the immunologic organ system.

BILAG Disease Activity:

- Percent of patients with not new BILAG A organ domain score or new 2 BILAG B organ domain scores compared with baseline: From Week 24 through Week 52 a significantly greater percentage of subjects in the belimumab SC group (81%) had no new BILAG 1A/2B organ domain scores from baseline compared with placebo (74%) (Odds ratio: 1.48; 95% CI [1.05, 2.09]; p=0.0259).
- Percent of patients with organ improvement by BILAG visit: Significantly higher proportions of subjects in the belimumab SC group with a BILAG A or B organ domain score at baseline had improvement in their BILAG organ domain score compared to placebo subjects at Week 52 in the following organ domains: musculoskeletal (p=0.0110), mucocutaneous (p=0.0107) and vasculitis (p=0.0041). Inconsistency was observed in the Week 52 results for the remaining organ domains with numerical trends in favor of the belimumab SC group observed in the general and hematology organ domains while favoring the placebo group for improvements in the renal and cardio-respiratory organ domains.
- Percent of patients with organ worsening by BILAG visit: The proportion of subjects experiencing worsening in BILAG organ domain scores was similar for the two treatment groups for the seven BILAG organ domains (e.g., general, cardio/respiratory, hematology, mucocutaneous, musculoskeletal, neurological, renal and vasculitis).

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

- Percent of patients with no worsening (increase of <0.30 points from baseline) in PGA by visit and Week 52 (LOCF): The by-visit analysis of this endpoint showed the response curves for the two treatment groups initially separating at Week 12 with a significantly higher proportion of subjects in the belimumab SC group (%) having no worsening in their PGA scores compared to placebo subjects starting at that visit which was maintained through the Week 52 visit (belimumab SC: 81% versus placebo: 73%; Odds ratio: 1.61; 95% CI [1.15, 2.27]; p=0.0061).
- Percentage of subjects with ≥ 0.30 points improvement (i.e., reduction) from baseline in PGA by visit and at Week 52: A higher percentage of belimumab SC subjects had a ≥ 0.30 point improvement compared to placebo subjects that was significantly different starting at Week 16 and was maintained through the Week 52 visit (belimumab SC: 69% versus placebo: 56%; Odds ratio: 1.72; 95% CI [1.27, 2.33]; p=0.0005).
- Mean percent change from baseline PGA: Numerical improvements for both treatment groups was observed with separation of the response curves starting at Week 8 that was statistically significant and maintained through the Week 52 visit compared to placebo (Week 52 Treatment difference: -12.77; 95% CI [-18.46, -7.09]; p<0.0001).

- Mean change from baseline PGA: Numerical improvements for both treatment groups was observed with separation of the response curves starting at Week 12 which became significantly different for the belimumab SC group compared to placebo starting at Week 16 that was maintained through Week 52 (Week 52 Treatment difference: -0.16; 95% CI [-0.24, -0.07]; p=0.0003)

SLICC/ACR Damage Index (SDI):

This endpoint is used to assess end organ damage in SLE patients. Baseline scores were comparable for the two treatment groups (belimumab SC: 0.6 and placebo: 0.7). The Week 52 scores were not consistent with disease progression (belimumab SC: 0.6 and placebo: 0.7).

- Mean change from baseline in SDI at Week 52: No differences were noted on the mean change from baseline to Week 52 in the SDI.
- Percent of subjects with any SDI worsening (change >0) at Week 52 compared with baseline: At Week 52, 2.3% belimumab SC subjects and 5.0 % placebo subjects had SDI worsening (LICF, change >0) compared to baseline (odds ratio: 0.47, 95% CI [0.22, 1.02]; p=0.0558). Numerically more subjects in the belimumab SC group (80.2%) versus the placebo group (72.5%) experience no worsening in the SDI compared to baseline (Odds ratio: 1.54; 95% CI [1.10, 2.16]; p=0.0123).

Renal Measures:

The overall number of subjects who experienced a post baseline renal flare was small (belimumab SC: 26 subjects; placebo group: 21 subjects) and was most likely due to the study's entry criteria which prohibited subjects with active nephritis from participating in the trial. However, patients with proteinuria were permitted to enroll in the trial resulting in a small subgroup of subjects upon which the following renal analyses were based.

- Time to first renal flare over 52 weeks: The median time to first renal flare was numerically longer for the placebo group (142 days) versus the belimumab SC group (130.5 days), but not clinically meaningful.
- Percent of patients developing at least 1 renal flare over 52 weeks: The number of subjects with at least one renal flared increased steadily over the 52-weeks of the study in both treatment groups. By the Week 52 visit 26 (4.7%) subjects overall in the belimumab SC group experienced a renal flare versus 21 (7.5%) subjects in the placebo group (Hazard Ratio: 0.57; 95% CI [0.32, 1.01]; p=0.0532).
- Doubling of serum creatinine: Due to the small number of subjects (less than 1% in either treatment group) whose serum creatinine doubled over the 52 weeks of the study, this analysis could not be conducted.
- Percent change by visit among subjects with baseline proteinuria >0.5 g/24h: A decrease in the median percent change in proteinuria from baseline over time was observed for both treatment groups with a greater decrease in proteinuria observed for subjects in the belimumab SC group that the placebo group that

was significantly different at the Week 20, 36 and 52 visits. (At Week 52: belimumab SC group median change from baseline in proteinuria: -60.35% versus -33.14% for the placebo group; $p=0.0335$).

- Proteinuria change from baseline by visit: No difference was observed on comparison of the two treatment groups for proteinuria change from baseline by visit.
- Proteinuria shifts by visit: In patients with high proteinuria at baseline, a higher percentage of subjects in the belimumab SC group had proteinuria levels shift to normal than the placebo group over the course of the study. At Week 52, 24% of placebo patients shifted from high to normal versus 49% of the belimumab subjects.

Patient Reported Outcomes:

- Mean change in FACIT-Fatigue Scale score at Week 52 and by visit: At Week 52, a numerical improvement in the mean change in FACIT-Fatigue score was observed for the belimumab SC group (2.7) as compared to placebo (4.4) that was significantly different for the belimumab group compared to placebo (treatment difference: 1.6; 95% CI [0.3, 2.9]; $p=0.0130$).
- Percent of subjects with improvement in FACIT-fatigue score exceeding the Minimally Important Clinical Difference (MCID) (≥ 4) at Week 52 and by visit: A separation in the response rate curves was observed starting at Week 24 with a significantly higher percentage of subjects in the belimumab SC group (44%) experiencing improvement in FACIT-Fatigue score exceeding the MCID (≥ 4) than in the placebo group (36%) at Week 52 (Odds ratio: 1.42; 95% CI [1.05, 1.94]; $p=0.0245$).

Biomarkers:

Results from the ancillary secondary biomarker endpoints are as follows:

- Significant reductions in median percent change and mean absolute change from baseline in serum IgG levels in the belimumab SC group versus placebo starting at Week 8 that were maintained through Week 52 ($p<0.0001$). Reductions in serum IgA starting at Week 8 and IgM starting at Wk 16 compared to placebo were also observed ($p<0.0001$).
- Significant reductions in median absolute and median percent change from baseline in anti-dsDNA antibody levels in subjects with measurable anti-dsDNA at baseline were observed for the belimumab SC group starting at Week 4 that was maintained through Week 52. Fewer belimumab SC subjects (5%) who were seronegative at baseline converted to seropositive at Week 52 as compared to the placebo group (8%).
- More patients in the belimumab SC group who were seropositive for aCL, lupus anticoagulant, anti-ribosomal P, ribonucleoprotein, and anti-SS-B antibodies converted to seronegative status at Week 52 than in the placebo group. Significant differences in median percent reduction in seropositive status for aCL IgM, beta-2-glycoprotein 1 IgA, ribonucleoprotein, anti-ribosomal P, and anti-

Smith antibody levels at Week 52 were observed in the belimumab SC group versus the placebo group.

- Significant improvements in the percent increase over baseline in C3 levels was observed for the belimumab SC group starting at Week 28 that was maintained through Week 52 as compared to placebo (Week 52 - belimumab SC: 11.6; placebo: 1.3; Treatment difference: 9.3; 95% CI [5.2, 13.4]; $p < 0.0001$). In patients who had low C3 levels at baseline, the mean percent increase from baseline C3 levels was significantly higher in the belimumab SC group compared to the placebo group starting at Week 12 that was maintained through Week 52 (Week 52 – belimumab SC: 24.6; placebo: 8.4; Treatment difference: 16.0; 95% CI [8.0, 23.9]; $p < 0.0001$). A significantly higher proportion of belimumab treated patients (42%) with low C3 at baseline converted to normal/high C3 at Week 52 as compared to the placebo group (21%) ($p = 0.0006$). A significantly lower proportion of belimumab SC treated patients (7.7%) with normal/high C3 at baseline converted to low C3 at Week 52 compared to the placebo group (22.5%) ($p < 0.0001$).
- Significant improvements in the percent increase over baseline in C4 levels was observed for the belimumab SC group starting at Week 4 that was maintained through Week 52 as compared to placebo (Week 52 - belimumab SC: 33.1; placebo: 7.0; Treatment difference: 25.4; 95% CI [17.0, 33.8]; $p < 0.0001$). In patients who had low C4 levels at baseline, the mean percent increase from baseline C4 levels was significantly higher in the belimumab SC group compared to the placebo group starting at Week 12 that was maintained through Week 52 (Week 52 – belimumab SC: 74.0; placebo: 11.9; Treatment difference: 63.7; 95% CI [37.7, 89.7]; $p < 0.0001$). A significantly higher proportion of belimumab SC treated patients (53%) with low C4 at baseline converted to normal/high C4 at Week 52 as compared to the placebo group (20%) ($p = 0.0002$). A significantly lower proportion of belimumab SC treated patients (2%) with normal/high C4 at baseline converted to low C4 at Week 52 compared to the placebo group (7%) ($p = 0.0036$).
- At Week 24, the median percent reduction in CD+19 B cells was 33% with belimumab SC treatment, while the reduction in the placebo group was approximately 2%. At Week 52 the median percent reduction with belimumab SC was 58% compared with 10% with placebo.
- The median reductions in naïve (CD+19/CD20+/CD27-) B cells in the belimumab SC group was 27% at Week 8, 55% at Week 24 and 70% at Week 52, while the reductions at the same time points in the placebo group were 3%, 5% and 11%, respectively. The median reduction in activated B cells at Week 52 was 54% for belimumab SC group versus 47% for the placebo group.
- There was a median percent increase of 150% in memory B cells at Week 8 in subjects treated with belimumab SC that was followed by a decrease of 86% at Week 24 and 22% at Week 52 while no increase (median:-20-0%) was observed in the placebo group.

- A median reduction of 62% in transitional B cells at Week 52 was observed in the belimumab SC group compared to 3% for the placebo group. A median reduction of 56% in the CD19+/CD38b+/CD27b+lymph B cell subset (i.e., SLE subset) at Week 52 was observed for the belimumab SC group versus 18% in the placebo group.

Efficacy Conclusions:

A significantly higher response rate as assessed by the primary endpoint, the SRI, was demonstrated for the belimumab SC 200 mg plus standard of care group 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. These results were supported by a similarly significant outcome for the first major secondary endpoint (e.g., the time to first severe SFI flare). However, the results from the second major secondary endpoint (e.g., the percent of subjects whose average prednisone dose was reduced by $\geq 25\%$ from baseline to ≤ 7.5 mg/day during Week 40 through Week 52) were less robust with numerical improvements observed in favor of the belimumab SC group compared to placebo. The results from remaining ancillary secondary endpoints of clinical interest (e.g., SLE disease flares, improvement or worsening in organ systems as assessed by the BILAG or SLENA SLEDAI, and FACIT-Fatigue) overall demonstrated improvements associated with belimumab SC treatment including in the patient-reported outcome of fatigue, 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 ancillary 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 these results should not be interpreted as predictors of response to treatment with the product.

6 Review of Efficacy

Efficacy Summary

The clinical data submitted in support of the subcutaneous formulation of belimumab as a treatment (b) (4) in adult patients with active, autoantibody-positive SLE on standard therapy was generated from a single phase 3 trial, C1115, in the context of the already approved intravenous belimumab formulation for the same indication. This was a multiregional, randomized, double-blind, placebo-controlled, parallel group study in 836 subjects with active, antibody-positive SLE on stable immunosuppressive medications that evaluated the efficacy of a single fixed dosing regimen of 200 mg of belimumab administered subcutaneously (SC) via prefilled syringe (PFS) once weekly compared to placebo. The study protocol, which was similar in design to the common protocol utilized by the two pivotal phase 3 studies reviewed in support of the licensing approval of the intravenous formulation of belimumab under BLA 125370, contained specifications regarding the use of concomitant SLE medications to treat patients' disease flares to minimize the potential for confounding. Consistent with the findings from the intravenous belimumab studies, in study C1115, patients treated with belimumab SC had a modest but statistically higher rate of response than placebo patients as assessed by the composite endpoint, the SLE Responder Index (SRI). The proportions of subjects achieving success for each of the subcomponents of the SRI were numerically higher in the belimumab group than the placebo group in this study and also reached statistical significance generating support for the robustness of the findings from the primary analysis. Additional support for the results from 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 26). 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 secondary analyses that employed higher reductions in SELENA SLEDAI thresholds (e.g. SELENA SLEDAI ≥ 5 through ≥ 8) for the SRI responder analysis as well as the EMA-modified SRI response rate in which the "no new BILAG 1A/2B domain score" component of the SRI endpoint is replaced with "no BILAG 1A/2B" domain score" corroborate the findings of the primary efficacy analysis.

The results from numerous secondary endpoints were also robust and generally consistent to those of the primary analysis. Since no multiplicity correction was planned in the protocol or implemented during the analyses of the ancillary secondary endpoints other than the two major secondary endpoints, declaring statistical significance of the ancillary secondary endpoints evaluated in this trial using unadjusted p-values would be inappropriate. The results from the analysis of the first major secondary endpoint showed a significant reduction in risk for severe disease flare over 52 weeks as assessed by the SELENA SLEDAI Flare Index (SFI) in favor of the belimumab SC

group which was associated with a prolongation in the median time to first severe flare of 171 days versus 118 days in the placebo group. Results from the other ancillary secondary disease flare assessments such as any SFI flare, severe SFI flare, and median time to first SFI flare as well as SFI flare rates from Week 24 to Week 52 following implementation of background medication restrictions were all robust and supportive of those for the first major secondary endpoint. A decrease in the risk for disease flares was not consistently observed in the IV studies (e.g., a reduction in risk was only observed in study 1057 for the 10 mg/kg belimumab IV treatment group which was not replicated in study 1056).

Although a numerically higher proportion of belimumab SC patients were able to reduce their baseline corticosteroids by at least 25% to ≤ 7.5 mg/day during Weeks 40 through 52, the results from this clinically relevant second major secondary endpoint were not significant on comparison to placebo.

Outcomes from the analyses of various ancillary secondary endpoints that assessed belimumab SC's effect on various organ system manifestations were also suggestive of a treatment benefit associated with belimumab SC (see Table 33 through Table 36).

Although a greater improvement over baseline FACIT-Fatigue score was observed in favor of the belimumab SC group as compared to placebo, and a higher proportion of subjects in the belimumab SC group achieved an improvement in their FACIT-Fatigue score exceeding the Applicant-proposed minimally important clinical difference (MCID) of ≥ 4 points versus the placebo group, these improvements were not consistently maintained over the course of the study. (b) (4)

Unlike what was observed in the pivotal studies reviewed in support of the IV formulation of this product, results from various subgroups analyses involving patients of African American or Black race suggest a favorable treatment effect for belimumab SC. However, the results from these analyses should be interpreted cautiously given the small number of subjects involved. Determination of efficacy in this population who is at risk for more aggressive disease and worse disease outcomes will have to be delayed until results from the ongoing phase 3, randomized, controlled study in SLE patients of African American or Black race become available.

Although a modest magnitude in treatment response was observed in study C1115, the results from the primary and numerous secondary endpoints evaluated in this trial appear overall to be more consistently positive in favor of belimumab SC than the results from the efficacy analyses of the two pivotal phase 3 studies, 1056 and 1057, reviewed in support of the licensing approval of the intravenous formulation of the product. As part of the review process for IV belimumab, a basis for the modest degree of efficacy observed in studies 1056 and 1057 was sought from a variety of sources

(i.e., concomitant use of background immunosuppressives, low baseline disease activity, etc.) but not identified. Despite requiring a higher baseline disease score (SELENA SLEDAI score of ≥ 8 instead of ≥ 6) as part of the entry criteria for study C1115, the magnitude of the treatment effect remarkably did not improve and no obvious cause again could be identified by this medical officer. 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 for potential treatments for this disease. Based on the totality of data generated from the well-controlled study C1115 when coupled with evidence of efficacy from the two well-controlled studies 1056 and 1057 that were conducted with IV belimumab and reviewed previously under BLA 125370, there appears to be adequate statistical evidence to support the efficacy of the 200 mg once weekly dose of belimumab SC as add-on treatment for patients with active, sero-positive SLE despite standard of care

6.1 Indication

For the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) receiving standard therapy.

6.1.1 Methods

The review of efficacy relies primarily on the findings of one pivotal, randomized, placebo-controlled efficacy and safety trial, C1115. The design and conduct of this trial is presented in further detail in Section 5.3.

6.1.2 Demographics

As summarized in the following tables (Table 17 and Table 18), the treatment groups within Study C1115 were generally well balanced with respect to baseline demographics, region, disease characteristics and activity.

The subjects who participated in this trial were predominantly Caucasian (60%) and female (94%). Ten percent (10%) of the patients were of African American/African in origin and 29% identified their ethnicity as Hispanic or Latino. The majority of the subjects were from the USA/Canada (28%) and Eastern Europe (23%). The mean age of subjects was 39 years and their mean BMI was 26 kg/m². No important imbalances in these demographic factors across the treatment groups were noted within Study C1115.

Table 17 – Demographic Characteristics of Subjects Enrolled in Study C1115

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Gender:			
Female	268 (96%)	521 (94%)	789 (94%)
Male	12 (4%)	35 (6%)	47 (6%)
Race¹:			
Caucasian	166 (59%)	336 (60%)	502 (60%)
Asian	63 (23%)	119 (21%)	182 (23%)
African American	30 (11%)	56 (10%)	86 (10%)
Alaskan Native/American Indian	21 (8%)	43 (8%)	64 (8%)
Native Hawaiian/Pacific Islander	0	2 (0%)	2 (0%)
Multiracial	3 (1%)	6 (1%)	9 (1%)
Hispanic Origin:	80 (29%)	160 (29%)	240 (29%)
Age (years):			
Mean (SD)	40 (13)	38 (12)	39 (12)
≤ 45	193 (69%)	403 (73%)	596 (71%)
> 45 to <65	80 (29%)	141 (25%)	221 (26%)
≥ 65	7 (3%)	12 (2%)	19 (2%)
≥ 65 to <75	7 (3%)	11 (2%)	18 (2%)
≥ 75	0	1 (0%)	1 (0%)
BMI (kg/m²)			
Mean (SD)	26 (7.2)	26 (6.3)	26 (6.6)
(Min, Max)	(16, 60)	(15, 51)	(15, 60)
Region and Country			
USA/Canada	84 (30%)	153 (28%)	237 (28%)
Americas (excluding USA/Canada)	57 (20%)	115 (21%)	172 (21%)
Western Europe/Israel	19 (7%)	48 (9%)	67 (8%)
Eastern Europe	59 (21%)	129 (23%)	188 (23%)
Asia	61 (22%)	111 (20%)	172 (21%)

¹Subjects who checked more than one race category are counted under individual race category according to the minority rule as well as multiracial category.
Source: Sponsor's Table 1.8; p. 405-406

As shown in Table 18 below, the overall mean duration of SLE disease was 7 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 10 with 58% 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, at least 1 flare measured by the SLE flare index, and proteinuria > 2 g/24 hours. (Note: Patients with a baseline SELENA SLEDAI score category 0 to 3 were unable to achieve a response of > 4 points necessary for a positive response as assessed by the primary endpoint, the SRI.)

Table 18 – Summary of Subject's Baseline Disease Characteristics for Study C1115

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
SLE Disease Duration (yr): Mean (SD)	7 (7)	6 (7)	7 (7)
BILAG Organ Domain Involvement¹:			
At least 1A or 2B	210 (75%)	388 (70%)	598 (72%)
At Least 1A	51 (18%)	87 (16%)	138 (17%)
At Least 1A or 1B	258 (92%)	499 (90%)	757 (91%)
No A or B	13 (5%)	29 (5%)	42 (5%)
SELENA SLEDAI Category:			
0 to 3	0 (0%)	4 (1%)	4 (1%)
≤9	112 (40%)	200 (36%)	312 (37%)
10 to 11	74 (26%)	161 (29%)	235 (28%)
≥ 12	94 (34%)	191 (34%)	285 (34%)
SELENA SLEDAI Score: Mean (SD)	10.3 (3.0)	10.5 (3.2)	10.4 (3.1)
SLE Flare Index¹:			
At Least 1 Flare	57 (20%)	92 (17%)	149 (18%)
At Least 1 Severe Flare	4 (1%)	8 (1%)	12 (1%)
PGA Category:			
0 to 1	19 (7%)	40 (7%)	59 (7%)
>1 to 2.5	255 (91%)	507 (91%)	762 (91%)
>2.5	5 (2%)	7 (1%)	12 (1%)
Missing	1 (0%)	2 (0%)	3 (0%)
PGA Scale: Mean (SD)	1.54 (0.45)	1.58 (0.43)	1.57 (0.44)
SLICC Damage Index Score Mean (SD)	0.7 (1.27)	0.6 (0.99)	0.6 (1.05)
Proteinuria Category (g/24 hr): ≥ 2	20 (7%)	19 (3%)	39 (5%)
Proteinuria Level (g/24 hr) Mean (SD)	0.44 (0.84)	0.39 (0.71)	0.40 (0.75)

¹Subjects may be included in more than one category
Source: Sponsor's Table 1.14; p.470-472.

As shown in Table 19, the majority of subjects who participated in study C1115 had musculoskeletal and/or mucocutaneous manifestations of SLE disease at baseline as assessed by the SELENA/SLEDAI disease activity index.

Table 19 - Summary of Baseline SELENA SLEDDAI Organ Involvement for Subjects Who Participated in Study C1115 (ITT Population)

Organ System	Number (%) of Patients		
	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Mucocutaneous	248 (89%)	487 (88%)	735 (88%)
Musculoskeletal	218 (78%)	438 (79%)	656 (79%)
Immunologic	210 (75%)	423 (76%)	633 (76%)
Renal	41 (15%)	58 (10%)	99 (12%)
Vascular	18 (6%)	46 (8%)	64 (8%)
Hematologic	23 (8%)	40 (7%)	63 (8%)
Cardiovascular and Respiratory	18 (6%)	29 (5%)	47 (6%)
Constitutional	3 (1%)	7 (1%)	10 (1%)
CNS	2 (1%)	7 (1%)	9 (1%)

Source: Sponsor's Table 1.16; p. 475-476.

A summary of moderate to severe BILAG organ system involvement (A or B score) at baseline is displayed in Table 20 below. The most common organ systems involved in subjects participating in study C1115 were musculoskeletal (65%), mucocutaneous (62%), and hematology (17%). Both treatment groups in this trial were generally well balanced for baseline organ involvement.

Table 20 – Baseline BILAG Organ Domain Grade A and B for Subjects Who Participating in Study C1115 (ITT Population)

BILAG Organ Domain ¹ / Grade	Number (%) of Patients		
	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
General			
A	0	1 (0%)	1 (0%)
B	29 (10%)	38 (7%)	67 (8%)
Mucocutaneous			
A	19 (7%)	30 (5%)	49 (6%)
B	182 (65%)	333 (60%)	515 (62%)
Neurological			
A	0	1 (0%)	1 (0%)
B	0	3 (1%)	3 (0%)
Musculoskeletal			
A	29 (10%)	54 (10%)	83 (10%)
B	180 (64%)	359 (65%)	539 (65%)
Cardiovascular and Respiratory			
A	2 (1%)	0	2 (0%)
B	5 (2%)	13 (2%)	18 (2%)
Vasculitis			
A	4 (1%)	9 (2%)	13 (2%)
B	20 (7%)	38 (7%)	58 (7%)
Renal			
A	3 (1%)	4 (1%)	7 (1%)
B	27 (10%)	49 (9%)	76 (9%)
Hematology			
A	0	1 (0%)	1 (0%)
B	48 (17%)	90 (16%)	138 (17%)

¹Organ Domain Categories: A= requires disease modifying treatment; B=mild reversible problems requiring only symptomatic therapy; C=stable mild disease; D=previously affected but currently inactive; and E=system never involved.

Source: Sponsor's Table 1.7; p. 477-478.

The majority (96%) of patients in this trial were overwhelmingly seropositive for ANA and/or anti-dsDNA as shown in Table 21. The treatment groups within the trial were also generally well balanced with respect to baseline biomarkers of disease activity with the following exceptions. Slightly lower proportions of patients in the placebo group were positive for the presence in aCL, had serum IgG levels that were below the lower limits of normal (LLN), or had had low levels of C3.

Table 21 – Summary of Subject’s Baseline Serologies, Immunoglobulins, Complement and Other Biomarkers for Study C1115

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Anti-dsDNA:			
Positive (≥ 30 IU/mL)	193 (69%)	404 (73%)	597 (71%)
Mean (SD)	516 (977)	629 (1588)	593 (1420)
ANA:			
Positive (≥ 80 Titer)	254 (91%)	492 (89%)	746 (89%)
Mean (SD)	622 (507)	644 (501)	636 (502)
ANA and/or Anti-dsDNA			
Positive:	270 (96.4%)	531 (96%)	801 (96%)
aCL:			
Positive¹	38 (14%)	94 (17%)	132 (16%)
IgG:			
Mean (SD)	15.3 (5.3)	15.6 (5.6)	15.5 (5.6)
>ULN (16.18 g/L)	3 (1%)	10 (2%)	13 (2%)
<LLN 6.94 g/L	97 (35%)	223 (40%)	320 (38%)
IgA:			
Mean (SD)	3.2 (1.5)	3.3 (1.7)	3.3 (1.6)
>ULN (4.63 g/L)	4 (1%)	7 (1%)	11 (1%)
<LLN (0.81 g/L)	34 (12%)	91 (16%)	125 (15%)
IgM:			
Mean (SD)	1.2 (0.8)	1.1 (0.8)	1.1 (0.8)
>ULN (2.71 g/L)	39 (14%)	74 (13%)	113 (14%)
<LLN (0.48 g/L)	12 (4%)	21 (4%)	33 (4%)
C3:			
Mean (SD)	99 (33)	98 (31)	98 (32)
Low (<90 mg/L)	111 (40%)	245 (44%)	356 (43%)
C4:			
Mean (SD)	16 (9)	16 (9)	16 (9)
Low (<10 mg/dL)	71 (25%)	146 (26%)	217 (26%)
BLyS:			
Above LOQ	259 (93%)	504 (91%)	763 (92%)
Mean (SD)	1.8 (1.3)	1.8 (1.4)	1.8 (1.4)

¹aCL was positive if any of the three aCL parameters (IgG, IgA, or IGM) were positive

Source: Sponsor’s Tables 1.18, 1.19, 1.20; p. 479-485.

The following Table 22 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 two treatment groups in this trial, however, higher proportions of patients in the placebo group were taking other immunosuppressives (49%) and NSAIDs (26%) as compared to the belimumab SC group (44% and 22%), respectively.

Table 22 – Summary of Concomitant SLE Medications Used by >10% of Subjects in Study C1115

	Placebo (N=280)	Belimumab (N=556)	Total (N=836)
Total Glucocorticoid Use:	241 (86%)	481 (87%)	722 (86%)
Methylprednisolone	44 (16%)	103 (19%)	147 (18%)
Prednisolone	51 (18%)	96 (17%)	147 (18%)
Prednisone	136 (49%)	258 (46%)	394 (47%)
Prednisone or Equivalent Dose at Baseline:			
0 mg/day	39 (14%)	75 (14%)	114 (14%)
>0 - ≤ 7.5 mg/day	73 (26%)	146 (26%)	219 (26%)
>7.5 mg/day	168 (60%)	335 (60%)	503 (60%)
Average Prednisone or Equivalent Dose at Baseline:			
Mean (SD)	11.2 (9.1)	10.8 (8.2)	10.9 (8.5)
Antimalarials:	189 (68%)	391 (70%)	580 (69%)
Other Immunosuppressives:	137 (49%)	244 (44%)	381 (46%)
Azathioprine	58 (21%)	107 (19%)	165 (20%)
Methotrexate	38 (14%)	52 (9%)	90 (11%)
Mycophenolate Mofetil	22 (8%)	46 (8%)	68 (8%)
NSAIDs	72 (26%)	124 (22%)	196 (23%)

Source: Sponsor's Table 1.24; p. 493-495.

6.1.3 Subject Disposition

A total of 839 subjects were randomized to the two treatment groups as follows: 280 patients to the placebo group and 556 to the belimumab 200 mg SC group. Overall, the proportions of patients who discontinued from the two treatment arms of this study were similar with a higher rate of early discontinuation occurring in the placebo group (24%) than in the belimumab group (17%) as shown in Table 23.

Table 23 – Subject Disposition for Study C1115

	Placebo	Belimumab	Total
Number of Patients Randomized	280	559	839
Number of Patients Treated (ITT)	280	556	836
Number of Patients Who Completed Week 52	214 (76%)	463 (83%)	677 (81%)
Number of Patients Withdrawn Prior to Week 52:	66 (24%)	93 (17%)	159 (19%)
Subject Request	15 (5%)	12 (2%)	27 (3%)
Adverse Event	25 (9%)	40 (7%)	65 (8%)
Disease Progression/Lack of Efficacy	10 (4%)	15 (3%)	25 (3%)
Non-Compliance	2 (1%)	1 (0%)	3 (0%)
Lost to Follow-Up	2 (1%)	6 (1%)	8 (1%)
Protocol Violation	3 (1%)	4 (1%)	7 (1%)
Investigator Decision	5 (2%)	1 (0%)	6 (1%)
Other¹	4 (1%)	14 (3%)	18 (2%)

¹Includes one subject in the placebo group (0.4%) and six subjects in the belimumab 200 mg SC group who withdrew due to pregnancy.

Source: Sponsor's Tables 1.2 and 1.4; p. 398 and 400.

6.1.4 Analysis of Primary Endpoint

As shown in Table 24, patients treated with belimumab 20 mg SC had a statistically higher rate of response than placebo patients in Study C1115. The results from the analyses of the subcomponents of the SRI were 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 group than the placebo group in the study and reached statistical significance.

Table 24 – Week 52 Primary Endpoint and Subcomponent Results for Study C1115 (ITT Population)

	Placebo (N=280)	Belimumab (N=556)
Response:	135/279 (48%)	340/554 (61%)
Observed Difference vs Placebo		13%
OR (95% CI)¹ vs Placebo		1.68 (1.25, 2.25)
P-value		0.0006
Subcomponents		
4-Point Reduction in SELENA SLEDAI:	137/279 (49%)	345/554 (62%)
OR (95% CI)¹ vs Placebo		1.69 (1.26, 2.27)
P-value		0.0005
No Worsening in PGA:	203/279 (73%)	450/554 (81%)
OR (95% CI)² vs Placebo		1.61 (1.15, 2.27)
P-value		0.0061
No New 1A/2B BILAG Domain Scores:	207/279 (74%)	448/554 (81%)
OR (95% CI)³ vs Placebo		1.46 (1.04, 2.07)
P-value		0.0305

Three ITT subjects did not have a baseline PGA assessment and were not included in the SRI/subcomponent analyses

OR=Odds Ratio; CI =Confidence Interval

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

²OR (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

³OR (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 25 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. Imbalances in disposition of response are noted not in favor of the placebo group for having less than a 4-point reduction in SELENA SLEDAI and “dropout not a medication failure”.

Table 25 – Summary of Disposition of Response for Week 52 for Study C1115

	Placebo (N=280)	Belimumab (N=556)
n	279	554
Response¹	135 (48%)	340 (61%)
No Response:	144 (52%)	214 (39%)
Dropout² – Not a Medication Failure	42 (15%)	55 (10%)
Medication Failure³	27 (10%)	42 (8%)
<4 Point Reduction in SELENA SLEDAI (SS)⁴	73 (26%)	112 (20%)
≥4 Point Reduction in SS with the following⁴:	2 (1%)	5 (1%)
Worsening in PGA only⁴	0	1 (0%)
New 1A/2B BILAG only⁴	1 (0%)	4 (1%)
Both Worsening in PGA and New 1A/2B BILAG⁴	1 (0%)	0

¹Three ITT subjects did not have a baseline PGA assessment and did not contribute to SRI/component analyses

²Subjects who withdrew early and had no data in the Day 364 +/- 28 day window

³Includes 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

⁴In subjects who did not dropout and were not medication failures.

Source: Sponsor's Table 2.4; p. 931

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 consistent with the primary efficacy analysis and are shown in Table 26.

Table 26 - Summary of Sensitivity Analyses for Primary Endpoint Response at Week 52 for Study C1115

	Placebo (N=280)	Belimumab (N=556)
Unadjusted Response (ITT Population)¹:		
Observed Difference vs Placebo	135/279 (48%)	340/554 (61%)
OR (95% CI)² vs Placebo		13
P-value		1.69 (2.27, 2.27)
		0.0004
LOCF Response (adjusted) (ITT Population)¹:		
Observed Difference vs Placebo	152/279 (55%)	362/554 (65%)
OR (95% CI)³ vs Placebo		11
P-value		1.56 (1.15, 2.10)
		0.0039
Completer Response (adjusted) (Completers Population)⁴:		
Observed Difference vs Placebo	135/214 (63%)	337/462 (73%)
OR (95% CI)³ vs Placebo		10
P-value		1.54 (1.07, 2.20)
		0.0185
Per Protocol Response (adjusted) (Per Protocol Population)⁵:		
Observed Difference vs Placebo	129/267 (48%)	322/520 (62%)
OR (95% CI)³ vs Placebo		14
P-value		1.75 (1.29, 2.37)
		0.0003

¹Three ITT subjects did not have a baseline PGA assessment and did not contribute to SRI/component analyses

²Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo without adjustment for any covariates

³Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELINA SLEDA (≤ 9 vs ≥ 10), baseline proteinuria level (<2 g/24 hr vs ≥ 2 g/24 hr equivalent) and race (African descent or indigenous-American descent vs other).

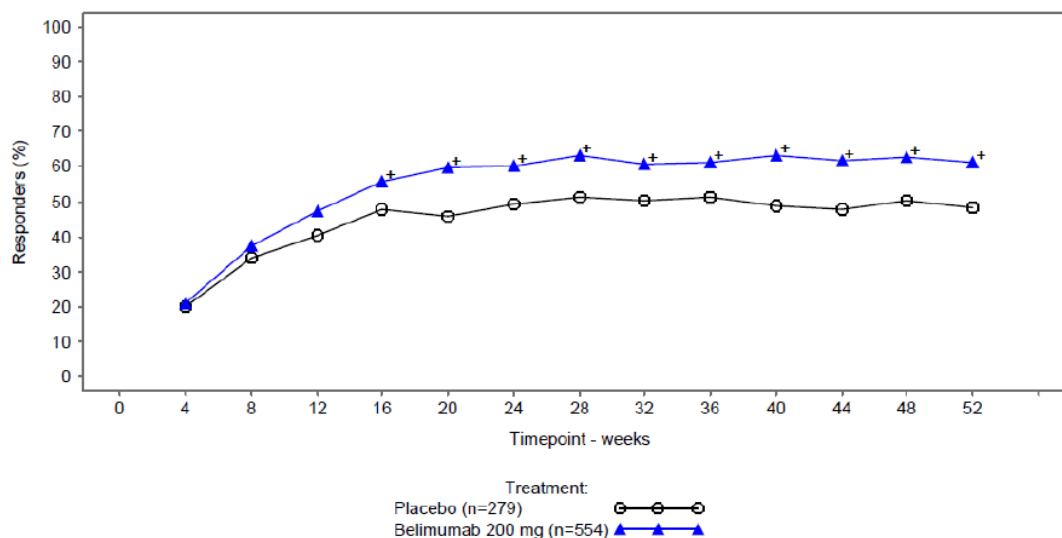
⁴One placebo subject did not have a baseline PGA assessment and did not contribute to this SRI analysis

⁵One belimumab subject did not have a baseline PGA assessment and did not contribute to this SRI analysis

Source: Sponsor's Tables 2.5, 2.6, 2.7 and 2.8; p. 932-935. .

The time course of the SRI response rate for both treatment groups in study C1115 is shown in Figure 2. An increasing proportion of subjects treated with belimumab SC achieved an SRI response over time that peaked at Week 28 and was maintained through Week 52 as compared to the placebo group.

Figure 2 – SRI Response by Visit During the Double-Blind Portion of Study C1115



Source: Figure 2.8

+ denotes p-value <0.05. p-values are from a logistic regression model for the comparison belimumab and placebo with covariates treatment group, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

Source: Sponsor's Fig. 4; p. 82.

6.1.5 Analysis of Secondary Endpoints

There were two major and numerous ancillary secondary endpoints for Study C1115 as shown in Table 27 below. A step-down sequential testing procedure controlling for type 1 error was used in analyzing the primary and major secondary endpoints. However, no multiplicity correction was implemented for the non-major secondary or ancillary endpoints. Therefore, declaring statistical significance of these ancillary secondary endpoints using unadjusted p-values may be inappropriate due to multiplicity concerns. The results from many of the ancillary endpoints evaluated in these trials were numerically supportive of the primary analysis. The remaining discussion will highlight the two major and selected secondary endpoints of interest.

Table 27 – Secondary Endpoints Evaluated in Study C1115

Major Secondary Endpoints: 1. Time to first severe flare (s measured by the modified SLE Flare Index [SFI]) 2. Percent of subjects whose average prednisone dose has been reduced by $\geq 25\%$ from baseline to ≤ 7.5 mg/day during weeks 40 through 52 in subjects receiving greater than 7.5 mg/day at baseline
Secondary Endpoints: <u>Endpoints Supporting Primary Efficacy Endpoint:</u> ▪ SRI by visit ▪ Percent of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI at Week 52 and by visit ▪ Percent of subjects with no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at Week 52 and by visit ▪ Percent of subjects without PGA worsening (increase of < 0.30 points from baseline at Week 52 and by visit) ▪ Percent of subjects with durable SRI from Week 44-52 ▪ Time to the first SRI that is maintained through Week 52 ▪ Duration of longest response among subjects with at least 1 SRI response ▪ SRI5-SRI8 at Week 52 and by visit <u>Disease Activity:</u> ▪ Mean percent change and mean change in PGA by visit ▪ Mean percent change and mean change in SELENA SLEDAI score by visit <u>Organ Specific:</u> ▪ Percent of subjects with organ improvement by SELENA SLEDAI by visit ▪ Percent of subjects with organ worsening by SELENA SLEDAI by visit ▪ Percent of subjects with organ improvement by BILAG by visit ▪ Percent of subjects with organ worsening by BILAG by visit ▪ Mean/median percent (inpatients with proteinuria at baseline) and mean/median (in all patients) change in proteinuria by visit ▪ Time to renal flare over 52 weeks ▪ Percent of patients developing at least 1 renal flare over 52 weeks ▪ Percent of patients with doubling of serum creatinine (the proportion of patients whose serum creatinine attains a level of double that of the baseline value and is confirmed with a second measurement at least 3 weeks later) <u>SFI Flare:</u> ▪ Time to flare over 52 weeks ▪ Time to flare after Week 24 ▪ Time to severe flare after Week 24 ▪ Rate of flare per 100 subject years ▪ Rate of severe flare per 100 subject years <u>Steroids (based on average steroid dose between visits):</u> ▪ Percent of subjects with daily prednisone dose reduced to ≤ 7.5 mg/day from > 7.5 mg/day at baseline by visit (Dropout/Treatment Failure= Non-Responder [DO/TR=NR]) ▪ Percent of subjects with daily prednisone dose increased to > 7.5 mg/day from ≤ 7.5 mg/day at baseline by visit (Last Observation Carried Forward [LOCF]) ▪ Percent of subjects with any increase in steroid use by visit (all patients, LOCF) ▪ Percent of subjects with a 50% decrease in steroids dose by visit (DO/TF=NR; in patients receiving steroids at baseline) ▪ Percent of subjects with a 50% increase in steroid dose by a minimum ≥ 5mg/day by visit (LOCF; in all patients) ▪ Mean/median changes in steroid dose (mg/day) by visit <u>Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index:</u> ▪ Mean change from baseline in SLICC Damage Index at Week 52 ▪ Percent of patients with any SLICC Damage Index worsening (change > 0) at Week 52 compared with baseline <u>Patient Reported Outcomes:</u> ▪ Mean change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score at Week 52 and by visit ▪ Percent of patients with improvement in FACIT-Fatigue score exceeding the Minimally Important Clinical Difference (MCID) (≥ 4) at Week 52 and by visit

Biomarkers:

- Median/mean percent change and median/mean change from baseline in absolute B cell subsets (CD20+, CD20+/27+ memory, CD20+/27-naïve, CD20+?69+ activated, CD20+/138+ plasmacytoid, CD19+/27BRIGHT/38BRIGHT SLE subset CD19+/CD24HIGH?CD38HIGH regulatory B cell, and CD20-/138+ plasma cells) by visit.
- Median/mean percent change and median/mean change from baseline by visit total serum IgG, IgM and IgA, anti-dsDNA, ANA, aCL, lupus anticoagulant, ENA, C3 and C4
- Percent of patients with normalized serological activity at Week 52 and over time: IgG, IGM and IgA (high to normal/low); anti-dsDNA, ANA, aCL, lupus anticoagulant and ENA (present to absent); C3 and C4 levels (low to normal/high)

Source: Section 2.2.2 and 2.2.23 of the Sponsor's Reporting and Analysis Plan for Study C1115

Major Secondary Endpoints

Time to First Severe Flare (as measure by the modified SFI)

The first major secondary endpoint in this study was the time to the first severe flare over 52 weeks assessed via the modified SELENA SLEDAI 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 28 below].

Table 28 –SELENA Trial Definition of SLE Flares

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

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

Table 29 shows that subjects in the belimumab SC group had a 49% reduction in the risk of experiencing a severe SFI flare during the 52 weeks of study C1115 which was significantly different as compared to the placebo group. The median time to first severe flare was 171 days for patients who flared in the belimumab SC group versus 118 days for those who flared in the placebo group (Table 29).

Table 29 – Time to First Severe Flare Over 52 Weeks for Study C1115 (ITT Population)

	Placebo (N=280)	Belimumab (N=556)
Severe SFI Flare^a [Number of Subjects (%)]^b	51 (18.2%)	59 (10.6%)
Median Time to First Flare in Days (25th percentile, 75th percentile)^c	-(-,-)	-(-,-)
Hazard Ratio (95% CI)^b vs Placebo		0.51(0.35, 0.74)
p-value^d		0.0004
Study Day of Severe Flare		
n^e	51	59
Median (25th percentile, 75th percentile)	118 (62, 259)	171 (57, 257)
(Min, Max)	(2, 364)	(5, 358)

a. Analysis excludes severe flares that were triggered only by increase in SELENA SLEDAI score >12. Data censored at least available visit by Week 52 visit. For subjects who died, data are censored at death if no flares occurred before death. Time to first flare is defined as (event date - treatment start date + 1).

b. Number (%) of subjects with a severe flare over 52 weeks. Only includes post-baseline severe flares.

c. Statistics are missing because the number of events was too low to estimate the value

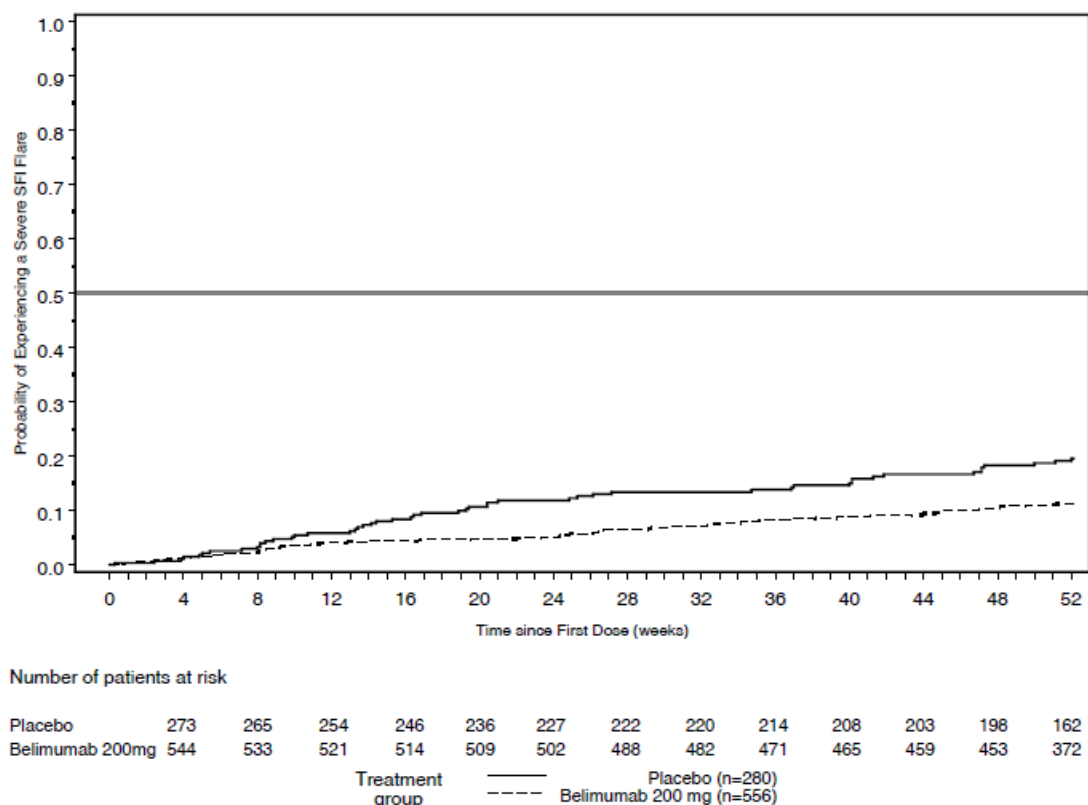
d. From Cox proportional hazard model for the comparison between belimumab and placebo adjusting for baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline complement levels (low C3 and/or C4 vs no low C3 or C4) and race (Black vs Other)

e. Among subjects experiencing a severe flare

Source: Sponsor's Table 2.22; p. 964

Figure 3 shows that overtime the probability of experiencing a severe flare increased for both treatment groups but at a slower rate for the belimumab SC group.

Figure 3 – Time to First Severe SFI Flare Over 52 Weeks (ITT Population)



Source: Sponsor's Fig. 2.31, p. 831.

Reduction in Corticosteroids:

In view of the morbidity associated with corticosteroids, reduction in corticosteroid use in patients whose SLE was controlled was the second major secondary endpoint. This clinically relevant endpoint was defined as the percentage of subjects whose average prednisone dose has been reduced by > 25% from baseline to < 7.5 mg/day during weeks 40 through 52 in subjects receiving greater than 7.5 mg/day at baseline. A total of 60% of the subjects who participated in this trial were eligible for this analysis. As shown in Table 30, a greater proportion of patients in the belimumab SC group (18%) were able to reduce prednisone use by $\geq$ 25% as compared to placebo (12%) but this difference between the treatment groups was not significant on comparison.

Table 30 – Proportion of Patients with Prednisone Reduction by $\geq 25\%$ from Baseline to ≤ 7.5 mg/day During Week 40 through Week 52 (ITT Population)

	Placebo (N=280)	Belimumab (N=556)
Reduction in prednisone^a, n/n (%)	20/168 (11.9%)	61/335 (18.2%)
Observed Difference vs Placebo		6.30
Odds Ratio (95% CI)^b vs Placebo		1.65 (0.95, 2.84)
P-value^b		0.0732

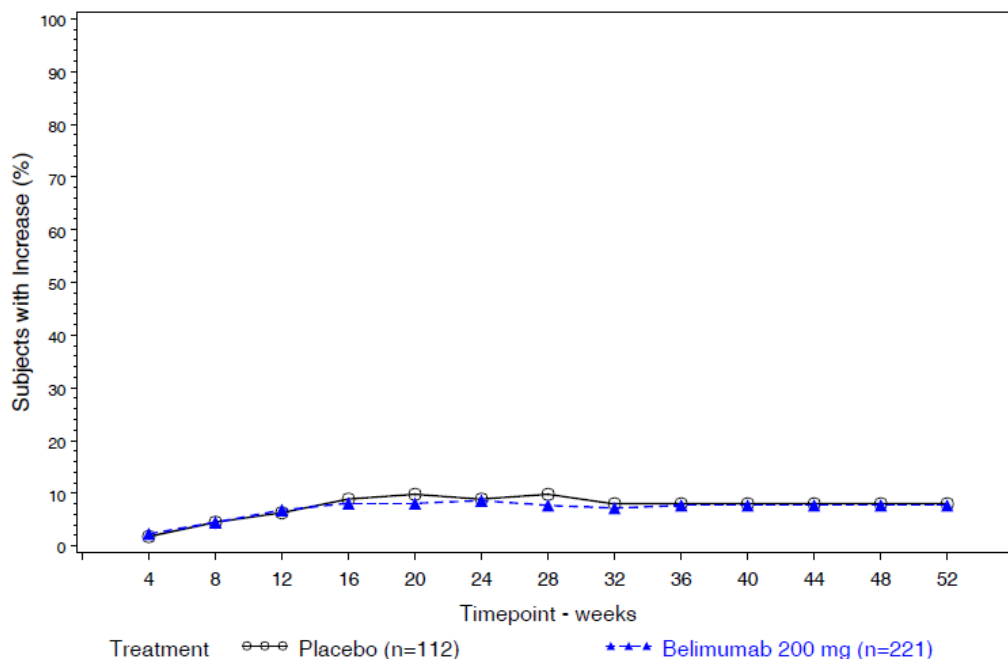
a. Includes only subjects with baseline prednisone >7.5 mg/day

b. Odds Ratio (95% CI) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline prednisone dose, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline complement levels (low C3 and/or C4 or no low C3 or C4) and race (Black vs Other).

Source: Sponsor's table 2.63; p1124.

Subjects in this trial were also evaluated for increase in concomitant corticosteroids. The following Figure 4 depicts the percentage of subjects whose daily prednisone dose was increased to >7.5 mg/day from < 7.5 mg/day at baseline over time in Study C1115. Over the 52-weeks of Study C1115, the percentage of subjects whose prednisone was increased to > 7.5 mg/day from < 7.5 mg/day was similar between the two groups (belimumab SC range: 2.3-8.6% versus placebo range: 1.8-9.8%).

Figure 4 – Percentage of Subjects Requiring an INCREASE in Daily Prednisone to > 7.5 mg/day from <7.5 mg/day at Baseline (LOCF)



All corticosteroids are converted to a prednisone equivalent average daily dose (mg/day).
 + denotes p-value <0.05
 P-values are from a logistic regression model for the comparison between Belimumab and Placebo without adjustment for any covariates.
 Source: Sponsor's Figure 2.71; p. 909

6.1.6 Other Endpoints

Disease Flares:

Additional flare analyses assessed by the modified SLE Flare Index are shown in Table 31. Overall, the results from these flare analyses support the robustness of the results from the first major secondary endpoint, the time to the first severe flare over 52 weeks assessed via the modified SFI, shown in the preceding Table 29.

Table 31 – Ancillary Analyses of SLE SFI Flare Rate for Study C1115 (ITT Population)

	Placebo (N=280)	Belimumab (N=556)
Any Flare^a:		
n (%)^b	192 (69%)	337 (61%)
Median Time to 1st Flare in Days (Min, Max)^c	141 (57, -)	190 (71, -)
Hazard Ratio (95% CI)^d vs Placebo		0.78 (0.65, 0.93)
P-value^d		0.0061
Subject-Years in Study	244.9	506.5
Any Flare (n)^a	493	847
Unadjusted Rate per Subject-Year^e	2.0	1.7
Adjusted Rate per Subject-Year	2.5	2.0
Adjusted Rate Ratio (95% CI)^f vs Placebo		0.81 (0.69, 0.97)
P-value		0.0186
Subject-Years in Study	244.9	506.5
Severe Flares (n)^a	70	82
Unadjusted Rate per Subject-Year^g	0.3	0.2
Adjusted Rate per Subject-Year	0.4	0.2
Adjusted Rate Ratio (95% CI)^f vs Placebo		0.54 (0.33, 0.88)
P-value		0.0128

Note: Five subjects did not have a post baseline flare assessment.

a. Severe flares that were triggered only by an increase in SELENA SLEDAI score to >12 are reported as mild/moderate flares if the change from the previous visit was at least 3 points and are excluded otherwise. Data censored at last available visit by Week 52 visit. For subjects who died, data are censored at death if no flares occurred before death. Time to first flare is defined as (even date – treatment start date + 1).

b. Number (%) of subjects with a flare over 52 weeks. Only includes post baseline flares.

c. Statistics will be missing when the number of events is too low to estimate the value.

d. From Cox proportional hazards model for the comparison between belimumab SC and placebo adjusting for baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10), baseline complement levels, (low C3 and/or C4 vs. no low C3 or C4) and race (black vs other).

e. Unadjusted rate per subject-year = total number of flares/total subject years in study

f. From negative binomial regression with the number of flares/sever flares as the dependent variable and adjusting for baseline SELENA SLEDAI score (< 9 vs. > 10), baseline complement levels, (low C3 and/or C4 vs. no low C3 or C4) and race (black vs other). Adjustment is also made for subject's follow-up time by including log follow-up time (years) as an offset variable in the model.

g. Unadjusted rate per subject-year = total number of severe flares/total subject years in study. The follow-up time (years) for each subject is calculated as (date of last available study visit) or date of first treatment failure) – treatment start date +1) /365.25.

Source: Sponsor's Tables 2.25, 2.28, and 2.29; p. 968, 972-973.

The occurrence of flares was also assessed from Weeks 24 to 52 following the implementation of background medication restrictions (Table 32 below). Significant decreases in the risk for experiencing a SFI disease flare or a severe SFI flare during this time period were observed in the belimumab SC group as compared to the placebo group in study C1115.

Table 32 – Ancillary Analyses of SLE SFI Flare Rates from Week 24 to Week 52 (ITT Population)

	Placebo (N=280)	Belimumab (N=556)
Any SFI Flare^a [Number of Subjects (%)]^b	136/248 (55%)	241/509 (47%)
Median Time to First Flare in Days (25th percentile, 75th percentile)^c	163 (57, -)	200 (58, - 0)
Hazard Ratio (95% CI)^d vs Placebo		0.80 (0.65, 0.99)
p-value^d		0.0415
Severe SFI Flare^a [Number of Subjects (%)]^e	28/248 (11%)	35/509 (7%)
Median Time to First Flare in Days (25th percentile, 75th percentile)^c	- (-, -)	- (-, -)
Hazard Ratio (95% CI)^d vs Placebo		0.56 (0.34, 0.92)
p-value^d		0.0215

Note: Five subjects did not have a post baseline flare assessment.

a. Severe flares that were triggered only by an increase in SELENA SLEDAI score to >12 are reported as mild/moderate flares if the change from the previous visit was at least 3 points and are excluded otherwise. For subjects who died, data are censored at death if no flares occurred before death. Time to first flare is defined as (event date – Week 24 visit date + 1).

b. Number (%) of subjects with a flare Week 24 to 52. Only includes post-baseline flares.

c. Statistics are missing because the number of events was too low to estimate the value.

d. From Cox proportional hazards model for the comparison between belimumab and placebo adjusting for baseline SELENA SLEDAI score (< 9 vs. > 10), baseline complement levels, (low C3 and/or C4 vs. no low C3 or C4) and race (black vs other

e. Number (5) of subjects with severe flare Week 24 to 52. Only includes post-baseline severe flares.

Source: Sponsor's table 2.24 and 2.27; p.

Improvement and Worsening by Organ Domains:

Although the SELENA 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. (Improvement and worsening by actual BILAG organ domains are summarized in Table 35 and Table 36 below). A treatment benefit in favor of belimumab SC was observed in the mucocutaneous, musculoskeletal, immunologic and vascular organ systems as compared to placebo.

Table 33 – SELENA-SLEDAI Organ System Improvement^a at Week 52 (ITT Population)

SELENA SLEDAI Organ System	Placebo (N=280)	Belimumab (N=556)
Mucocutaneous Baseline Involvement Number (%) Improved at Week 52 P-value ^b	n=248 135 (54%)	n=487 312 (64%) 0.0132
Musculoskeletal Baseline Involvement Number (%) Improved at Week 52 P-value ^b	n=218 110 (51%)	n=438 282 (64%) 0.0007
Immunologic Baseline Involvement Number (%) Improved at Week 52 P-value ^b	n=211 34 (16%)	n=427 127 (30%) 0.0002
Renal Baseline Involvement Number (%) Improved at Week 52 P-value ^b	n=41 15 (37%)	n=59 25 (42%) 0.6788
Hematological Baseline Involvement Number (%) Improved at Week 52 P-value ^b	n=25 9 (36%)	n=49 22 (45%) 0.6190
Vascular Baseline Involvement Number (%) Improved at Week 52 P-value ^b	n=18 5 (28%)	n=46 29 (63%) 0.0138
Cardiovascular and Respiratory Baseline Involvement Number (%) Improved at Week 52 P-value ^b	n=18 10 (56%)	n=29 20 (69%) 0.3710
CNS Baseline Involvement Number (%) Improved at Week 52 P-value ^b	n=2 1 (50%)	n=7 4 (57%) 1.000

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

a. Among subjects with organ system involvement at baseline (DO/TF= NR)

b. Fisher's exact test

Source: Sponsor's Table 2.40; p. 996-1003.

With respect to new organ involvement, as summarized in Table 34, the rates for organ system worsening were generally comparable for both treatment groups with the exceptions of the immunologic and the musculoskeletal organ systems. A higher

proportion of placebo subjects experienced worsening or new involvement in the immunologic system as compared to the belimumab SC group while there was a numerical trend for subjects in the belimumab SC group to experience new involvement in the musculoskeletal system.

Table 34 – Worsening (New Involvement) by SELENA SLEDAI organ Domains (ITT Population)

SELENA SLEDAI Organ System	Placebo (N=280)	Belimumab (N=556)
Mucocutaneous Without Baseline Involvement Number (%) Involved at Week 52 P-value ^b	n=32 3 (9%)	n=69 6 (9%) 1.000
Musculoskeletal Without Baseline Involvement Number (%) Involved at Week 52 P-value ^b	n=62 0 (0%)	n=118 6 (5%) 0.0949
Immunologic Without Baseline Involvement Number (%) Involved at Week 52 P-value ^b	n=69 10 (15%)	n=129 13 (10%) 0.3611
Renal Without Baseline Involvement Number (%) Involved at Week 52 P-value ^b	n=239 18 (8%)	n=497 33 (7%) 0.6449
Hematological Without Baseline Involvement Number (%) Involved at Week 52 P-value ^b	n=255 8 (3%)	n=507 22 (4%) 0.5543
Vascular Without Baseline Involvement Number (%) Involved at Week 52 P-value ^b	n=262 0 (0%)	n=510 3 (1%) 0.5548
Cardiovascular and Respiratory Without Baseline Involvement Number (%) Involved at Week 52 P-value ^b	n=642 0 (0%)	n=527 3 (1%) 0.5547
CNS Without Baseline Involvement Number (%) Involved at Week 52 P-value ^b	n=278 1 (0%)	n=549 2 (0.2%) 1.000

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

a. Among subjects with organ system involvement at baseline (DO/TF= NR)

b. Fisher's exact test

Source: Sponsor's Table 2.41; p. 1004-1010

When using BILA domains to assess improvement, a treatment benefit in favor of belimumab SC was observed in the mucocutaneous, musculoskeletal, and vascular

organ domains as compared to placebo (Table 25) which was similar to the results of the SELENA SLEDAI organ system improvement shown in Table 33 above.

Table 35 – BILAG Organ Domain Improvement from Baseline to Week 52 for Study C1115

	Placebo (N=280)	Belimumab (N=556)
BILAG: General Baseline Domain Score A or B Number (%) improved at Wk 52 p-value of difference ^a	29 22 (76%)	39 32 (82%) 0.5586
BILAG: Mucocutaneous Baseline Domain Score A or B Number (%) improved at Wk 52 p-value of difference ^a	201 88 (44%)	363 201 (55%) 0.0107
BILAG: Musculoskeletal Baseline Domain Score A or B Number (%) improved at Wk 52 p-value of difference ^a	209 116 (56%)	413 273 (66%) 0.0110
BILAG: Neurological Baseline Domain Score A or B Number (%) improved at Wk 52 p-value of difference ^a	0 0 (0%)	4 4 (100%) --
BILAG: Cardio-Respiratory Baseline Domain Score A or B Number (%) improved at Wk 52 p-value of difference ^a	7 4 (57%)	13 7 (54%) 1.000
BILAG: Vasculitis Baseline Domain Score A or B Number (%) improved at Wk 52 p-value of difference ^a	24 9 (38%)	47 35 (75%) 0.0041
BILAG: Renal Baseline Domain Score A or B Number (%) improved at Wk 52 p-value of difference ^a	30 19 (63%)	53 30 (57%) 0.6446
BILAG: Hematology Baseline Domain Score A or B Number (%) improved at Wk 52 p-value of difference ^a	48 13 (27%)	91 32 (35%) 0.3492

^aFishers exact test

Dropouts/Medication failure = No Improvement

Source: Sponsor's Table 2.48; p. 1046-1053.

However, the proportion of subjects experiencing worsening in BILAG organ domain scores was similar for both treatment groups (Table 36).

Table 36 – BILAG Organ Domain Worsening from Baseline to Week 52 for Study C1115 (LOCF)

	Placebo (N=280)	Belimumab (N=556)
BILAG: General		
No Baseline Domain Score A	280	555
Number (%) worsened at Wk 52	3 (1%)	9 (2%)
p-value of difference ^a		0.7599
BILAG: Mucocutaneous		
No Baseline Domain Score A	261	526
Number (%) worsened at Wk 52	10 (4%)	15 (3%)
p-value of difference ^a		0.5183
BILAG: Musculoskeletal		
No Baseline Domain Score A	251	502
Number (%) worsened at Wk 52	7 (3%)	12 (2%)
p-value of difference ^a		0.8064
BILAG: Neurological		
No Baseline Domain Score A	280	555
Number (%) worsened at Wk 52	1 (0.4%)	2 (0.4%)
p-value of difference ^a		1.000
BILAG: Cardio-Respiratory		
No Baseline Domain Score A	278	556
Number (%) worsened at Wk 52	0	2 (0.4%)
p-value of difference ^a		0.5550
BILAG: Vasculitis		
No Baseline Domain Score A	276	547
Number (%) worsened at Wk 52	0 (0%)	4 (1%)
p-value of difference ^a		0.3068
BILAG: Renal		
No Baseline Domain Score A	277	552
Number (%) worsened at Wk 52	17 (6%)	35 (6%)
p-value of difference ^a		1.000
BILAG: Hematology		
No Baseline Domain Score A	280	555
Number (%) worsened at Wk 52	23 (8%)	31 (6%)
p-value of difference ^a		0.1791

^aFishers exact test

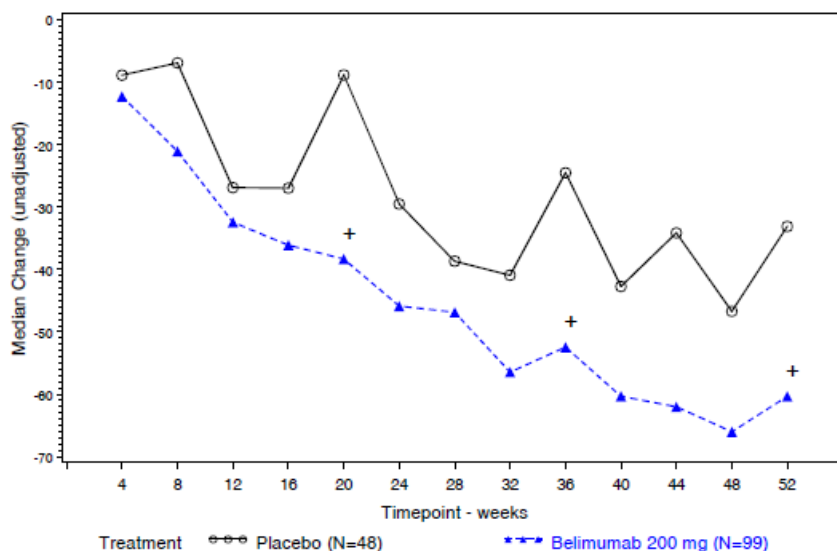
Dropouts/Medication failure = No Improvement

Source: Sponsor's Table 2.49; p. 105-1061.

Since the renal system is frequently affected by SLE, a number of ancillary secondary endpoints also evaluated belimumab SC's effect on proteinuria. Figure 5 shows that amongst subjects with baseline proteinuria >0.5 g/24 hours, a decrease in proteinuria was observed in both treatment groups as assessed by the median proteinuria percent change over baseline that was significantly greater in the belimumab treatment group as compared to placebo at Weeks 20, 36 and 52. However, no definitive conclusions should be drawn from this analysis due to an imbalance in patients with proteinuria ≥ 2g/24 hours randomized to the placebo group (20/280 subjects; 7%) as compared to belimumab SC (19/556; 3%) which may have had an impact on these results and the

lack of supportive results from the other secondary proteinuria assessments evaluated in this study.

Figure 5 – Proteinuria Percent Change from Baseline by Visit Among Subjects with Baseline Proteinuria >0.5 g/24 hr: No-Parametric Sensitivity Analysis (Observed) in Study C1115



+ denotes p-value <0.05
 P-values are from a Wilcoxon rank sum test comparing Belimumab and Placebo.
 N=number of subjects with proteinuria at baseline.
 Source: Sponsor's Fig. 102.61; p. 921.

Organ Damage:

Whereas instruments such as the SELENA 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, The SLICC/ACR Damage Index records damage occurring in patient 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 37, the results were not consistent with respect to progression in the damage index and therefore definitive conclusions cannot be made.

Table 37 - Change in SLICC/ACR Damage Index at Week 52^a

	Placebo (N=280)	Belimumab (N=556)
Baseline Mean ($\pm$ SE)	0.7 (1.19)	0.6 (1.00)
Change at Week 52		
Mean ($\pm$ SE)	0.1 (0.22)	0.0 (0.19)
LS mean ($\pm$ SE)	0.11 (0.02)	0.0 (0.01)
Treatment Difference (95% CI) with Placebo		-0.0 (-0.1, 0.0)
P-value^b		0.1174

^aOnly subjects with a baseline and post baseline assessment are included in the analysis

^bAll statistics are from an analysis of covariance (ANCOVA) model comparing belimumab and placebo with covariates for treatment group, baseline, SLICC/ACR Damage Index score, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline complement levels (low C3 and/or C4 vs no low C3 or C4) and race (black vs other).

Source: Sponsor's Table 2.32; p. 976.

Health Outcomes:

The health-related quality of life assessment tool used in study C1115 was the FACIT-Fatigue Scale. Although this parameter was designated as a secondary endpoint by the statistical analysis plan without controls for multiplicity, (b) (4)

As shown in Table 38, the mean change from baseline in the FACIT-Fatigue Score was significantly greater for the belimumab SC group as compared the placebo group.

Table 38 – FACIT-Fatigue Scale Score Change from Baseline to Week 52 for Study C1115 (LOCF)

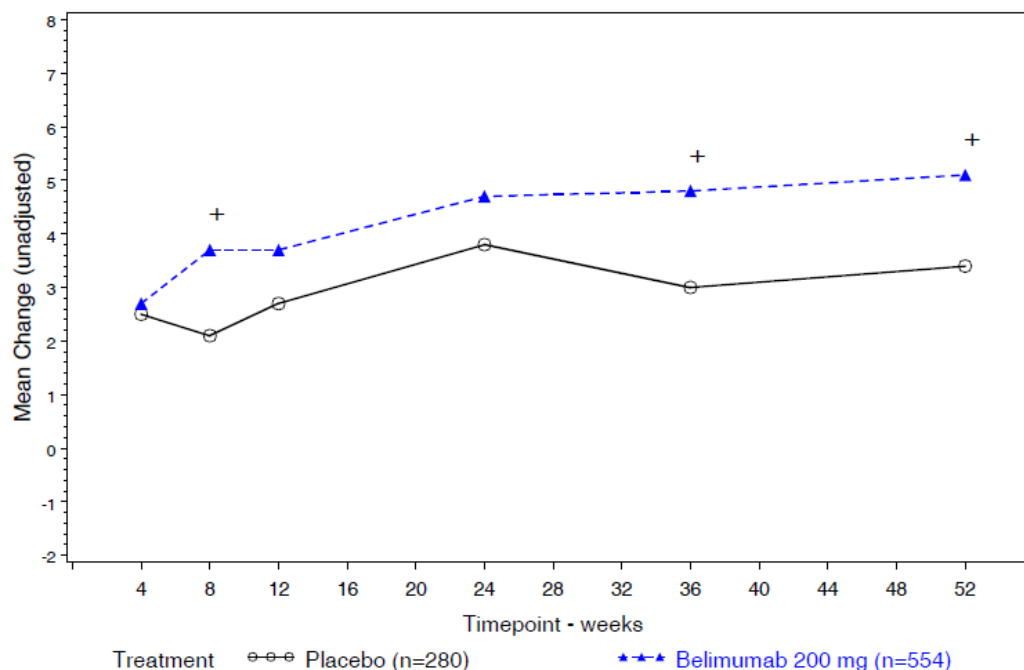
	Placebo (N=280)	Belimumab (N=556)
Mean ($\pm$ SD)	3.4 (9.22)	5.1 (10.28)
LS mean ($\pm$ SE)	2.7 (0.65)	4.4 (0.55)
Treatment Difference (95% CI) with Placebo		1.6 (0.3, 2.9)
P-value^a		0.0130

^aAll statistics are from an analysis of covariance (ANCOVA) model comparing belimumab and placebo with covariates for treatment group, baseline, SLICC/ACR Damage Index score, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline complement levels (low C3 and/or C4 vs no low C3 or C4) and race (black vs other).

Source: Sponsor's Table 2.73; p. 1157-1160.

The time course of the mean change over baseline in the FACIT-Fatigue Score for both treatment groups in study C1115 is shown in Figure 6. Although a significant improvement over baseline score for this parameter was observed as early as Week 8 in the belimumab SC group as compared to placebo, it was not consistently maintained over the 52-week course of the trial.

Figure 6 – FACIT-Fatigue Scale Score Change from Baseline by Visit (LOCF) Study C1115 (ITT Population)



+ denotes p-value <0.05

P-values are from an analysis of covariance (ANCOVA) model comparing Belimumab and Placebo with covariates treatment group, baseline FACIT-Fatigue scale score, baseline SELENA SLEDAI score (<=9 vs. >=10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (black vs. other).

Source: Sponsor's Fig. 2.72; p. 910

According to the Applicant, the minimally important clinical difference (MCID) for the FACIT-Fatigue Score is ≥ 4 points. Table 39 shows that a significantly higher proportion of patients in the belimumab SC group achieved an improvement in their FACIT-Fatigue score exceeding the MCID ≥ 4 points as compared to the placebo group at Week 52 in study C1115.

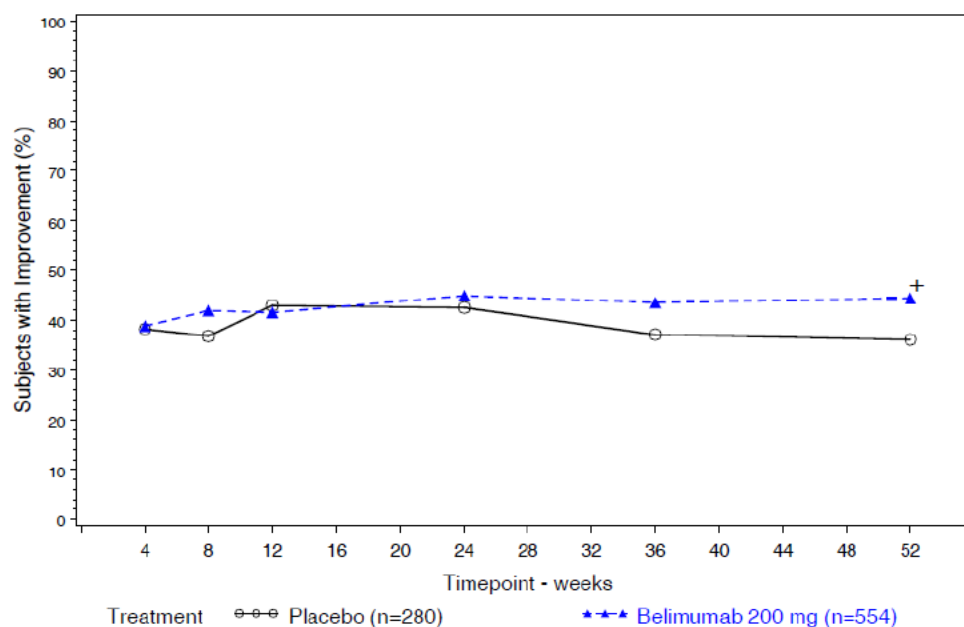
Table 39 – Improvement in FACIT-Fatigue Scale Score Exceeding the MCID ≥ 4 at Week 52 for Study C1115 (ITT Population)

	Placebo (N=280)	Belimumab (N=556)
Improvement ≥ 4 in FACIT-Fatigue Scale Score	101 (36%)	246 (44%)
Observed difference vs Placebo		8.335
Odds ratio (95% CI) vs. Placebo		1.42 (1.05, 1.94)
P-value^a		0.0245

^aOdds ratio (95% CI) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline FACIT-Fatigue Scale score, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline complement levels (low C3 and/or C4 vs no low C3 or C4) and race (black vs other).
Source: Sponsor's Table 2.75; p. 1170.

However, Figure 7 shows the proportion of patients who achieved a significant improvement in the FACIT-Fatigue Scale score exceeding the MCID ≥ 4 points was only achieved at the Week 52 time point by the belimumab SC group.

Figure 7 – Improvement in FACIT-Fatigue Scale Score Exceeding the MCID (≥ 4 Points) by Visit During Study C1115 (ITT Population)



+ denotes p-value <0.05

P-values are from a logistic regression model for the comparison between Belimumab and Placebo with covariates for treatment group, baseline FACIT-Fatigue Scale score, baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10), baseline complement levels (low C4 and/or C4 vs. no low C3 or C4) and race (black vs. other).

Source; Sponsor's Fig. 2.74; p. 913.

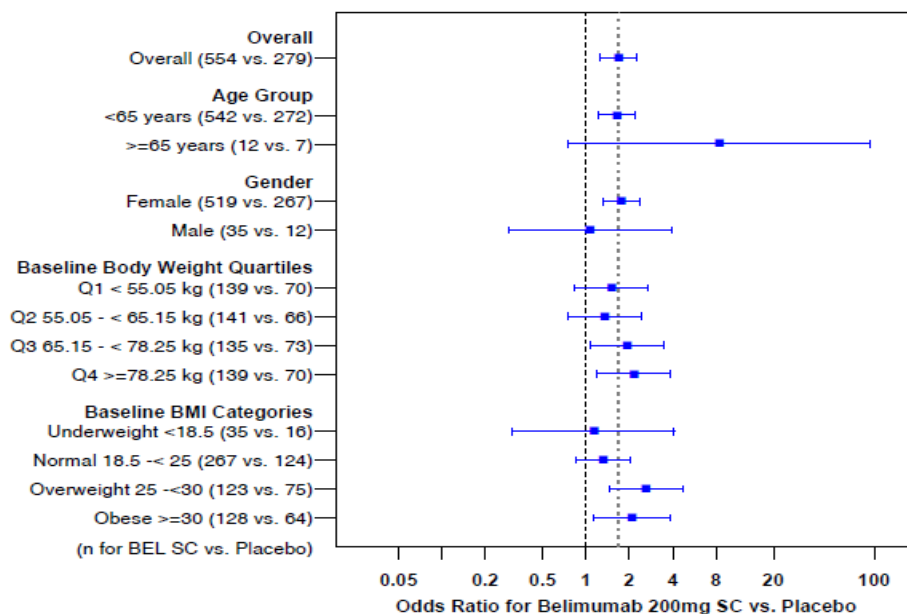
(b) (4)

(b) (4)

6.1.7 Subpopulations

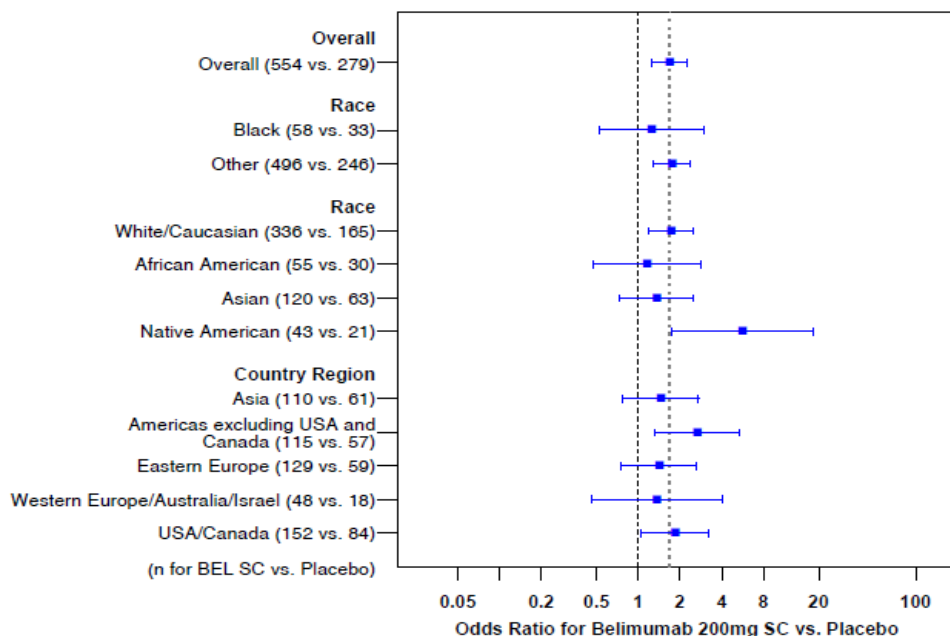
Pre-specified subgroup analyses of the primary efficacy endpoint by age, gender, baseline body weight quartile, BMI, race, and region as well as baseline SELENA SLEDAI score, C3 or C4 levels, anti-dsDNA, medications (prednisone and MMF use), and immunogenicity status were provided by the Applicant. Also provided were post hoc analyses exploring the primary efficacy endpoint by race (Black versus Other), baseline immunosuppressant use and baseline SELENA SLEDAI score ≥ 8 . Figure 8 through Figure 11 contain forest plot analyses of the primary SRI response at Week 52 by various subgroups. Review of these data generally shows a treatment benefit associated with belimumab SC observed in most of the subgroup analyses. Due to the small sample size for age ≥ 65 years and males, no definitive conclusions can be drawn based on these subgroup analyses.

Figure 8- Forest Plot With Odds Ratio of Primary SRI Response at Week 52 by Subgroup for Study C1115



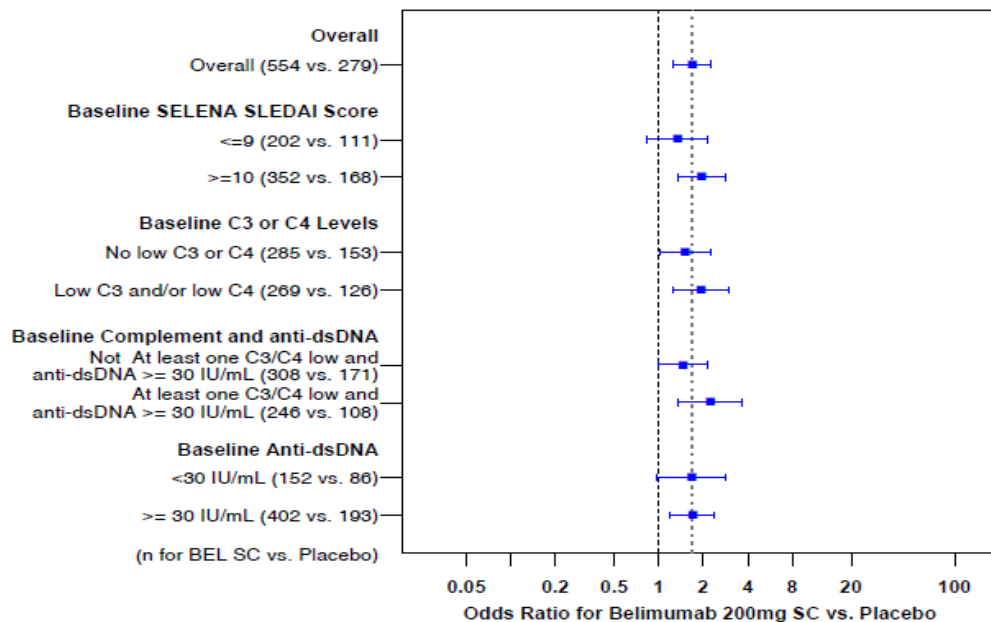
Source: Sponsor's Figure 2.80; p. 916.

Figure 9 – Forest Plot With Odds Ratio of Primary SRI Response at Week 52 by Subgroup for Study C1115 (cont.)



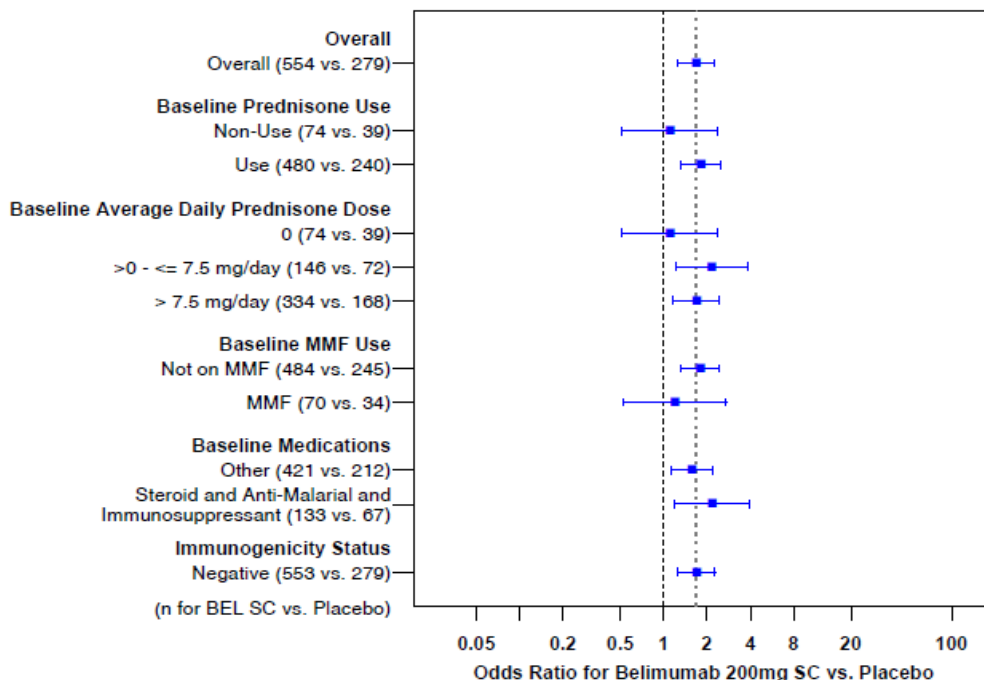
Source: Sponsor's Fig. 2.80; p. 918.

Figure 10 – Forest Plot With Odds Ratio of Primary SRI Response at Week 52 by Subgroup for Study C1115 (cont.)



Source: Sponsor's Fig. 2.80; p.918.

Figure 11 – Forest Plot With Odds Ratio of Primary SRI Response at Week 52 by Subgroup for Study C1115 (cont.)



Source: Sponsor's Fig. 2.80; p. 919.

SLE patients of African American or African heritage have been reported to have more aggressive disease, often leading to worse outcomes. Since the results from post hoc analyses involving small numbers of subjects of African American or African heritage who participated in the two pivotal phase 3 studies reviewed in support of the IV formulation of belimumab suggested an unfavorable response to the product in this demographic group, the Applicant provided one prespecified analysis of race by classification and one post hoc analysis of race classification for "Black vs Other" based on the demographic stratification variable used in study C1115. Review of the results from these various demographic subgroup analyses (Table 40) reveals a treatment effect for belimumab SC in all of the subgroups, however, the SRI response rates for African Americans and Black race subjects randomized to belimumab SC were markedly lower on cross-group comparison to the other demographic subgroups. Due to the small numbers of African American and Black race subjects as well as Native American subjects who participated in this trial, no definitive conclusions regarding the effectiveness of belimumab SC in these demographic groups can be drawn. Of note, the Applicant is conducting a study in SLE patients of African American or African heritage as a post-marketing commitment.

Table 40 – Week 52 SRI Response by Race for Study C1115

	Placebo (N=280)	Belimumab (N=556)
Racial Subgroups		
White/Caucasian Response: Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	81/165 (49%)	210/336 (63%) 13.4% 1.73 (1.19, 2.52) 0.0044
African American Response: Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	12/30 (40%)	24/55 (44%) 3.6% 1.16 (0.47, 2.87) 0.7458
Asian Response: Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	32/63 (51%)	70/120 (58%) 7.5% 1.36 (0.73, 2/50) 0.3298
Native American Response: Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	10/21 (48%)	36/43 (84%) 36% 5.66 (1.74, 18.38) 0.0040
Race Classification for Study Stratification (Race vs Other)		
Black Response: Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	13/33 (39%)	26/58 (45%) 5.4% 1.25 (0.52, 2.98) 0.6148
Other Response: Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	122 (246 (50%))	314/496 (63%) 13.7% 1.75 (1.29, 2.39) 0.0004

¹Odds Ratio (95% CI) and p-values are from a logistic regression model for the comparison between belimumab SC and placebo without adjustment for any covariates.

Source: Sponsor's Tables 2.79 and 2.80; p. 1177 and 1178.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Due to concerns for differing exposure to belimumab in patients with low and/or high body weight as a result of the product's fixed dosing regimen, the Applicant submitted Week 52 SRI response by body weight quartiles (Q1 <55 kg, Q2 <55.05 - <65.15 kg, Q3 <65.15 - <78.25 kg, and Q4 ≥ 78.25 kg) as well as by BMI categories (underweight, normal, overweight and obese). Table 41 shows numerically higher proportions of belimumab SC subjects achieved a SRI response as compared to placebo in each weight quartile and BMI category with the highest rates occurring in the higher weight quartiles Q3 and Q4 and the overweight and obese BMI categories. These data suggest

that lower exposures to belimumab SC as result of higher weight or BMI category did not have an impact on efficacy.

Table 41 – SRI Response at Week 52 by Baseline Body Weight Quartiles and BMI for Study C1115

	Placebo (N=280)	Belimumab (N=556)
Baseline Body Weight Quartiles		
Q1 <55.05 kg Response: n/n Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	38/70 (54%)	89/139 (64%) 9.7% 1.50 (0.84, 2.69) 0.1744
Q2 <55.05 - <65.15 kg Response: n/n Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	32/66 (49%)	79/141 (56%) 7.5% 1.35 (0.75, 2.43) 0.3111
Q3: 65.15 - < 78.25 kg Response: n/n Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	36/73 (49%)	88/135 (65%) 15.9% 1.92 (1.08, 3.440) 0.0269
Q4: ≥ 78.25 kg Response: n/n Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	29/70 (41%)	84/139 (60%) 19.0% 2.16(1.20, 3.87) 0.0099
BMI Categories		
Underweight <18.5 kg/m² Response: n/n Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	11/16 (69%)	25/35 (71%) 2.7% 1.14 (0.31, 4.11) 0.8456
Normal 18.5 - <25 kg/m² Response: n/n Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	62/124 (50%)	152/267 (57%) 6.9% 1.32 (0.86, 2.03) 0.2007
Overweight 25 - <30 kg/m² Response: n/n Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	34/75 (45%)	84/123 (68%) 23.0% 2.6 (1.44, 4.70) 0.0016
Obese ≥ 30 kg/m² Response: Observed Difference vs PLO OR (95% CI) ¹ vs PLO P-value ¹	28/64 (44%)	79/128 (62%) 18% 2.07 (1.13, 3.81) 0.0190

¹Odds Ratio (95% CI) and p-values are from a logistic regression model for the comparison between belimumab SC and placebo without adjustment for any covariates.

Source: Sponsor's Tables 2.82 and 2.83; p. 1181 and 1182.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This application did not contain any analyses in support of belimumab SC's persistence of efficacy and/or tolerance effects.

6.1.10 Additional Efficacy Issues/Analyses

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 Applicant also submitted the results from analyses that employed higher reductions in SLEDNA SLEDAI thresholds (e.g., SELENA SLEDAI ≥ 5 through ≥ 8) for the SRI responder analysis for study C1115 at the Week 52 time point. As shown in Table 42 below, significantly higher response rates were observed for the belimumab SC group compared to placebo for the SRI5 through SRI8 at Week 52. In addition to supporting the robustness of the primary efficacy analysis for this study, these results suggest that a higher magnitude of treatment effect may have occurred in patients who participated in this trial with higher levels of SLE disease activity at baseline

Table 42 – SRI 5-8 Response at Week 52 for Study C1115 (ITT Population)

	Placebo (N=280)	Belimumab (N=556)
SRI5 using SELENA SLEDAI ≥ 5 point reduction, n/n (%)	95/279 (34%)	283/554 (51%)
Observed Difference vs Placebo		17
Odds Ratio (95% CI) vs Placebo		2.04 (1.50, 2.78)
p-value		<0.0001
SRI6 using SELENA SLEDAI ≥ 6 point reduction, n/n (%)	94/279 (34%)	274/554 (50%)
Observed Difference vs Placebo		16
Odds Ratio (95% CI) vs Placebo		1.94 (1.43, 2.65)
p-value		<0.0001
SRI7 using SELENA SLEDAI ≥ 7 point reduction, n/n (%)	53/279 (19%)	178/554 (32%)
Observed Difference vs Placebo		13
Odds Ratio (95% CI) vs Placebo		2.06 (1.43, 2.96)
p-value		0.0001
SRI8 using SELENA SLEDAI ≥ 8 point reduction, n/n (%)	50/279 (18%)	174/554 (31%)
Observed Difference vs Placebo		13
Odds Ratio (95% CI) vs Placebo		2.15 (1.48, 3.11)
p-value		<0.0001

^aA SRI5, SRI6, SRI7 or SRI8 response is defined as ≥ 5 , ≥ 6 , ≥ 7 , or ≥ 8 point reduction from baseline in SELENA SLEDAI score, respectively, and no worsening (increase of <0.3 points from baseline) in 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.

^bOdds Ratio (95% CI) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline complement levels (low C3 and/or C4 vs no low C3 or C4) and race (black vs other)

^cThree ITT subjects did not have a baseline PGA assessment and therefore, do not contribute to SRI/component analyses.

Source: Sponsor's Tables 2.11, 2.12, 2.13, and 2.14; p. 941-956.

This application also contained the results from the EMA modified SRI response rate at Week 52 which involves replacing the “No New BILAG 1A/2B domain score” component of the SRI with “No BILAG 1A/2B domain score.” The results of this modified analysis of the SRI endpoint at Week 52 (Table 43) are consistent with those from the primary endpoint (Table 24).

Table 43 – EMA Modified SRI Response^a at Week 52 for Study C1115 (ITT Population)

	Placebo (N=280)	Belimumab (N=556)
Response^b, n/n (%)	124/279 (44%)	314/554 (57%)
Observed Difference vs Placebo		12
Odds Ratio (95% CI)^c vs Placebo		1.62 (1.20, 2.17)
p-value		0.0014

^aThe EMA response endpoint replaced the “no new BILAG 1A/2B” domain score component with “no BILAG 1A/2B domain score”.

^bThree ITT subjects did not have a baseline PGA assessment and therefore, do not contribute to SRI/component analyses.

^cOdds Ratio (95% CI) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline SELENA SLEDAI score (< 9 vs >10), baseline complement levels (low C3 and/or C4 vs no low C3 or C4) and race (black vs other)

7 Review of Safety

Safety Summary

Review of the belimumab SC's safety database identified concerns in four areas: 1) deaths, 2) serious infections particularly sepsis, 3) depression and suicidality and 4) injection site reactions including hypersensitivity spectrum reactions and anaphylaxis. All of these are labeled events for intravenous belimumab, except for injection site reactions.

Overall, the types of death were consistent with immunosuppressive therapies (e.g., infection) and uncontrolled underlying SLE disease as well as with the risks related to the underlying concomitant medical conditions (e.g., cardiovascular disease) and were consistent with what had been observed during the review of the safety database submitted in support of IV belimumab. Although numerically more deaths occurred during the controlled portion of study C1115, exposure-adjusted mortality rates for both the placebo and belimumab SC treatment groups suggest no apparent difference exists in mortality on cross group comparison. Additionally, the exposure-adjusted mortality rates for both the placebo and belimumab groups in this study were lower than what has been reported in the literature but comparable to the exposure-adjusted mortality rate observed in the pooled safety database review in support of IV belimumab (0.79 deaths/100 subject years) which provides some reassurance to this medical officer that this is not a spurious finding.

A numeric imbalance in both the number of serious infections and cases of sepsis was also observed not in favor of belimumab SC. This is not an unexpected finding since belimumab SC is an immunosuppressive agent. Although the exposure-adjusted incidence of serious infections for study C1115 suggests no difference in the rates for serious infections for the two treatment groups, the exposure –incidence rate for all cases of sepsis was higher for the belimumab SC group compared to placebo. Two out of the three deaths in the belimumab SC group were due to sepsis and both of these subjects had body weights in the lowest weight quartile (e.g., < 55 kg). Given the very small number of events, definitive conclusions could not be drawn about a potential association between an increase in risk for fatal infections (sepsis) and higher exposure to belimumab. Further, a weight-based quartile analysis for serious adverse events including infections did not support such an association and there was no increase in infections or serious infections observed in belimumab SC treated patients with treatment-related reductions in immunoglobulins as compared to placebo patients who participated in this study. As there was an increase in risk for fatal infections (b) (4) associated with this formulation of belimumab, continuation of the Warnings and Precaution statement contained in the USPI for belimumab IV in the labeling for the SC formulation is warranted.

Although the protocol for study C1115 prohibited the enrollment of potential subjects with evidence of serious suicide risk and/or any suicidal ideation on the Columbia Suicide Severity Rating Scale (C-SSRS) and required suicidality assessment at each study visit with this assessment tool as a result of psychiatric safety signals noted on review of the safety database in support of the IV formulation, there were subjects in both treatment groups who experienced depression and suicide/self-injury over the course of the trial. A numeric imbalance was again noted not in favor of the belimumab SC treatment group for depression for which the exposure-adjusted incidence rates suggested no apparent difference exists on cross group comparison. However, there were two cases of suicide/self-injury reported to have occurred in patients treated with belimumab SC and none in the placebo group which supports continuing the current Warning and Precaution statement listed in the USPI for belimumab IV regarding these types of adverse events in the USPI for belimumab SC.

Not unexpectedly, a higher proportion of subjects in the belimumab SC group had injection site reactions as compared to placebo patients. Since many patients who participated in this trial were taking concomitant corticosteroids, this may have resulted in an underestimation of the risk for injection site reactions as well as hypersensitivity spectrum reactions including anaphylaxis to occur with belimumab administered via the subcutaneous route.

No discernable pattern or increase in risk for malignancies associated with belimumab SC exposure was identified once again during this review of the product's safety database. However, the controlled study C1115 was also not specifically designed to determine the risk for developing a malignancy as a result of treatment with belimumab SC. Although no apparent risk for malignancies was identified on review of long-term exposure data from two recently completed open-label extension studies conducted with the IV formulation or by the recently completed FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary for IV belimumab, it would be prudent to continue monitoring safety data from the ongoing phase 3 postmarketing required and commitment studies for IV belimumab for the development of potential safety signals such as malignancies to occur with increasing exposure to the product.

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 SC on these assessments. No safety concerns were identified from the review of the belimumab AI study 200339.

Examination of long-term safety data generated from the ongoing open-label extension of study C1115, the numerous ongoing open-label extensions, and postmarketing required and commitment studies in Asian patients, Black race patients, BLYS activity signature test, pregnancy and adverse event of interest registries being conducted with the IV formulation of belimumab as well as a review of the postmarketing worldwide literature also did not reveal any new safety signals.

Although the protocol for study C1115 mandated that subjects of childbearing potential practice effective forms of contraception for the duration of their study participation, 11 pregnancies occurred in this phase 3 trial. Since SLE typically affects young women of childbearing potential, a pregnancy registry is currently underway that is collecting prospective information for pregnancies and pregnancy outcomes in subjects with SLE exposed to IV belimumab that the Applicant is proposing to amend to collect information regarding pregnancy exposure to the SC formulation.

Limitations associated with the belimumab SC safety database are the same as those identified for IV belimumab and include the lack of concomitant IV cyclophosphamide or other biologics including those that target B cells (e.g., rituximab), the lack of patients with severe renal lupus and central nervous system disease, and the small number of subjects available for subgroup analyses of gender (males) and age (≥ 65 years of age as well as children ≤ 17 years of age) which precludes determination of the product's safety profile in these subgroups.

In view of the consistency in the efficacy and product safety profile as well as the lack of new safety signals identified, the risk/benefit assessment supports approving the fixed dosing regimen of 200 mg of belimumab administered subcutaneously once weekly with the same Warnings and Precaution statements listed in the IV formulation's USPI applied to the labeling for the subcutaneous formulation.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In support of this BLA, the Applicant submitted safety data from a total of six completed SLE studies that evaluated subcutaneous administration of the to-be-marketed 06-D formulation of belimumab: three phase 1 studies (HGS1006-C11105/BEL114448, BEL116119, and BEL117100), two phase 2 trials (BEL112232/HGS1005-C1070 and 200339), and one phase 3 trial (BEL112341/HGS1006-C1115). A tabular summary of these trials can be found in Table 1. Safety data from a fourth phase 1 study (C1058) was not included in this application's safety database as this trial evaluated the 05-D formulation of belimumab via subcutaneous administration for which the Applicant is not seeking marketing approval and the safety data generated from it had been previously reviewed in support of the safety profile of IV belimumab. (Refer to the medical officer review for BLA 125370 dated February 18, 2011 for additional information regarding this trial.) Interim serious adverse event (SAE) data generated from the ongoing open-label extension of BEL112341/HGS1006-C1115 were also provided as of the cut-off data March 8, 2016.

For comparative purposes, the Applicant also provided pooled analyses of safety data from the phase 3 IV belimumab studies (C1056, C1057, LBSL02) as well as of interim long-term safety data with a cut-off date of September 8, 2014 from the open-label extensions of these aforementioned IV formulation studies (BEL112233, BEL112234 and BEL112626, respectively). Additionally, the Applicant included SAE data from BEL112234 and BEL112626 occurring from September 9, 2014 through the cut-off date of March 8, 2016 as well as SAE data collected from 11 ongoing SLE IV belimumab studies (in Asian patients, Black race patients, long-term safety, post-vaccination, treatment holiday, B-cell immunomodulation, BLyS activity signature test, pregnancy and adverse event of interest registries) as of the cut-off date of March 8, 2016 that are only considered where pertinent in the discussion that follows.

Deaths and SAEs occurring through month/day/year through month/day/year from ongoing studies in the SLE clinical development program for the 06-D formulation of belimumab for subcutaneous injection were submitted in the 120-day safety update on month/day/year and are included in pertinent areas of the following discussion.

Safety data from the 6 belimumab SC 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 performed on the double-blind safety population from the 52-week study BEL112341/HGS1006-C1115 and the single and multiple dose phase 1 and 2 studies and ongoing open label extension of BEL112341/HGS1006-C1115 conducted by the Applicant as well as the data contained in the 120-day safety update were examined by this medical officer. (Note: For the purpose of the following discussion, study BEL112341/HGS1006-C1115 will be referred as C1115.)

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 17.1). 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 study C1115 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

The application contained 52-weeks of double-blind, controlled safety data for the subcutaneous administration of the 06-D formulation of belimumab generated from study C1115. This study is the focus of the following safety review since it was the only adequate and well controlled phase 3 study that assessed the to-be-marketed

formulation and dose of 100 mg administered once weekly via subcutaneous injection via prefilled syringe of belimumab in patients with SLE. Assessment of pooled safety data from the remaining five studies to increase the probability of identifying potential safety signals associated with the subcutaneous administration of belimumab would be inappropriate for this application since studies HGS1006-C11105/BEL114448, BEL116119, and BEL117100 were single-dose, open label, phase 1 studies conducted in healthy volunteers while study BEL112232/HGS1005-C1070 was a 24-week, phase 2 study in SLE patients which evaluated a different formulation of belimumab SC administered at different dose intervals than the to-be-marketed formulation. The remaining phase 2 study, 200339, was an 8-week, open label, actual study in SLE evaluating the to-be-marketed autoinjector presentation of belimumab SC. In view of these differences, assessment of pooled data from these studies could potentially result in a mischaracterization of belimumab SC's safety profile.

7.2 Adequacy of Safety Assessments

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

The extent of exposure to belimumab SC in the controlled portion of study C1115 is shown in Table 44. Approximately 322 patients with SLE have been treated with the to-be-marketed dose of 100 mg via subcutaneous injection once weekly for a year. This number satisfies the minimum safety database recommendations for 6-months and 12-months exposure for chronic use products as outlined in the ICH E1A guidance document.

Table 44 – Exposure to Belimuamb SC in Controlled Portion of Study C115 (ITT Population)

	Belimuamb SC 200 mg N=556
Number (%) of Subjects Receiving:	
1-12 injections	28 (5%)
13-24 injections	24 (4%)
25-36 injections	26 (5%)
25-36 injections	26 (5%)
37-51 injections	156 (28%)
>51 injections	322 (58%)
Duration of Exposure¹ (days)	
Mean (SD)	330 (85)
Median (Min, Max)	364 (7, 378)

¹Duration was calculated as last injection date – first injection date + 7
Source: Modified Sponsor's Table 1.29; p. 659.

7.2.2 Explorations for Dose Response

The objective of the product development program for the subcutaneous formulation of belimumab was to develop a liquid formulation for fixed dose administration via PFS or AI that approximated the approved marketed dose-by-weight 10 mg/kg intravenous formulation of the drug. In view of this, the Applicant did not conduct any dose response explorations other than evaluating doses of 200 mg, 240 mg and 2x120 mg of the 06-D formulation of belimumab SC in the bioavailability study HGS-C1105/BEL114448 in order to establish dose proportionality with the IV formulation. Since belimumab SC will be administered via a fixed dose regimen, the Applicant included weight quartiles and BMI category based analyses of efficacy and safety of the product. (Refer to the above Section 6.1.8 and Section 7.5.1 below for additional information regarding the results of these analyses.) Exposure variations for 200 mg SC weekly dosing were not clinically relevant since they did not impact the efficacy or safety response in SLE patients, thus lending support to the fixed dose regimen for belimumab SC.

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 Study C1115 in support of belimumab SC's safety profile:

- Symptom driven physical exam and weight
- Vital signs: systolic and diastolic blood pressure, respiratory rate and temperature
- 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, extractable nuclear antigens [ENAs], aCl, lupus anticoagulant, and beta-2-glycoprotein-1), and serum complement (C3 and C4)
- BLyS protein and immunogenicity
- FACS of peripheral lymphocytes (B cells: CD20+, CD20+/27-naïve, CD20+/27+ memory, CD20+/69+ activated, CD20+/138+ plasmacytoid, CD19+/27bright/38bright SLE subset, CD19+/CD24 high/CD38 high regulatory B

cell and CD20-/138+ plasma cells) (in countries/regions where assessment of B cells was feasible)

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 this trial.

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

The intravenous formulation of belimumab is the only member of the B lymphocyte stimulator (BLyS) antagonist pharmacologic class that is currently marketed. The safety profile of the IV formulation has been well documented and includes an increased risk for mortality, serious infections, depression and suicidality as well as hypersensitivity reactions including anaphylaxis. As a result of its B-cell modulating effects, decreases in lymphocytes and immunoglobulins may also occur with its administration. Rare postmarketing cases of progressive multifocal leukoencephalopathy (PML) have been reported since its marketing approval in 2011.

In support of belimumab SC's safety profile, the Applicant also submitted analyses of adverse events of interest that included deaths, infections including opportunistic infections, depression/suicidality/self-injury, malignancy and post-injection systemic reactions in support of belimumab SC's safety profile. The results of these analyses are discussed in sections 7.3.1, 7.5.3 and 7.6.1 of the following safety review.

7.3 Major Safety Results

All safety analyses were performed on the population who received at least one dose of study medication (the Intention-To-Treat [ITT] population). Table 45 summarizes adverse events (AEs) that were reported in the safety database for the 52-weeks of the controlled study C1115 by treatment group. The majority of patients experienced at least one AE while participating in this trial. The proportion of patients who experienced a serious adverse event (SAE) was higher in the placebo group compared to belimumab SC. The proportions of patients who experienced an infection, serious infection, or at least 1 AE leading to discontinuation of study treatment was similar between the two treatment groups. Overall, the number of malignancies and deaths were both low in both treatment groups. However, closer examination reveals numerical imbalances exist for all of these categories not in favor of belimumab SC. These imbalances may exist as a result of the uneven randomization utilized by the study's

protocol. An indepth examination of these imbalances between the treatment groups starting with deaths follows below.

Table 45 – Summary of Adverse Events and Deaths in the Controlled Study C1115

	Placebo (N=280)	Belimumab SC (N=556)
Number of Subjects with at Least 1 AE	236 (84%)	449 (81%)
Number of Subjects with At Least 1 Serious AE	44 (16%)	60 (11%)
Number of Subjects with at Least 1 Infection	159 (57%)	308 (55%)
Number of Subjects with at Least 1 Serious Infection	15 (5%)	23 (4%)
Number of Subjects with at Least 1 Malignancy	1 (0.4%)	2 (0.4%)
Number of Subjects with at Least 1 AE Leading to Discontinuation	25 (9%)	40 (7%)
Deaths	2 (0.7%)	3 (0.5%) ¹

Subject (b) (6) died 143 days after she had received her last injection of study medication after withdrawing from the study on Day 28 due to an AE of localized erythema at the injection site.

Source: Sponsor's Tables 3.2, 3.3 and 3.6

7.3.1 Deaths

As of the 120-day safety cut-off January 18, 2017, there were a total of 8 deaths that occurred over the course of the ongoing study C1115. Of these 8 deaths which are summarized in Table 45, two deaths (Subjects (b) (6)) occurred in the placebo group and 4 deaths (b) (6) occurred in the belimumab SC group during the 52-week controlled portion of this trial. (Note: The death of Subject (b) (6) which occurred 143 days after she received her last injection of study medication after she withdrew from the study on Day 28 due to an adverse event of localized erythema at the injection site should not be attributed to belimumab SC. It is only included for completeness and will not be discussed further in this review.) The remaining 2 deaths occurred during the uncontrolled portion of study C1115 and involved 1 patient (Subject (b) (6)) initially randomized to placebo and 1 patient (Subject (b) (6)) initially randomized to belimumab SC during the controlled portion of the trial.

Table 46 – Summary of Deaths in the Controlled and Open Label Extension of Study C1115

Subject Number	Age/Sex	Cause of Death	Days Since 1 st Injection	Days Since Last Injection	Pertinent History
Placebo					
(b) (6)	38yo/F	Cardiac Arrest	159	18	H/O SLE and HTN. Concomitant meds: desogestrel, steroids, ASA, enalapril, atenolol, diazepam and escitalopram. Pt. presented to hospital in asystole 11 days S/P vaginal hysterectomy, with vaginal vault fixation, colpoperineoplasty and blood transfusion. She was resuscitated and intubated. Following a complicated hospital course during which she was RX'd with valproic acid, furosemide, enalapril, insulin, propranolol, steroids, clonidine, ivermectin, tramadol, enoxaparin, polymixin B, vancomycin, clonazepam, midazolam, meropenem, nitroglycerin, phenytoin, fentanyl, piperacillin/tazobactam and ranitidine, she suffered a cardiac arrest and died on Day 18 of her hospitalization. Autopsy was not performed but death certificate stated the pt. had septicemia, pneumonia, SLE, acute pulmonary edema, and cardiopulmonary arrest.
(b) (6)	21yo/F	SLE- Related Thrombocytopenia	175	6	H/O SLE and thrombocytopenia. Concomitant meds: steroids and hydroxychloroquine. Presented with metromenorrhagia and thrombocytopenia. RX'd with pulse steroids and ↑oral steroids, iron and folate with resolution of bleeding and ↑platelets. Oral steroids were tapered but she developed hematoma with petechia on lower extremity associated with ↓platelet count and ↓hemoglobin. Despite ↑ oral steroids, she was hospitalized with severe thrombocytopenia and mental status changes and subsequently died later that day due to severe thrombocytopenia.

H/O= history of; SLE= systemic lupus erythematosus; HTN= hypertension; ASA= aspirin; pt.=patient; S/P =status post; RX'd= treated; IVF= intravenous fluids; TIA= transient ischemic attack; CT=computed tomography; CSF= cerebral spinal fluid; UGI=upper gastrointestinal; RBCs= red blood cells; UTI= urinary tract infection; abd.= abdominal; ARF= acute renal failure; bilat. = bilateral; LE= lower extremity; PMD= private medical doctor; SOB=shortness of breath

Table 46 – Summary of Deaths in the Controlled and Open-Label of Extension of Study C1115 (cont.)

Subject Number	Age/Sex	Cause of Death	Days Since 1 st Injection	Days Since Last Injection	Pertinent History
Belimumab SC					
(b) (6)	54yo/F	Tuberculosis of Central Nervous System	176	7	H/O SLE, depression and anxiety. Concomitant meds: azathioprine, prednisone, fluoxetine, clonazepam, calcium carbonate, Vitamin D, and omeprazole. Pt. was hospitalized and intubated after presenting with fever, prostration, decreased consciousness, left hemiparesis with left ptosis and meningeal signs. Hypodense lesion in left parietal lobe noted on brain CT suggestive of brain abscess with signs of intracranial hypertension. CSF was positive for acid-alcohol resistant bacillus (BAAR), ↑protein and ↓glucose but culture was negative for any additional unusual bacteria. Despite RX with ampicillin, metronidazole, heparin, ceftriaxone, ganciclovir, mannitol, fentanyl, dexamethasone, midazolam, bromopride, dipyrone, rifampicin, isoniazid, ethambutol, and pyrazinamide the pt. died on Day 21 of her hospitalization due to tuberculosis abscess of brain.
(b) (6)	52yo/F	Urosepsis	142	15	Concomitant meds: Celecoxib and steroids. Pt. developed anorexia with low grade fever and hypotension due to acute pyelonephritis with sepsis and acute renal failure. She was hospitalized and RX'd with steroids, paracetamol, metoclopramide, piperacillin/tazobactam, dopamine, sodium bicarbonate and IVF. Pt. went on to develop hospital acquired pneumonia requiring intubation and subsequently become comatose. In addition to broad spectrum antibiotics, she was RX'd with fluconazole and meropenem but develop generalized seizures RX'd with diazepam and phenytoin. She developed disseminated intravascular coagulation S/P UGI bleed with thrombocytopenia. Despite resuscitation, the pt. died on Day 9 of hospitalization due to cardiopulmonary arrest.

Table 46 – Summary of Deaths in the Controlled and Open Label of Extension of Study C1115 (cont.)

Subject Number	Age/Sex	Cause of Death	Days Since 1 st Injection	Days Since Last Injection	Pertinent History
Belimumab SC					
(b) (6)	28yo/F	Bacterial Sepsis	375	38	H/O SLE and iron deficiency anemia. Concomitant meds: Steroids, fentanyl, doxazosin, amlodipine, lorazepam, iron, calcium citrate, Brown mixture, and amboxol. Developed sudden onset right sided weakness and slurred speech C/W TIA. Brain CT unremarkable for hemorrhage or hematoma. Neurological findings resolved S/P RX with dipyridamole, RBCs and plateletpheresis. Developed UTI with bacteremia due to E.coli which progressed to septic shock and respiratory failure necessitating intubation. She went on to develop oliguria with ARF and was placed on hemodialysis. Following successful weaning off of ventilator, she developed a pulmonary hemorrhage with thrombocytopenia, was re-intubated and received plasma exchange therapy. Pulmonary hemorrhage resolved but her acute renal failure persisted necessitating hemodialysis. Pt. developed P. aeruginosa pneumonia that progressed to septic shock with hypotension. Despite antibiotics, pressors and aggressive medical supportive care, the pt. died due to septic pneumonia.
(b) (6)	40yo/F	Septic shock	150	143	H/O SLE, Sjogren's syndrome, hypothyroidism and diverticulosis. Concomitant meds: none listed. On Day 28 withdrew from study due to injection site erythema S/P first injection of study medication. Presented to hospital on Day 125 S/P last injection of study meds with hemorrhagic shock 2° to bleeding esophageal varices from liver cirrhosis. Hospital course complicated by C. difficile colitis, acute abd. due to paralytic ileus and peritonitis, bilat. pneumonia with respiratory insufficiency requiring intubation and mechanical ventilation, and ARF requiring intermittent dialysis. Despite broad spectrum antibiotics, she developed sepsis and subsequently died due to septic shock with multi-organ failure on Day 143 S/P last study med injection.

Table 46 – Summary of Deaths in the Controlled and Open Label of Extension of Study C1115 (cont.)

Subject Number	Age/Sex	Cause of Death	Days Since 1 st Injection	Days Since Last Injection	Pertinent History
OLE Belimumab SC					
(b) (6)	39yo/M	Metabolic Acidosis with Multiorgan Failure Secondary to Antiphospholipid Syndrome	31	30	H/O SLE, herpes zoster, peripheral venous insufficiency, viral pharyngitis and erectile dysfunction. Concomitant meds: indomethacin, folate, steroids, celecoxib, sildenafil, diosmin, and ASA. Pt. presented to ER with sudden edema of LE, numbness, blistering eruption, pain, fever and ecchymoses. He subsequently developed ARF, metabolic acidosis, with multiorgan failure. Doppler confirmed femoropopliteal pelvic limb thrombosis due to antiphospholipid syndrome. Pt. was intubated, and RX'd with dopamine, enoxaparin, bicarbonate, steroids, cyclophosphamide, ketorolac, omeprazole, and IVF but went into shock and could not be resuscitated following cardiac arrest and died later that day.
(b) (6)	36yo/F	Acute Respiratory Failure Secondary to Pneumonia	395	2	H/O SLE and community acquired pneumonia. Concomitant meds: tacrolimus and enalapril. Pt. was RX'd by PMD for community acquired pneumonia with levofloxacin and montelukast after C/O product cough without SOB or fever. Subsequently developed difficulty breathing and was hospitalized with thrombocytopenia (platelet count 33,000) that continued to worsen with ↑dyspnea. Despite broad spectrum antibiotics and steroids she went into acute respiratory failure was intubated but could not be resuscitated following cardiac arrest.

H/O= history of; SLE= systemic lupus erythematosus; HTN= hypertension; ASA= aspirin; pt.=patient; S/P =status post; RX'd= treated; IVF= intravenous fluids; TIA= transient ischemic attack; CT=computed tomography; CSF= cerebral spinal fluid; UGI=upper gastrointestinal; RBCs= red blood cells; UTI= urinary tract infection; abd.= abdominal; ARF= acute renal failure; bilat. = bilateral; LE= lower extremity; PMD= private medical doctor; SOB=shortness of breath

Five of these subjects died as a result of infectious etiologies, 1 subject died due to a cardiovascular event, and 2 subjects died as a result of SLE-related complications. Overall, the types of death listed in the preceding table are consistent with the risks related to the underlying and concomitant medical conditions as well as the use of immunosuppressive therapies. As noted in the preceding Table 45, there is a numeric

imbalance against belimumab in deaths that occurred during the double-blind portion of study C1115. However, as shown in Table 47, the exposure –adjusted incidence rates for mortality in both treatment groups are low and comparable with a rate ratio <1 on comparison suggesting no difference in mortality rates between the two treatment groups. Additionally, both of these exposure-adjusted mortality rates are lower than what has been reported in the literature for SLE patients (1.63 deaths/100 subject-years) by Bernatsky et al⁴, and the mortality rate of 0.6 deaths/100 subject-years observed in the belimumab SC group is similar to that observed for the pooled safety database reviewed in support of IV belimumab (0.79 deaths/100 subject-years). (Note: Reader is referred to clinical review of BLA 125370 for belimumab IV for additional information.)

Table 47 – Exposure-Adjusted Incidence of Death During the Double-Blind Portion of Study C1115

	Placebo (Subject-Years=249)	Belimumab SC N=556 (Subject-Years=512)	Rate Ratio (95% Confidence Ratio)^a
Number of Deaths	2	3	
Death Rate/100 Subject Years	0.8	0.6	0.73 (0.12, 4.36)

^aRatio of belimumab versus placebo. A value greater than 1 indicates a higher event rate for belimumab. Confidence intervals are from a Poisson regression.

7.3.2 Nonfatal Serious Adverse Events

Table 48 is an abridged summary of the serious adverse events (SAEs) observed during the controlled portion of study C1115 by MedDRA system organ class (SOC) and preferred terms (PT). A higher proportion of patients experienced treatment-emergent serious adverse events in the placebo group than in the belimumab group. The overall adjusted-exposure incidence rate for serious adverse events was also higher for the placebo group (29.8 SAEs/100 subject-years) as compared to the belimumab SC group (21.1 SAEs/100 subject-years). However, the corresponding rate ratio and 95% CI for the comparison between the two treatment groups was 0.71(0.53, 0.95) suggesting no difference between the two treatment groups. Six SOC's contributed to the higher overall rates of SAEs in the placebo group: infections and infestations, renal and urinary disorders, nervous system disorders, blood and lymphatics system disorders, reproductive and breast disorders and investigations. Review of the data in Table 48 did not reveal any potential patterns or safety signals due to the small numbers of SAEs observed during the controlled portion of this study. Serious infections and infestations will be discussed further with adverse events of special interest (AESIs). No other safety signals were identified on review of the data collected from the ongoing open-label

⁴ Bernatsky S, Boivin JF, Joseph L, et al. Mortality in Systemic Lupus Erythematosus. Arth Rheu 2006;54(8):2550-7.

extension of study C1115 contained in the 120-safety follow-up, or in the phase 1 or 2 studies conducted in support of SC formulation program.

Table 48 – Serious Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC)/Preferred Term (PT) During the Controlled Portion of C1115 (ITT Population)

MedDRA System Organ Class (SOC)/Preferred Term (PT)	Placebo N=280	Belimumab SC N=556
Any Treatment Emergent Serious Adverse Event	74 (16%)	60 (11%)
Exposure-Adjusted Incidence Rate for Any SAE per 100 Subject-Years	29.8	21.1
Infections and Infestations	15 (5%)	23 (4%)
Cellulitis	2 (0.7%)	3 (0.5%)
Pneumonia	1 (0.4%)	4 (0.7%)
Pneumonia bacterial	2 (0.7%)	3 (0.5%)
Urosepsis	0	3 (0.5%)
Urinary Tract Infections	1 (0.4%)	3 (0.5%)
Renal and Urinary Disorders	7 (3%)	8 (1%)
Renal Failure Acute	0	4 (0.7%)
Lupus Nephritis	1 (0.4%)	2 (0.4%)
Nephritis	1 (0.4%)	2 (0.4%)
Renal Tubular Necrosis	0	1 (0.2%)
Nervous System Disorders	6 (2%)	8 (1%)
Cerebrovascular Event	1 (0.4%)	2 (0.4%)
Neuropsychiatric Lupus	0	2 (0.4%)
Syncope	1 (0.4%)	1 (0.2%)
Generalized Tonic-Clonic Seizure	0	1 (0.2%)
Intracranial Venous Sinus Thrombosis	0	1 (0.2%)
Transient Ischemic Attack	0	1 (0.2%)
Gastrointestinal Disorders	3 (1%)	8 (1%)
Abdominal Pain	1 (0.4%)	1 (0.2%)
Small Intestinal Obstruction	0	2 (0.4%)
Abdominal Hernia	0	1 (0.2%)
Diarrhea	0	1 (0.2%)
Hemorrhoids Thrombosed	0	1 (0.2%)
Mouth Ulceration	0	1 (0.2%)
Pancreatitis Chronic	0	1 (0.2%)
Musculoskeletal and Connective Tissue Disorders	3 (1%)	6 (1%)
SLE Arthritis	1 (0.4%)	1 (0.2%)
Arthralgia	0	1 (0.2%)
Osteoarthritis	0	1 (0.2%)
Pain in Extremity	0	1 (0.2%)
Polyarthritis	0	1 (0.2%)
Synovitis	0	1 (0.2%)

Subjects are only counted once per SOC/PT.
Source: Sponsor's Table 3.7; p. 1530-1537.

Table 48 (cont.) – Serious Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC)/Preferred Term (PT) During the Controlled Portion of C1115 (ITT Population)

MedDRA System Organ Class (SOC)/Preferred Term (PT)	Placebo N=280	Belimumab SC N=556
Any Treatment Emergent Serious Adverse Event	74 (16%)	60 (11%)
Exposure-Adjusted Incidence Rate for Any SAE per 100 Subject-Years	29.8	21.1
Blood and Lymphatic System Disorders	5 (2%)	3 (1%)
Anemia	1 (0.4%)	1 (0.2%)
Disseminated Intravascular Coagulation	0	1 (0.2%)
Hypochromic Anemia	0	1 (0.2%)
General Disorders and Administration Site Conditions	1 (0%)	7 (1%)
Non-Cardiac Chest Pain	1 (0.4%)	2 (0.4%)
Pyrexia	0	3 (0.5%)
Peripheral Swelling	0	1 (0.2%)
Systemic Inflammatory Response Syndrome	0	1 (0.2%)
Cardiac Disorders	3 (1%)	4 (1%)
Myocardial Infarction	0	2 (0.4%)
Cardiac Failure Congestive	0	1 (0.2%)
Pericarditis	0	1 (0.2%)
Respiratory, Thoracic and Mediastinal Disorders	2 (1%)	5 (1%)
Pleurisy	1 (0%)	1 (0.2%)
Acute Respiratory Failure	0	1 (0.2%)
Alveolitis	0	1 (0.2%)
Pulmonary Arterial Hypertension	0	1 (0.2%)
Pulmonary Hemorrhage	0	1 (0.2%)
Vascular Disorders	3 (1%)	4 (1%)
Deep Venous Thrombosis	1 (0.4%)	1 (0.2%)
Hypertension	0	1 (0.2%)
Orthostatic Hypotension	0	1 (0.2%)
Thrombosis	0	1 (0.2%)
Skin and Subcutaneous Tissue Disorders	2 (1%)	4 (1%)
Systemic Lupus Erythematosus Rash	1 (0.4%)	2 (0.4%)
Angioedema	0	1 (0.2%)
Skin Ulcer	0	1 (0.2%)
Urticaria	0	1 (0.2%)
Neoplasms Benign, Malignant, and Unspecified (incl. Cysts and Polyps)	2 (1%)	3 (1%)
Breast Cancer	1 (0.4%)	0
Endometrial Cancer	0	1 (0.2%)
Intraductal Proliferative Breast Lesion	0	1 (0.2%)
Thyroid Neoplasm	0	1 (0.2%)
Reproductive System and Breast Disorders	3 (1.1%)	2 (0.4%)
Ovarian Cyst	0	1 (0.2%)
Vaginal Hemorrhage	0	1 (0.2%)
Investigations	3 (1.1%)	1 (0.2%)
Troponin Increased	0	1 (0.2%)

Subjects are only counted once per SOC/PT.
Source: Sponsor's Table 3.7; p. 1530-1537.

Table 48 (cont.) – Serious Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC)/Preferred Term (PT) During the Controlled Portion of C1115 (ITT Population)

MedDRA System Organ Class (SOC)/Preferred Term (PT)	Placebo N=280	Belimumab SC N=556
Any Treatment Emergent Serious Adverse Event	74 (16%)	60 (11%)
Exposure-Adjusted Incidence Rate for Any SAE per 100 Subject-Years	29.8	21.1
Eye Disorders	1 (0.4%)	1 (0.2%)
Exfoliative Syndrome	1 (0.4%)	1 (0.2%)
Metabolism and Nutrition Disorders	0	2 (0.4%)
Electrolyte Imbalance	0	1 (0.2%)
Hypernatremia	0	1 (0.2%)
Pregnancy, Puerperium and Perinatal Conditions	0	2 (0.4%)
Abortion Spontaneous	0	2 (0.4%)
Ear and Labyrinth Disorders	1 (0.4%)	0
Hepatobiliary Disorders	1 (0.4%)	0
Immune System Disorders	0	1 (0.2%)
Drug Hypersensitivity	0	1 (0.2%)
Injury, Poisoning and Procedural Complications	1 (0.4%)	0
Psychiatric Disorders	0	1 (0.2%)
Suicidal Ideation	0	1 (0.2%)

Subjects are only counted once per SOC/PT.
Source: Sponsor's Table 3.7; p. 1530-1537.

7.3.3 Dropouts and/or Discontinuations

Table 49 is an abridged summary of adverse events by SOC and preferred term that resulted in patients discontinuing treatment during the controlled portion of study C1115. A higher proportion of subjects discontinued treatment with placebo as compared to belimumab SC. The exposure adjusted incidence rate for any discontinuation in the belimumab SC group was 8.4 events per 100-subject-years compared to 10.9 events for the placebo group with the rate ratio for the comparison <1 (0.77; 95% CI [0.48, 1.25]) which again suggests no apparent difference between the two treatment groups for premature discontinuations from the study. Examination of the data in this table reveals that Renal and Urinary disorders, Infections and infestations, and Blood and Lymphatic System were the most common types of AEs resulting in patients withdrawing prematurely from this trial. The higher rate of discontinuations from study treatment seen in the Renal and Urinary Disorders was due to a higher rate of renal involvement in the placebo group. Similarly, the higher rate of discontinuation in the Blood and Lymphatics System was due to underlying SLE disease manifestations. Withdrawals due to infection are an expected finding in clinical trials evaluating immunosuppressive therapies. However, the imbalance observed in the placebo group may be related to continuation of corticosteroid therapy as a result of inability to taper due to underlying disease activity.

Table 49 – Treatment Emergent Adverse Events (TEAE) Leading to Discontinuation of Randomized Study Medication by MedDRA System Organ Class/ Preferred Term During the Controlled Portion of Study C1115 (ITT Population)

MedDRA System Organ Class (SOC)/Preferred Term (PT)	Placebo N=280	Belimumab SC N=556
Any Treatment Emergent AE Leading to Discontinuation	25 (8.9%)	40 (7.2%)
Exposure-Adjusted Incidence Rate for Any Discontinuation per 100 Subject-Years	10.9	8.4
Renal and Urinary Disorders	6 (2.1%)	8 (1.4%)
Lupus Nephritis	2 (0.7%)	4 (0.7%)
Nephritis	0	2 (0.4%)
Nephrotic Syndrome	2 (0.7%)	0
Proteinuria	2 (0.7%)	0
Renal Failure Acute	0	1 (0.2%)
Renal Tubular Necrosis	0	1 (0.2%)
Infections and Infestations	7 (2.5%)	4 (0.7%)
Pulmonary Tuberculosis	2 (0.7%)	1 (0.2%)
Corynebacterium Sepsis	1 (0.45)	0
Groin Abscess	0	1 (0.2%)
Meningitis Bacterial	1 (0.45)	0
Osteomyelitis Bacterial	1 (0.4%)	0
Pneumonia	1 (0.4%)	0
Pyelonephritis	1 (0.4%)	0
Tuberculosis of CNS	0	1 (0.2%)
Urosepsis	0	1 (0.2%)
Blood and Lymphatic System Disorders	4 (1.4%)	3 (0.5%)
Thrombocytopenia	3 (1.1%)	0
Hemolytic Anemia	0	1 (0.2%)
Iron Deficiency Anemia	1 (0.4%)	0
Leukopenia	0	1 (0.2%)
Neutropenia	0	1 (0.2%)
Skin and Subcutaneous Tissue Disorders	2 (0.7%)	5 (0.9%)
Systemic Lupus Erythematosus Rash	1 (0.4%)	1 (0.2%)
Butterfly Rash	0	1 (0.2%)
Drug Eruption	1 (0.4%)	0
Pruritus Allergic	0	1 (0.2%)
Rash	0	1 (0.2%)
Swelling Face	0	1 (0.2%)
Urticaria	0	1 (0.2%)
Investigations	1 (0.4%)	4 (0.7%)
Renal Function Test Abnormal	1 (0.4%)	1 (0.2%)
Alanine Aminotransferase Increased	0	1 (0.2%)
Gamma-Glutamyltransferase Increased	0	1 (0.2%)
Urine Protein/Creatinine Ratio Increased	0	1 (0.2%)
Gastrointestinal Disorders	2 (0.7%)	2 (0.4%)
Nausea	1 (0.4%)	1 (0.2%)
Dysphagia	1 (0.4%)	0
Lip Swelling	0	1 (0.2%)
Vomiting	1 (0.4%)	0

Subjects are only counted once per SOC/PT.
Source: Sponsor's Table 3.16; p. 1579-1583.

Table 49 (cont.) – Treatment Emergent Adverse Events (TEAEs) leading to Discontinuation of Randomized Study medication by MedDRA System Organ Class Preferred Term During the Controlled Portion of Study C1115 (ITT Population)

MedDRA System Organ Class (SOC)/Preferred Term (PT)	Placebo N=280	Belimumab SC N=556
Any Treatment Emergent AE Leading to Discontinuation Exposure-Adjusted Incidence Rate for Any Discontinuation per 100 Subject-Years	25 (8.9%) 10.9	40 (7.2%) 8.4
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)	1 (0.4%)	3 (0.5%)
Breast Cancer	1 (0.4%)	0
Endometrial Cancer	0	1 (0.2%)
Intraductal Proliferative Breast Lesion	0	1 (0.2%)
Myelodysplastic Syndrome	0	1 (0.2%)
General Disorders and Administration Site Conditions	0	3 (0.5%)
Injection Site Erythema	0	1 (0.2%)
Injection Site Induration	0	1 (0.2%)
Systemic Inflammatory Response Syndrome	0	1 (0.2%)
Nervous System Disorders	2 (0.7%)	1 (0.2%)
Cerebrovascular Accident	0	1 (0.2%)
Migraine	1 (0.4%)	0
Peripheral Motor Neuropathy	1 (0.4%)	0
Psychiatric Disorders	0	3 (0.5%)
Acute Psychosis	0	1 (0.2%)
Depression	0	1 (0.2%)
Suicidal Ideation	0	1 (0.2%)
Cardiac Disorders	1 (0.4%)	1 (0.2%)
Cardiac Arrest	1 (0.4%)	0
Myocardial Infarction	0	1 (0.2%)
Hepatobiliary Disorders	0	1 (0.2%)
Hepatotoxicity	0	1 (0.2%)
Immune System Disorders	0	1 (0.2%)
Anaphylactic Reaction	0	1 (0.2%)
Musculoskeletal and Connective Tissue Disorders	0	1 (0.2%)
SLE Arthritis	0	1 (0.2%)
Pregnancy, Puerperium and Perinatal Conditions	0	1 (0.2%)
Abortion Spontaneous	0	1 (0.2%)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (0.2%)
Pleuritic Pain	0	1 (0.2%)

Subjects are only counted once per SOC/PT.
Source: Sponsor's Table 3.16; p. 1579-1583.

7.3.4 Significant Adverse Events

Table 50 is a tabular listing of adverse events observed during the double-blind portion of study C1115 by treatment group that were rated as severe in nature by study investigators. A higher proportion of subjects in the placebo group experienced severe treatment emergent adverse events compared to the belimumab SC group. The most

common severe treatment emergent adverse events in this study were: lupus nephritis, leukopenia, proteinuria, SLE rash, and urine protein/creatinine ratio increased which are all manifestations of underlying SLE disease activity. No safety signals were identified on review of severity data from the other phase 1 and 2 studies included in the belimumab SC safety database.

Table 50 – Summary of Number (%) of Subjects with Severe Treatment Emergent Adverse Event Reactions Reported by ≥ 2 Subjects During the Controlled Portion of Study C1115 (ITT Population)

MedDRA Preferred Term (PT)	Placebo N=280	Belimumab SC N=556
All Severe TEAEs	40 (14%)	55 (10%)
Lupus Nephritis	3 (1.1%)	6 (1.1%)
Leukopenia	0	4 (0.7%)
Proteinuria	3 (1.1%)	1 (0.2%)
Systemic Lupus Erythematosus Rash	3 (1.1%)	1 (0.2%)
Urine Protein/Creatinine Ratio Increased	2 (0.7%)	2 (0.4%)
Headache	1 (0.4%)	2 (0.4%)
Nephritis	1 (0.4%)	2 (0.4%)
Neutropenia	1 (0.4%)	2 (0.4%)
Thrombocytopenia	3 (1.1%)	0
Urosepsis	0	3 (0.5%)
Arthralgia	0	2 (0.4%)
Bacterial Sepsis	0	2 (0.4%)
Cellulitis	0	2 (0.4%)
Gamma-Glutamyltransferase Increased	2 (0.7%)	0
Hypoalbuminemia	2 (0.7%)	0
Lupus Vasculitis	2 (0.7%)	0
Myocardial Infarction	0	2 (0.4%)
Nephrotic Syndrome	2 (0.7%)	0
Pyrexia	0	2 (0.4%)
Renal Failure Acute	0	2 (0.4%)
Urticaria	0	2 (0.4%)
Vomiting	2 (0.7%)	0

Subjects are only counted once per PT.
Source: Sponsor's Table 3.11; p. 1551-1555.

7.3.5 Submission Specific Primary Safety Concerns

a. Infections

Because of its mechanism of action, belimumab would also be anticipated to increase the risk of infections, including serious infections which were prespecified as adverse events of interest. Although serious infections were the most common SOC reported, the exposure adjusted incidence of serious infections was comparable for the belimumab SC group compared to placebo (6.1 versus 6.8 per 100 subject-years,

respectively, with a rate ratio: 0.89; 95% CI [0.49, 1.60]) (Table 51). The types of infections listed in Table 51 are similar to those observed in the safety database reviewed in support of IV belimumab and are not unexpected given that study C1115 was an international study.

Table 51 – Serious Infections by Preferred Term During the Controlled Portion of Study C1115

Serious Infections and Infestations/ Preferred Term	Placebo N=280	Belimumab SC N=556
Any Serious Infection	15 (5.4%)	23 (4.1%)
Exposure-Adjusted Incidence Rate per 100 Subject-Years	6.8	6.1
Cellulitis	2 (0.7%)	3 (0.5%)
Pneumonia	1 (0.4%)	4 (0.7%)
Pneumonia Bacterial	2 (0.7%)	3 (0.5%)
Urosepsis	0	3 (0.5%)
Urinary Tract Infection	1 (0.4%)	3 (0.5%)
Bacterial Sepsis	0	2 (0.4%)
Amoebic Dysentery	0	1 (0.2%)
Bronchitis	1 (0.4%)	0
Corynebacterium Sepsis	1 (0.4%)	0
Dengue Fever	0	1 (0.2%)
Diarrhea Infectious	0	1 (0.2%)
External Ear Cellulitis	1 (0.4%)	0
Gastroenteritis Viral	0	1 (0.2%)
Herpes Virus Infection	0	1 (0.2%)
Herpes Zoster	0	1 (0.2%)
Meningitis Bacterial	1 (0.4%)	0
Oral Candidiasis	0	1 (0.2%)
Osteomyelitis Bacterial	1 (0.4%)	0
Perirectal Abscess	1 (0.4%)	0
Pulmonary Tuberculosis	1 (0.4%)	0
Pyelonephritis	1 (0.4%)	1 (0.2%)
Respiratory Syncytial Virus Bronchitis	0	1 (0.2%)
Salmonellosis	0	1 (0.2%)
Septic Shock	1 (0.4%)	0
Subcutaneous Abscess	1 (0.4%)	0
Tuberculosis of CNS	0	1 (0.2%)
Viral Upper Respiratory Tract Infection	0	1 (0.2%)

Subjects are only counted once per PT.

Source: Modified Sponsor's Table 3.7; p. 1530-1531.

Table 52 shows higher incidence rates for active tuberculosis and herpes zoster were associated with the placebo treatment group while the rate of sepsis was comparable between the two treatment groups. Of note, the safety database submitted in support of

the IV formulation of belimumab also contained cases of tuberculosis, disseminated herpes zoster and sepsis.

Table 52 – Infections of Special Interest During the Controlled Portion of Study C1115

Infections of Special Interest	Placebo N=280	Belimumab SC N=556
All Infections of Special interest	21 (7.5%)	30 (5.4%)
All Opportunistic Infections by GSK Adjudication	1 (0.4%)	2 (0.4%)
Opportunistic Infections per GSK Adjudication Excluding Tuberculosis and Herpes Zoster	1 (0.4%)	0
Active Tuberculosis	2 (0.7%)	2 (0.4%)
Non-Opportunistic	2 (0.7%)	1 (0.2%)
Opportunistic	0	1 (0.2%)
All Herpes Zoster	13 (4.6%)	18 (3.2%)
Non-Opportunistic	13 (4.6%)	17 (3.1%)
Opportunistic	0	1 (0.2%)
Recurrent	0	0
Disseminated	0	1 (0.2%)
Sepsis	3 (1.1%)	6 (1.1%)
Serious	2 (0.7%)	4 (0.7%)

Source: Modified Sponsor's Table 3.28 and 3.33; p. 1747 and 1757

The exposure adjusted incidence for all cases of active tuberculosis, pneumonia, sepsis, and herpes zoster are listed in Table 53. The event rate for sepsis was the only one not in favor of belimumab SC.

Table 53 – Exposure-Adjusted Incidence Rates per 100 Subject-Years with Rate Ratios and 95% Confidence Intervals for Cases of Active Tuberculosis, Pneumonia, Sepsis and Herpes Zoster in the Double-Blind Portion of Study C1115 (ITT Population)

	Placebo (Subject-Years=249) Events (Rate)	Belimumab SC (Subject-Years=512) Events (Rate)	Rate Ratio (95% Confidence Interval)
Active Tuberculosis (Any Event)	2 (0.8%)	2 (0.4%)	0.49 (0.07, 3.45)
Pneumonia (Any Event)^a	7 (2.8%)	11 (2.2%)	0.76 (0.30, 1.97)
Sepsis (Any Event)^b	3 (1.2%)	7 (1.4%)	1.13 (0.29, 4.38)
Herpes Zoster (Any Event)	13 (5.2%)	19 (3.7%)	0.71 (0.35, 1.44)

^aPer the BEL 112341 RAP, the custom MedDRA query for pneumonia included 72 pre-specified preferred terms including pneumonia and pneumonia bacterial. The individual subject preferred terms reported in this study were as follows: Placebo: pneumonia (1), pneumonia bacterial (4), pulmonary tuberculosis (2); Belimumab SC: pneumonia (6), pneumonia bacterial (4), and pulmonary tuberculosis (1).

^bPer the BEL 112341 RAP, the custom MedDRA query for sepsis included 87 pre-specified preferred terms including sepsis, urosepsis, bacterial sepsis, and septic shock. The individual subject preferred terms reported in this study were as follows: Placebo: Corynebacterium sepsis (1), septic shock (1), viral sepsis (2); Belimumab SC: urosepsis (3), bacterial sepsis (2), and viral sepsis (2).

Rate = number of events per 100 subject-years; Subject years = sum across all subjects [(date of last treatment period visit in double blind – date of first exposure to treatment +1)/365]

b. Injection Site Reactions

Because belimumab is a protein for infusion that contains foreign sequences, a certain level of injection site reactions, hypersensitivity spectrum reactions including anaphylaxis would be expected. Since the subcutaneous formulation represents a new route of administration for belimumab, the occurrence of injection site reactions was prespecified as an adverse even of interest along with hypersensitivity reactions and anaphylaxis which will be discussed in the next subsection. Not unexpectedly, a higher proportion of belimumab SC subjects experienced a variety of injection site reactions as compared to the placebo group (Table 54). These were all mild to moderate in nature since no serious injection site reactions were reported in this study. No difference was noted in the occurrence of injection site reactions with belimumab SC based on the location of the injection (e.g., thigh [0.3%; 29/9638 injections] versus the abdomen [0.2%; 35/16154 injections]).

Table 54 – Summary of Treatment Emergent Injection Site Reactions by MedDRA Preferred Term (PT) During the Controlled Portion of Study C1115 (ITT Population)

MedDRA Preferred Term (PT)	Placebo N=280	Belimumab SC N=556
Any Injection Site TEAE	7 (2.5%)	34 (6.1%)
Exposure-Adjusted Incidence Rate per 100 Subject-Years	4.8	12.5
Injection Site Pain	1 (0.4%)	10 (1.8%)
Injection Site Hematoma	2 (0.7%)	8 (1.4%)
Injection Site Erythema	0	9 (1.6%)
Injection Site Pruritus	1 (0.4%)	4 (0.7%)
Injection Site Induration	1 (0.4%)	3 (0.5%)
Injection Site Bruising	1 (0.4%)	2 (0.4%)
Injection Site Reaction	1 (0.4%)	2 (0.4%)
Application Site Erythema	0	2 (0.4%)
Injection Site Urticaria	0	2 (0.4%)
Application Site Burn	0	1 (0.2%)
Application Site Pain	1 (0.4%)	0
Injection Site Discomfort	0	1 (0.2%)
Injection Site Hemorrhage	0	1 (0.2%)
Injection Site Hypersensitivity	0	1 (0.2%)
Injection Site Rash	1 (0.4%)	0
Injection Site Swelling	0	1 (0.2%)

Subjects are only counted once per PT.
Source: Sponsor's Table 103.90; p. 3022.

c. Hypersensitivity Spectrum Reactions Including Anaphylaxis

Hypersensitivity spectrum reactions including anaphylaxis were also designated as adverse events of interest since the current USPI for belimumab IV contains Warnings and Precaution statements regarding these types of events. Due to the overlap in symptoms with infusion reactions, hypersensitivity reactions, and anaphylaxis, it is difficult to ensure that these adverse events were adequately captured and classified during the study. Because of this, the Applicant employed various search terms including a MedDRA customized MedDRA query (CMQ) involving broad, narrow and algorithmic searches for “anaphylactic reactions” as well as the Sampson Criteria⁵ preferred by the review division. Cases thus identified were also adjudicated by the Applicant. The results of these various analyses are presented in Table 55 below.

⁵ Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, et al, J Allergy Clin Immunol, 2006; 117(2):391-397.

Table 55 – Post-Injection Anaphylaxis/Hypersensitivity Adverse Events During the Controlled Portion of Study C1115 (ITT Population)

	Placebo N=280	Belimumab SC N=556
Post-Injection Systemic Reactions:	25 (8.9%)	38 (6.8%)
Per Anaphylactic Reaction CMQ Narrow Search	1 (0.4%)	2 (0.4%)
Per Anaphylactic Reaction CMQ Broad Search	24 (8.6%)	38 (6.8%)
Per Anaphylactic Reaction CMQ Algorithmic Search	1 (0.5%)	2 (0.4%)
Serious Anaphylaxis per Sampson Criteria	0	0
Serious Acute Post-Injection Systemic Reactions/Hypersensitivity per GSK Adjudication	0	0
Serious Acute Post-Injection Systemic Reactions Excluding Excluding Hypersensitivity per GSK Adjudication	0	0
Serious Acute Hypersensitivity Reactions per GSK Adjudication	0	0
Serious Delayed Acute Hypersensitivity Reactions per GSK Adjudication	0	0
Serious Delayed Non-Acute Hypersensitivity Reactions per GSK Adjudication	1 (0.4%)	0

Source: Modified Sponsor's Tables 3.28 and 3.31; p. 1746-1747 and 1752.

The results from the MedDRA CMQ queries raise concerns regarding their accuracy in capturing and identifying cases of hypersensitivity reactions since the placebo rates of post-injection systemic anaphylactic reactions for these various searches are higher than those for belimumab SC. Although the results from the Sampson Criteria did not reveal any cases of serious anaphylaxis for either treatment group, one serious case of delayed non-acute hypersensitivity reaction that occurred in a placebo subject (this patient had a drug eruption related to a concomitant medication) was identified via adjudication by the Applicant. For completeness, the Applicant also submitted the results of an analysis that looked at post-injection anaphylactic reactions identified by the MedDRA CMQ broad search during the first six injections of the controlled portion of study C1115 which showed a higher incidence of these types of events occurred following the administration of the first and fourth injections of belimumab SC suggesting sensitization to belimumab SC with increasing exposure (Table 56).

Table 56 – Post-Injection Anaphylactic Reactions via Customized MedDRA Query (CMQ) Broad Search During the First Six Injections of the Controlled Portion of Study C1115 (ITT Population)

	Number (%) of Subjects					
	Injection Number					
	1	2	3	4	5	6
Placebo, N	280	276	273	273	273	272
	1 (0.4%)	1 (0.4%)	0	0	1 (0.4%)	3 (1.1%)
Belimumab 200 mg SC, N	556	553	549	548	546	545
	5 (0.9%)	2 (0.4%)	2 (0.4%)	5 (0.9%)	0	1 (0.2%)

Source: Sponsor's Table 3.36; p. 1764-1767.

d. Depression and Suicidality Adverse Events

Since a safety signal for depression and suicidality was noted during the review of the safety database in support of the IV formulation of belimumab which resulted in a Warnings and Precaution statement in the product's USPI, depression and suicidality were also prespecified as adverse events of interest for belimumab SC. Although the protocol for study C1115 prohibited the enrollment of potential subjects with evidence of serious suicide risk and/or any suicidal ideation on the Columbia Suicide Severity Rating Scale (C-SSRS) and required suicidality assessments at each study visit, there were subjects in both treatment groups who experienced depression and suicide/self-injury in both treatment groups over the course of the trial (Table 57). The exposure-adjusted incidence rate for any cases of depression per 100 subject-years was 3.1 for belimumab SC versus 4.4 for the placebo group with a corresponding rate ratio and 95% confidence interval of 0.71 (0.33, 152) suggesting no apparent difference between the two treatment groups. However, the rate ratio could not be calculated for suicide/self-injury cases per GSK adjudication because the rate was zero for the placebo arm.

Table 57 – Depression/Suicide/Self-Injury Adverse Events of Special Interest by Category During the Controlled Portion of Study C1115 (ITT Population)

	Placebo N=280	Belimumab SC N=556
Depression/Suicide/Self-Injury	10 (3.6%)	17 (3.1%)
Depression	10 (3.6%)	15 (2.7%)
Serious	0	0
Suicide/Self-Injury	0	2 (0.4%)
Serious	0	1 (0.2%)
Serious Suicide/Self-Injury per GSK Adjudication	0^a	2 (0.4%)
Suicidal Behavior per GSK Adjudication	0	0
Suicidal Ideation per GSK Adjudication	0 ^a	2 (0.4%)
Self-Injurious Behavior W/O Suicidal Intent per GSK Adjudication	0	0

^aSubject (b) (6) experienced suicidal ideation as per GSK adjudication of the SAE narrative which was not counted as suicidal ideation in Table 3.28 since the study investigator stated it was not an adverse event.
Source: Modified Sponsor's Table 3.28; p. 1748.

For completeness, the Applicant included an analysis of suicidal ideation or behavior based on the required C-SSRS assessments at each visit which showed no subjects had suicidal behavior during the double-blind portion of the study (Table 58).

Table 58 – Summary of C-SSRS Suicidal Ideation or Behavior During the Controlled Portion of Study C1115 (ITT Population)

	Placebo N=280	Belimumab SC N=556
Number of Subjects with ≥ 1 On-Treatment C-SSRS Assessment	277	554
Suicidal Ideation or Behavior (1-10), Any Event	2 (0.7%)	7 (1.3%)
Any Suicidal Ideation	2 (0.7%)	7 (1.3%)
1. Wish to be dead	2 (0.7%)	3 (0.5%)
2. Non-specific active suicidal thoughts	0	1 (0.2%)
3. Active suicidal ideation with any methods (not plan) without intent to act	0	3 (0.5%)
4. Active suicidal ideation with some intent to act, w/o specific plan	0	0
5. Active suicidal ideation with specific plan and intent	0	0
Any Suicidal Behavior (6-10)	0	0
6. Preparatory acts or behavior	0	0
7. Aborted Attempt	0	0
8. Interrupted Attempt	0	0
9. Non-fatal actual suicidal attempt	0	0
10. Completed suicide	0	0

Note: Percentages are based on the number of subjects with at least one on-treatment C-SSRS assessment. For behavior, the numbers of subjects (n) are those with the specified behavior at least once during treatment. For ideation, n refers to the number whose maximum ideation at any on-treatment assessment is the specified ideation. Subjects may have more than one type of ideation and/or behavior.

Source: Sponsor's Table 3.41.

Fourteen (14) subjects randomized to placebo and 36 subjects randomized to belimumab SC in this study had prior histories of suicidal ideation or behavior. Table 59 shows that 3 subjects in the belimumab SC group who had no C-SSRS pre-treatment suicidal ideation or behavior by history reported on-treatment suicidal ideation, however, no subject reported on-treatment suicidal behavior as assessed by this instrument.

Table 59 – Summary of Treatment-Emergent¹ C-SSRS Suicidal Ideation or Behavior During the Controlled Portion of Study C1115 (ITT Population)

	Placebo N=280	Belimumab SC N=556
Number of Subjects with > 1 On-Treatment C-SSRS Assessment	277	554
Suicidal Ideation or Behavior (1-10)	0	3 (0.5%)
Suicidal Ideation (1-5) ²	0	3 (0.5%)
More Severe Suicidal Ideation (4-5) ²	0	0
Suicidal Behavior (6-10)	0	0

¹Treatment emergent for suicidal ideation means that specified event is newly appearing or worsening, relative to the lifetime history, current history and baseline. Treatment emergent for suicidal behavior is relative to the lifetime history. All subjects in this table must have at least one on-treatment C-SSRS assessment and a pre-treatment assessment.

²The denominator is the number of subjects with maximum pretreatment C-SSRS ideation score <5.

Source: Sponsor's Table 3.42; p.

Table 60 lists all of the subjects with either suicide/self-injury and or treatment-emergent C-SSRS suicidal ideation or behavior relative to pre-treatment history during the double-blind portion of study C1115.

Table 60 – Summary of Subjects with Either Suicide/Self-Injury Adverse Events and/or Treatment-Emergent C-SSRS Suicidal Ideation or Behavior Relative to Pre-Treatment History for the Controlled Portion of Study C1115

Subject Number	Age/Sex/Race	AESI Suicide/Self-Injury Preferred Term	C-SSRS Suicidal Ideation Pretreatment History/ During Treatment	Status
Placebo				
(b) (6)	47yo/F/White	Suicidal Ideation (GSK Adjudication)	No/No	Completed Study
Belimumab 20 mg SC				
(b) (6)	21yo/F/American Indian or Alaska Native	Suicidal Ideation (SMQ)	No/Yes (Item 3) ¹	Completed Study
	31yo/F/Asian	Suicidal Ideation (Serious) (SMQ and GSK Adjudication)	No/Yes (Item 2) ¹	Discontinuation of Study Medications
	18yo/F/White	Neuropsychiatric Lupus (Serious) (GSK Adjudication)	Yes/Yes (Item 3) ¹	Discontinuation of Study Medications
	23yo/F/White	None reported	No/Yes (Item 3) ¹	Completed Study

¹Item 2 = Non-specific active suicidal thoughts; Item 3 = Active suicidal ideation with any methods (not plan) without intent to act

CMQ = Customized MedDRA Query

Source: Modification of Sponsor's Table47; p. 135 and review of case narratives for Subjects (b) (6)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Most subjects (>81%) experienced a treatment-emergent adverse event during the controlled portion of study C1115. Table 61 lists the frequency of the adverse events observed in this study by SOC and treatment group. The proportions of subjects who had a treatment emergent adverse event were comparable for the two treatment groups. Infections and Infestations, Gastrointestinal Disorders, Musculoskeletal and Connective Tissue Disorders, Nervous System and Skin and Subcutaneous Tissue Disorders were the most common 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.

Table 61 – Summary of Common Treatment Emergent Adverse Events by MedDRA System Organ Class (SOC) for the Controlled Portion of Study C1115 (ITT Population)

MedDRA System Organ Class (SOC)	Placebo N=280	Belimumab SC N=556
Any Event	236 (84%)	449 (81%)
Infections and Infestations	159 (57%)	308 (55%)
Gastrointestinal Disorders	68 (24%)	125 (23%)
Musculoskeletal and Connective Tissue Disorders	66 (24%)	124 (22%)
Nervous System Disorders	53 (19%)	111 (20%)
Skin and Subcutaneous Tissue Disorders	60 (21%)	80 (14%)
Gen. Disorders and Administration Site Conditions	43 (15%)	96 (17%)
Respiratory, Thoracic and Mediastinal Disorders	48 (17%)	81 (15%)
Investigations	34 (12%)	58 (10%)
Injury, Poisoning and Procedural Complications	35 (13%)	56 (10%)
Blood and Lymphatic System Disorders	24 (9%)	53 (10%)
Vascular Disorders	28 (10%)	43 (8%)
Psychiatric Disorders	32 (11%)	35 (6%)
Renal and Urinary Disorders	25 (9%)	38 (7%)
Reproductive System and Breast Disorders	18 (6%)	42 (8%)
Eye Disorders	21 (8%)	37 (7%)
Metabolism and Nutrition Disorders	21 (8%)	32 (6%)
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)	9 (3%)	15 (3%)
Cardiac Disorders	7 (3%)	16 (3%)
Ear and Labyrinth Disorders	7 (3%)	13 (2%)
Immune System Disorders	4 (1%)	9 (2%)
Endocrine Disorders	3 (1%)	8 (1%)
Hepatobiliary Disorders	3 (1%)	8 (1%)
Pregnancy, Puerperium and Perinatal Conditions	0	2 (0%)

Subjects are only counted once per SOC/PT.

Source: Sponsor's Table 3.3; p. 1463-1464.

Table 62 lists common adverse events by preferred terms reported by 2% or more patients in any treatment group during the controlled portion of study C1115. The treatment emergent adverse events most commonly reported by belimumab SC treated patients were: headache, viral upper respiratory tract infection, nasopharyngitis, nausea, bacterial urinary tract infection and back pain. Overall, the incidences for individual adverse events were similar for the two treatment groups as well as what had been reviewed in support of the safety data submitted in support of the IV formulation's safety profile. No other safety issues were identified on review of the adverse event data generated from the other belimumab SC studies included in the application's safety database.

Table 62 – Summary of Common Treatment Emergent Adverse Events by MedDRA Preferred Term Occurring ≥ 2% of Subjects Treated with Belimumab SC During the Controlled Portion of Study C1115 (ITT Population)

MedDRA Preferred Term (PT)	Placebo N=280	Belimumab SC N=556
Headache	26 (9%)	57 (10%)
Viral Upper Respiratory Tract Infection	24 (9%)	49 (9%)
Nasopharyngitis	22 (8%)	38 (7%)
Nausea	22 (8%)	38 (7%)
Urinary Tract Infection Bacterial	18 (6%)	42 (8%)
Back Pain	16 (6%)	28 (5%)
Upper Respiratory Tract Infection Bacterial	14 (5%)	30 (5%)
Arthralgia	11 (4%)	32 (6%)
Diarrhea	14 (5%)	28 (5%)
Cough	19 (7%)	22 (4%)
Hypertension	14 (5%)	25 (5%)
Insomnia	20 (7%)	18 (3%)
Pyrexia	12 (4%)	21 (4%)
Herpes Zoster	13 (5%)	18 (3%)
Influenza	8 (3%)	21 (4%)
Bronchitis Bacterial	8 (3%)	19 (3%)
Upper Respiratory Tract Infection	9 (3%)	18 (3%)
Pain in Extremity	10 (4%)	16 (3%)
Dizziness	11 (4%)	14 (3%)
Vomiting	7 (3%)	18 (3%)
Abdominal Pain Upper	6 (2%)	18 (3%)
Abdominal Pain	6 (2%)	17 (3%)
Bronchitis	8 (3%)	12 (2%)
Urinary Tract Infection	6 (2%)	14 (3%)
Migraine	6 (2%)	13 (2%)
Edema Peripheral	7 (3%)	11 (2%)
Oral Herpes	8 (3%)	10 (2%)
Sinusitis Bacterial	6 (2%)	12 (2%)
Dry Eye	4 (1%)	13 (2%)
Gamma-Glutamyltransferase Increased	6 (1%)	11 (2%)
Vulvovaginal Mycotic Infection	2 (1%)	14 (3%)
Dyspepsia	3 (1%)	12 (2%)
Constipation	3 (1%)	11 (2%)
Epistaxis	3 (1%)	11 (2%)
Muscle Spasms	3 (1%)	11 (2%)
Contusion	1 (0%)	11 (2%)

Subjects are only counted once per PT.

Source: Sponsor's Table 3.5; p. 1498-1529.

7.4.2 Laboratory Findings

Laboratory data from the randomized, controlled Phase 3 trial C1115 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.

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 63, mean hematology parameter values were generally similar across the two treatment groups and no clinically relevant mean changes from baseline were noted in any of the hematological parameters on comparison of the treatment groups.

Table 63 – Mean Changes Over Baseline in Hematology Parameters During the Controlled Portion of Study C1115 (ITT Population)

Indices	Placebo N=280		Belimumab SC N=556	
	Baseline	Week 52	Baseline	Week 52
Hematocrit (%)				
<i>N</i>	280	209	556	455
<i>Mean (SD)</i>	37.9 (4.5)	-0.35 (3.8)	38.1 (4.4)	0.53 (3.6)
<i>Median</i>	38.5	-0.30	38.1	0.30
<i>(Min, Max)</i>	(26.1, 52.2)	(-16.1, 11.5)	(25.3, 51.2)	(-16.6, 15.0)
WBC (x10³/mcl)				
<i>N</i>	280	208	556	452
<i>Mean (SD)</i>	6.25 (2.82)	-0.26 (2.27)	6.02 (2.55)	0.26 (2.44)
<i>Median</i>	5.80	-0.20	5.45	0.20
<i>(Min, Max)</i>	(1.1, 19.2)	(-8.4, 7.2)	(1.3, 13.9)	(-8.0, 15.4)
Basophils (%)				
<i>N</i>	280	208	556	452
<i>Mean (SD)</i>	0.02 (0.02)	0.00 (0.02)	0.02 (0.02)	0.00 (0.02)
<i>Median</i>	0.01	0.00	0.01	0.00
<i>(Min, Max)</i>	(0.00, 0.10)	(-0.05, 0.11)	(0.00, 0.15)	(-0.14, 0.16)
Eosinophils (%)				
<i>N</i>	280	208	556	452
<i>Mean (SD)</i>	0.07 (0.11)	0.02 (0.17)	0.07 (0.08)	0.02 (0.12)
<i>Median</i>	0.04	0.00	0.04	0.01
<i>(Min, Max)</i>	(0.00, 0.82)	(-0.64, 1.7)	(0.00, 0.67)	(-0.53, 1.2)
Lymphocytes (%)				
<i>N</i>	280	208	556	452
<i>Mean (SD)</i>	1.40 (0.84)	-0.036 (0.64)	1.33 (0.73)	0.25 (0.70)
<i>Median</i>	1.27	0.01	1.20	0.03
<i>(Min, Max)</i>	(0.12, 5.08)	(-3.41, 2.42)	(0.17, 4.60)	(-3.49, 4.80)
Monocytes (%)				
<i>N</i>	280	208	556	452
<i>Mean (SD)</i>	0.30 (0.20)	0.00 (0.19)	0.31 (0.20)	0.05 (0.21)
<i>Median</i>	0.26	0.00	0.28	0.04
<i>(Min, Max)</i>	(0.00, 1.33)	(-0.75, 0.54)	(0.00, 1.88)	(-1.35, 0.80)
Neutrophils (%)				
<i>N</i>	280	208	556	452
<i>Mean (SD)</i>	4.4 (2.4)	-0.25 (2.2)	4.23 (2.2)	0.17 (2.2)
<i>Median</i>	3.8	-0.065	3.8	0.12
<i>(Min, Max)</i>	(0.65, 16.0)	(-8.67, 7.13)	(0.45, 12.75)	(-6.69, 15.27)
Platelets (x10³/mcl)				
<i>N</i>	280	207	554	449
<i>Mean (SD)</i>	246 (74)	5 (51)	241 (74)	13 (49)
<i>Median</i>	241	5.0	236	11.0
<i>(Min, Max)</i>	(72, 518)	(-314, 168)	(55, 555)	(-185, 189)
Prothrombin Time (sec)				
<i>N</i>	279	209	556	454
<i>Mean (SD)</i>	11.1 (2.95)	0.21 (3.95)	11.4 (4.2)	0.10 (3.79)
<i>Median</i>	10.5	0.10	10.4	0.10
<i>(Min, Max)</i>	(9.1, 34.8)	(-23.6, 48.0)	(9.1, 51.1)	(-33.3, 37.0)
Activated Partial Thromboplastin Time (sec)				
<i>N</i>	279	209	556	453
<i>Mean (SD)</i>	30.5 (6.84)	-0.2 (4.64)	30.4 (7.74)	0.2 (5.74)
<i>Median</i>	29.0	0.0	29.0	0.0
<i>(Min, Max)</i>	(21, 70)	(-33, 20)	(21, 104)	(-42, 28)

Source Modified Sponsor's Table 3.49; p. 1954-2012.

As shown in Table 64, reference range shifts from baseline are observed for a number of hematological indices, however, these shifts were generally similar on cross comparison of the two treatment groups with exception of shifts from normal/low to high and normal/high to low in red blood cells, normal/low to high in eosinophils and shift from normal/high to low in lymphocytes. A decrease in lymphocyte counts associated with belimumab is not unexpected in view of its mechanism of action which targets B lymphocytes. Eosinophil counts are known to be higher in patients with collagen vascular disorders such as SLE. The shifts for the remaining parameters do not appear to be clinically relevant.

Table 64 – Tabular Summary of Hematology Reference Range Shifts from Baseline During the Controlled Portion of Study C1115

Indice	Placebo N=280	Belimumab SC N=556
Hematocrit	n=208	n=452
Shift from Normal/High to Low	23 (11%)	36 (8%)
Shift from Normal/Low to High	20 (10%)	46 (10%)
Red Blood Cells	n=208	n=452
Shift from Normal/High to Low	18 (9%)	9 (2%)
Shift from Normal/Low to High	20 (10%)	70 (15%)
Basophils	n=208	n=452
Shift from Normal/High to Low	0	0
Shift from Normal/Low to High	0	0
Eosinophils	n=208	n=452
Shift from Normal/High to Low	25 (12%)	50 (11%)
Shift from Normal/Low to High	33 (16%)	107 (24%)
Lymphocytes	n=208	n=452
Shift from Normal/High to Low	14 (5%)	53 (12%)
Shift from Normal/Low to High	22 (11%)	47 (10%)
Monocytes	n=208	n=452
Shift from Normal/High to Low	27 (13%)	37 (8%)
Shift from Normal/Low to High	27 (13%)	75 (17%)
Neutrophils	n=208	n=452
Shift from Normal/High to Low	7 (3%)	15 (3%)
Shift from Normal/Low to High	8 (4%)	21 (5%)

Source: Modified Sponsor's Table 3.65; p. 2140-2172.

To ensure that these observed shifts were not clinically meaningful, additional explorations of the hematology parameters were undertaken. Table 65 lists the hematological parameters that had grade 3 or 4 values reported over the course of study C1115. The incidence of Grade 3 and 4 toxicities for these laboratory parameters were again similar on cross group comparison and were very low overall. Review of these data does not reveal any clinically significant changes or unexpected safety signals.

Table 65 – Tabular Summary of Hematology Parameters by Worst Toxicity Grade During the Controlled Portion of Study C1115

Worst Grade Observed	Placebo N=280	Belimumab SC N=556
Hemoglobin	(n=277)	(n=554)
Grade 3	9 (3.2%)	11 (2.0%)
Grade 4	0	1 (0.2%)
Leukocyte Count	(n=277)	(n=554)
Grade 3	7 (2.5%)	19 (3.4%)
Grade 4	0	0
Neutrophil Count	(n=277)	(n=554)
Grade 3	11 (4.0%)	25 (4.5%)
Grade 4	0	3 (0.5%)
Platelet	(n=277)	(n=554)
Grade 3	0	5 (0.9%)
Grade 4	1 (0.4%)	0
Prothrombin Time (PT)	(n=275)	(n=549)
Grade 3	13 (4.7%)	37 (6.7%)
Grade 4	4 (1.5%)	10 (1.8%)
Partial Thromboplastin Time (PTT)	(n=275)	(n=549)
Grade 3	0	3 (0.5%)
Grade 4	0	0
Prothrombin Time (PT)	(n=275)	(n=549)
Grade 3	13 (4.7%)	37 (6.7%)
Grade 4	4 (1.5%)	10 (1.8%)

Source: Sponsor's Table 3.53; p. 2118-2119.

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 66). Mean liver and renal parameter values were generally similar across the two 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 66 – Summary of Chemistry Reference Range Shifts from Baseline During the Controlled Portion of Study C1115

Chemistry Parameter	Placebo N=280		Belimumab SC N=556	
	Baseline	Week 52	Baseline	Week 52
Alk Phos (U/L)				
N	280	213	556	462
Mean (SD)	67.3 (22.6)	67.5 (23.4)	69.1 (26.5)	71.6 (28.4)
Median	62.5	63.0	64.0	67.0
(Min, Max)	(28, 174)	(24, 178)	(21, 236)	(22, 348)
ALT/SGPT (U/L)				
N	280	213	556	462
Mean (SD)	17.9 (11.1)	17.9 (12.2)	18.7 (14.6)	19.0 (17.5)
Median	15.0	15.0	15.0	15.0
(Min, Max)	(4, 7)	(4, 81)	(4, 158)	(4, 232)
AST/SGOT (U/L)				
N	280	213	556	462
Mean (SD)	21.6 (11.1)	22.4 (11.8)	22.3 (11.4)	22.4 (12.3)
Median	19.0	19.0	20.0	20.0
(Min, Max)	(7, 144)	(9, 103)	(7, 173)	(9, 155)
GGT (U/L)				
N	280	213	556	462
Mean (SD)	29.4 (28.6)	30.1 (29.0)	33.9 (38.9)	32.7 (35.70)
Median	22.0	20.0	22.0	22.0
(Min, Max)	(7, 324)	(7, 282)	(6, 562)	(7, 401)
LDH				
N	280	213	556	462
Mean (SD)	177 (43.9)	169 (42.7)	176 (45.1)	169 (44.8)
Median	172	160	168	161
(Min, Max)	(49, 333)	(64, 351)	(61, 445)	(89, 519)
Bilirubin (umol/L)				
N	280	213	556	462
Mean (SD)	6.91 (2.80)	7.10 (3.14)	7.22 (3.24)	7.64 (3.47)
Median	6.84	6.83	6.84	6.84
(Min, Max)	(3.42, 20.5)	(1.71, 25.7)	(1.71, 30.8)	(3.42, 34.2)
Albumin (g/L)				
N	280	213	556	462
Mean (SD)	40.6 (4.66)	-0.8 (3.81)	40.5 (4.71)	1.3 (3.77)
Median	41.0	0.0	41.0	1.0
(Min, Max)	(23, 53)	(-20, 10)	(18, 55)	(-15, 27)
BUN/Creat Ratio				
N	280	213	556	462
Mean (SD)	19.6 (5.65)	-0.7 (5.26)	19.7 (6.12)	-1.1 (5.33)
Median	19.0	-1.0	19.0	-1.0
(Min, Max)	(8, 39)	(-15, 20)	(9, 48)	(-17, 19)
BUN (mmol/L)				
N	280	213	556	462
Mean (SD)	5.27 (2.14)	-0.11 (1.56)	5.24 (2.03)	-0.09 (2.17)
Median	5.0	0.0	5.0	0.0
(Min, Max)	(1.43, 21.8)	(-6.78, 4.28)	(1.79, 16.8)	(-9.64, 33.2)
Creat. (umol/L)				
N	280	213	556	462
Mean (SD)	67.3 (20.9)	0.0 (14.8)	67.3 (18.8)	2.4 (14.5)
Median	61.9	0.0	61.9	0.0
(Min, Max)	(35.4, 212)	(-61.9, 133)	(26.5, 185)	(-44.2, 194)

Source Modified Sponsor's Tables 3.45 and 3.52; p. 1840-1869 and 2078-2112.

Table 66 (cont.) – Summary of Chemistry Reference Range Shifts from Baseline During the Controlled Portion of Study C1115

Chemistry Parameter	Placebo N=280	Belimumab SC N=556	Chemistry Parameter	Placebo N=280
	Baseline	Week 52	Baseline	Week 52
Creat. Cl (ml/s)				
<i>N</i>	280	213	556	462
<i>Mean (SD)</i>	1.92 (0.71)	-0.05 (0.30)	1.92 (0.68)	-0.05 (0.30)
<i>Median</i>	1.80	-0.03	1.80	-0.02
<i>(Min, Max)</i>	(0.46, 4.83)	(-1.07, 0.98)	(0.58, 5.88)	(-1.2, 0.97)
Protein (g/L)				
<i>N</i>	280	213	556	462
<i>Mean (SD)</i>	71.3 (6.64)	-0.2 (5.59)	71.6 (7.14)	-0.6 (5.33)
<i>Median</i>	71.0	0.0	72.0	-1.0
<i>(Min, Max)</i>	(52, 91)	(-24, 13)	(37, 100)	(-24, 36)

Source Modified Sponsor's Tables 3.45 and 3.52; p. 1840-1869 and 2078-2112.

Table 67 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 carbon dioxide and are not suggestive of any belimumab-related toxicity.

Table 67 – Summary of Chemistry Range Shifts at Week 52 from Baseline During the Controlled Portion of Study C1115

Chemistry Parameter	Placebo N=280	Belimumab SC N=556
Carbon Dioxide		
Shift from Normal/High to Low	20 (7%)	44 (8%)
Shift from Normal/Low to High	20 (7%)	51 (9%)
Lactate Dehydrogenase		
Shift from Normal/High to Low	6 (2%)	11 (2%)
Shift from Normal/Low to High	7 (3%)	27 (5%)
Protein		
Shift from Normal/High to Low	3 (1%)	7 (1%)
Shift from Normal/Low to High	7 (3%)	11 (2%)
BUN		
Shift from Normal/High to Low	2 (1%)	5 (1%)
Shift from Normal/Low to High	3 (1%)	4 (1%)
Creatinine Clearance		
Shift from Normal/High to Low	6 (2%)	17 (3%)
Shift from Normal/Low to High	5 (2%)	10 (2%)

Source: Modified Sponsor's Tables 3.66, 3.67 and 3.68; p. 2173-2177, 2182-2187 and 2192-2207.

The Applicant also analyzed liver and renal function as well as electrolyte results by toxicity grades. Table 68 summarizes these parameters for which Grade 3 and 4 toxicities were observed during the controlled portion of Study C1115. The incidence of Grade 3 and 4 toxicities for these laboratory parameters were again similar on cross

comparison of the two 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.

Table 68 – Chemistry, Hepatic and Renal Function Worst Toxicity Grade During Controlled Portion of Study C1115

Lab Test Worse Grade Observed	Placebo N=280	Belimumab SC N=556
Hypophosphatemia	(n=277)	(n=554)
Grade 3	1 (0.4%)	4 (0.7%)
Grade 4	0	0
Hyperkalemia	(n=277)	(n=554)
Grade 3	0	1 (0.2%)
Grade 4	1 (0.4%)	0
Hypernatremia	(n=277)	(n=554)
Grade 3	1 (0.4%)	0
Grade 4	0	0
ALT (SGPT)	(n=277)	(n=554)
Grade 3	1 (0.4%)	3 (0.5%)
Grade 4	0	1 (0.2%)
AST (SGOT)	(n=277)	(n=554)
Grade 3	0	2 (0.4%)
Grade 4	1 (0.4%)	0
Gamma-Glutamyl-Transferase	(n=277)	(n=554)
Grade 3	4 (1.4%)	6 (1.1%)
Grade 4	1 (0.4%)	6 (1.1%)
Albumin	(n=277)	(n=554)
Grade 3	4 (1.4%)	3 (0.5%)
Grade 4	3 (1.1%)	1 (0.2%)
Creatinine	(n=277)	(n=554)
Grade 3	0	1 (0.2%)
Grade 4	0	0
Hyperglycemia	(n=277)	(n=554)
Grade 3	6 (2.2%)	2 (0.4%)
Grade 4	0	0
Hypoglycemia	(n=277)	(n=554)
Grade 3	2 (0.7%)	6 (1.1%)
Grade 4	0	0

Source: Modified Sponsor's Tables 3.54, 3.55 and 3.56; p. 2120-2121, 2122-2124, and 2125-2126.

c. Urinalysis

Although the protocol for study C1115 prohibited the entry of patients with severe lupus nephritis, some of the participating patients had disease activity in this organ system.

Urinalysis was done via dipstick at each study visit along with collection of spot urines for assessment of protein/creatinine ratio. Table 69 shows that no clinically meaningful differences in proteinuria over the course of the study on cross group comparison.

Table 69 – Mean Change Over Baseline in Proteinuria for the Controlled Portion of Study C1115

Urinalysis Parameter	Placebo N=280		Belimumab SC N=556	
	Baseline	Week 52	Baseline	Week 52
Protein (mg/L)				
N	280	211	556	456
Mean (SD)	0.44 (0.84)	0.01 (0.85)	0.39 (0.71)	-0.09 (0.49)
Median	0.13	-0.01	0.12	-0.01
(Min, Max)	(0.03, 6.33)	(-5.21, 7.15)	(0.02, 6.23)	(1.79, 0.32)

Source: Modified Sponsor's Table 102.60; p. 1205-1210.

A higher proportion of subjects in the belimumab SC group (49%) had proteinuria levels shift to normal as compared to the placebo group (24%) at Week 52 (Table 70). Due to the small sample size, no definitive conclusions regarding belimumab's effectiveness in treating lupus nephritis can be drawn. A randomized, controlled phase 3 study (BEL114054) is underway evaluating belimumab IV as a treatment for patients with lupus nephritis following induction therapy

Table 70 – Proteinuria Shifts Over Baseline at Week 52 During the Controlled Portion of Study C1115

Urinalysis Parameter	Placebo N=280	Belimumab SC N=556
Proteinuria:		
Number of Subjects with Normal Proteinuria	162	342
Normal to High	10 (6%)	10 (3%)
Number of Subjects with High Proteinuria	29	67
High to Normal	7 (24%)	33 (49%)

Source: Sponsor's Table 2.61; p. 1116-1121

For completeness, the Applicant also analyzed urinalysis results by toxicity grades. Table 71 summarizes these parameters for which Grade 3 and 4 toxicities were observed during the controlled portion of Study C1115. Overall, the incidence of Grade 3 and 4 toxicities for these laboratory parameters were low and similar on cross group comparison.

Table 71 – Urinalysis Parameter Worst Toxicity Grade During the Controlled Portion of Study C1115

Urinalysis Parameter Worst Grade Observed	Placebo N=280	Belimumab SC N=556
Protein/Creatinine Ratio	(n=277)	(n=554)
Grade 3	13 (4.7%)	25 (4.5%)
Grade 4	20 (7.2%)	27 (4.9%)
Protein (Dipstick)	(n=277)	(n=554)
Grade 3	0	0
Grade 4	0	0
Red Blood Cells	(n=277)	(n=554)
Grade 3	0	0
Grade 4	0	0

Source: Sponsor's Table 3.57; p. 2127

d. Immunoglobulins

As shown in Table 72, shifts in IgM levels from normal/high to low were highest in the belimumab SC group which is not unexpected since this immunoglobulin has the ability to change most acutely. The proportion of subjects with IgG less than the lower limit of normal at baseline increased over time from 1.8% to 2.4% by Week 52 while the proportion of patients with IgA less than the lower limit of normal at baseline increased from 1.3% to 1.9% over the course of study C1115. However, the proportion of subjects with IgM levels less than the lower limit of normal increased from 13% to 33% by the end of this study. As per the Applicant, a corresponding increase in infections or serious infections in the belimumab SC treatment group was not observed with these changes in immunoglobulins.

Table 72 – Immunoglobulin Reference Range Shifts from Baseline to Week 52 During the Controlled Portion of Study C1115

Immunoglobulins	Placebo N=280	Belimumab SC N=556
IgA		
Shift from Normal/High to Low	0	5 (0.9%)
Shift from Normal/Low to High	1 (0.5%)	1 (0.2%)
IgG		
Shift from Normal/High to Low	4 (1.4%)	6 (1.1%)
Shift from Normal/Low to High	1 (0.5%)	4 (0.7%)
IgM		
Shift from Normal/High to Low	7 (2.5%)	95 (17%)
Shift from Normal/Low to High	2 (0.7%)	0

Source: Modified Sponsor's Tables 3.70 and 4.3; p. 2209-2212 and 2586-2594.

B cell numbers were also evaluated in study C1115. At Week 24, the median percent reduction in CD19+ B cells was 33% with belimumab treatment, while the reduction in the placebo group was approximately 3%; at Week 52 the median percent reduction with belimumab SC was 58% compared with 10% with placebo. Similar effects on B cells were observed in the safety database reviewed in support of the licensing of IV belimumab. Low levels of B cells and immunoglobulins can increase the risk for infection. The current USPI for belimumab IV contains a Warning and Precaution for an increased risk for serious and fatal infections associated with its administration.

7.4.3 Vital Signs

According to the protocol for Study C1115, patients underwent measurement of blood pressure (BP) and weight at each study visit, but assessment of oral temperature, heart rate or respiratory rate were not required. Review of the mean changes from baseline by visit for diastolic and systolic BP as well as weight for Study C1115 failed to identify any clinically relevant safety issues associated with belimumab SC.

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 a thorough QT study as part of their pre-clinical and clinical development programs for the IV or SC formulations. Serial ECGs were also not performed on subjects who participated in the trials in support of the safety profile of the subcutaneous formulation of belimumab.

7.4.5 Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

Immunogenicity assay results for study C1115 are summarized in Table 73. Based on these data, belimumab SC does not appear to be immunogenic.

Table 73 – Immunogenicity Results from Study C1115

	Placebo N=280	Belimumab SC N=556
Baseline		
n	279	553
Negative	277 (99.3%)	550 (99.5%)
Transient Positive	2 (0.7%)	3 (0.5%)
Persistent Positive	0	0
Week 52		
n	213	462
Negative	213 (100%)	462 (100%)
Transient Positive	0	0
Persistent Positive	0	0

Source: Sponsor's Table 3.75; p. 2217

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Since belimumab SC will be administered via a fixed dose, the safety database did not contain an analysis for dose dependent adverse events. However, the Applicant did submit the results of analyses of adverse events and serious adverse events by weight-based quartile which showed that the overall rates for adverse events and serious adverse events by weight quartiles increased as body weight increased (range: 76-86%) but were comparable or less than that observed in the corresponding placebo groups (range: 77-90%). Of note, three of the five deaths that occurred during the double blind portion of study C1115 involved subjects whose body weight was in the first or lowest quartile (e.g., <55 kg). Two of these deaths occurred in subjects in the belimumab SC group and 1 death occurred in the placebo group. All three were due to infections which is not unexpected since belimumab is an immunosuppressive agent. Given the very small number of events, definitive conclusions could not be drawn about a potential association between an increase in risk for fatal infections (sepsis) and higher exposure to belimumab. Further, a weight-based quartile analysis for serious adverse events including infections did not support such an association. The current USPI for IV belimumab contains a Warning and Precaution for the increase in risk for serious and fatal infections associated with its administration.

7.5.2 Time Dependency for Adverse Events

Review of the cumulative long term exposure data generated from the ongoing open label extension of study C1115 did not reveal any new safety signals associated with prolonged exposure to belimumab SC. Reviews of cumulative long term exposure data from patients who had received up to 11-plus years of treatment with belimumab IV

from the completed post-marketing commitment studies BEL112626 and BEL112233 which were long term continuation studies of SLE subjects who had completed the phase 2 and 3 studies LBSL99 and 1056, respectively, that were reviewed in support of IV belimumab's marketing approval also did not reveal any new potential safety signals associated with the product.

7.5.3 Drug-Demographic Interactions

Subgroup analyses of adverse events were conducted for the double-blind portion of study C1115 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 this study was overwhelmingly comprised of female patients (789/836; 94%). Due to the paucity of male patients (n=47) and geriatric patients (n=19) who participated in this trial, no definitive conclusions regarding the risk for developing adverse events associated with belimumab treatment can be made for either of these demographic groups. (Note: This is consistent with what occurred with the subgroups analyses for the safety database reviewed in support of IV belimumab.)

Table 74 shows the race based analysis of adverse events for four of the racial groups represented in this trial. [Note: The number of subjects who were Native Hawaiian/Pacific Islander (n=2) and multiracial (n=9) were too small to be included in this racial subgroup analysis.] No overall safety differences are noted on cross treatment group comparison. Of the four racial subgroups, the Black/African American racial subgroup had the highest rate of adverse events. The overall incidence of serious adverse events was also higher for the Black/African American racial subgroup in study C1115 (21% placebo versus 19% belimumab SC) as compared to an "other race" subgroup comprised of the three other racial subgroups (15% placebo versus 10% belimumab SC). Rates for adverse events of interest were comparable between the Black/African American subgroup and the combined "other race" subgroup. Due to efficacy concerns identified during the review of the licensing application for IV belimumab, the Applicant is conducting a randomized, controlled phase 3 study of IV belimumab in subjects of Black race (Study BEL115471) which should provide the necessary efficacy and safety data to determine belimumab's risk/benefit profile in this subpopulation.

Table 74 - Summary of the Number (%) of Subjects with ≥ 1 Adverse Event by Race while Participating in the Double-Blind Portion of Study C1115

Race	Placebo N=280	Belimumab SC N=556
White/Caucasian with ≥ 1 Adverse Event	(n=166) 134 (81%)	(n=336) 261 (78%)
Asian with ≥ 1 Adverse Event	(n=63) 55 (87%)	(n=121) 107 (88%)
Black/African American with ≥ 1 Adverse Event	(n=30) 29 (97%)	(n=56) 51 (91%)
Alaska Native/American Indian ≥ 1 Adverse Event	(n=21) 18 (86%)	(n=43) 30 (70%)

Source: Sponsor's Table 3.81; p. 2328-2393.

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

Belimumab is a therapeutic biologic protein and is not expected to interact with CYP450 enzymes or p-glycoproteins. Although no formal drug-drug interaction studies were conducted by the Applicant in support of belimumab SC's safety, the application did contain the results of a population PK analysis which evaluated the effects of concomitant medications such as corticosteroids, anti-malarials, and other immunosuppressants (e.g., methotrexate, mycophenolate mofetil, azathioprine), NSAIDs, aspirin, angiotensin-converting enzyme (ACE) inhibitors, and statins on belimumab's PK parameters which showed a 6% and 9% increase in the clearance of belimumab by corticosteroids and ACE inhibitors, respectively. No clinically relevant drug-drug interactions were identified by this analysis. (Note: The reader is referred to the clinical pharmacology review of this application for additional information regarding the findings from this population PK analysis for drug-drug interactions.)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Because belimumab targets B cells, immunosuppression is an expected effect, and chronic immunosuppression has been associated with an increase in the risk for developing a malignancy. Therefore, the safety database from the controlled portion of study C1115 was examined for cases of malignancy. As shown in Table 75, there were

a total of 3 confirmed malignancies reported during the double-blind portion of study C1115. No discernible pattern for malignancies was observed.

Table 75 – Malignancies By Randomized Treatment Group During the Controlled Portion of Study C1115 (ITT Population)

Malignancies	Placebo N=280	Belimumab SC N=556
All Malignancies Including NMSC	1 (0.4%)	2 (0.4%)
Exposure-Adjusted Incidence Rate per 100 Subject-Years (Any Malignancy Including NMSC)	0.4	0.4
NMSC	0	0
Solid Tumor:	1 (0.4%)	2 (0.4%)
Breast Cancer	1 (0.4%)	0
Endometrial Cancer	0	1 (0.2%)
Intraductal Proliferative Breast Lesion	0	1 (0.2%)

Source: Sponsor's Table 3.28; p. 1746

The controlled study C1115 was not designed to determine the risk for developing a malignancy due to exposure to belimumab SC. Nonetheless, the exposure-adjusted incidence rate for malignancies including non-melanoma skin cancers was calculated based on the number of cases observed in this study. The exposure –adjusted incidence rates for malignancies in the placebo and belimumab SC treatment groups were both low with a rate ratio of <1 suggesting once again no apparent difference between the two treatment groups (placebo: 0.4 malignancies/100 subject-years; belimumab SC: 0.4 malignancies/ 100 subject –years with rate ratio: 0.97; 95% CI [0.09, 10.72]). The exposure adjusted incidence rate for malignancies for belimumab SC in study C1115 was similar to that observed in the pooled phase 3 studies reviewed in support of the IV formulation in addition to what has been reported in the literature for a large, international cohort of SLE patients.⁶

No additional malignancies were reported in the 120-day safety follow-up for the ongoing, open-label extension of study C1115 or in the phase 2 actual use study 200339 that evaluated the belimumab SC autoinjector. Review of the safety database submitted in support of the SC formulation revealed two other cases of malignancy that occurred in study BEL112232 which evaluated the 06-C formulation that the Applicant is not bringing forward for licensure. These two cases of malignancy (1 case of breast cancer and 1 case of malignant thymoma) were reviewed in support of the safety profile of the IV formulation of belimumab and will not discussed further in this review.

⁶ Bernatsky et al. 2005.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant and breast feeding females were prohibited from participating in study C1115. Although the study's entry criteria required women of reproductive potential to practice effective forms of contraception for 1 month prior to receiving study treatment and for 8 weeks after the last dose of belimumab, there were a total of 11 pregnancies as listed in Table 76 that occurred over the course of the double-blind portion of study C1115.

Table 76 – Summary of Pregnancies During the Double-Blind Portion of Study C1115

Pregnancy Outcomes	Placebo N=280	Belimumab SC N=556
Total	3	8
Ongoing	1 (33%)	1 (12.5%)
Live Birth Without Congenital Abnormality	0	4 (50%)
Elective Termination	1 (33%)	1 (12.5%)
Spontaneous Abortion	0	2 (25%)
Unknown Outcome (Lost to Follow-Up)	1 (33%)	0

As of the 120-day safety update cut-off date of October 22, 2016, the Applicant reports having collected 155 pregnancies from post-marketing sources and 12 new cases from clinical trial subjects treated with belimumab or blinded drug product. Since SLE typically affects young women of childbearing potential, a pregnancy registry is currently underway that is collecting prospective information for pregnancies and pregnancy outcomes in patients with SLE who received IV belimumab within 4 months prior to conception and/or during pregnancy. The Applicant reports that no new safety information regarding the use of belimumab during pregnancy has been identified from the ongoing registry or from the postmarketing pregnancy case reports they have received as of the above cut-off date. They are proposing to amend this registry to collect information regarding pregnancy exposure to the subcutaneous formulation of belimumab.

7.6.3 Pediatrics and Assessment of Effects on Growth

This application did contain any data generated from assessments of belimumab's effect on growth since the Applicant's postmarketing required study evaluating the IV formulation of belimumab as a treatment for children and adolescents with SLE was ongoing at the time this application was submitted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to the Applicant, there is limited overdose data for belimumab. Doses of up to 20mg/kg of the IV formulation were evaluated in a phase 1 dose escalation study of the product without signs of dose limiting toxicity. Since the IV formulation has been

approved for marketing, the Applicant reports receiving 12 spontaneous case reports of adverse events associated with overdoses of IV belimumab as a result in a change in the patients' weight. The majority of the adverse events were non-serious in nature and included influenza, nausea, dizziness, and vaginal infections. However, there was 1 case report categorized as serious in nature involving a patient who received a single dose of 2400 mg of belimumab that resulted in her hospitalization for treatment of an infusion reaction associated with complaints of feeling bad, headache and palpitations. Since belimumab SC is a monoclonal antibody which has to be administered via injection and is associated with serious adverse events such as infections and hypersensitivity reactions including 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 by this medical officer during the review of the follow-up data collected from patients who participated in the multidose, long term studies post-withdrawal of belimumab IV. (Refer to medical officer's review of BLA 125370 dated February 18, 2011 for additional information.) The Applicant is currently conducting study BEL116027 to evaluate the efficacy of a 24-week withdrawal followed by a 28-week reintroduction of belimumab 10 mg/kg IV therapy compared with uninterrupted belimumab 10 mg/kg IV therapy for 52 weeks in subjects with low SLE disease activity receiving belimumab 10 mg/kg plus standard therapy in order to generate data regarding treatment holidays and rebound phenomenon associated with the product.

7.7 Additional Submissions / Safety Issues

Additional safety information that was contained in the Applicant's 120-day safety updated submitted on January 18, 2017 has been incorporated into the deaths, SAEs and postmarketing subsections of this review.

8 Postmarket Experience

Belimumab SC has not been approved for marketing in any country. The IV formulation of belimumab was FDA-approved for marketing in this country on March 9, 2011 for the treatment of adult patients with active, autoantibody positive SLE who are receiving standard of care therapy. According to the Applicant the IV formulation is approved for marketing in over 60 countries worldwide and has not been withdrawn or suspended from marketing due to safety reasons. Based on sales data they estimate cumulative postmarketing exposure as of the cut-off date of June 30, 2016 to be 45,446 patient years with most of the patients having been treated in the United States. In support of belimumab's safety profile, the Applicant included a review of spontaneous postmarketing adverse event reports they have received since product launch to October 22, 2016. A total of 5,869 spontaneous reports containing BENLYSTA as a suspect drug contained in the GSK safety database from 43 countries were included in

this postmarketing safety review. The majority of these postmarketing case reports were from the United States. These 5,869 reports reportedly contained 20,068 adverse events, out of which 3,181 were classified as serious in nature. According to the Applicant the system organ classes with $\geq 5\%$ in decreasing incidence were as follows: general disorders and administration site conditions, nervous system, gastrointestinal disorders, musculoskeletal and connective tissue disorders, infection and infestations, skin and subcutaneous tissue disorders, respiratory, thoracic, and mediastinal disorders, injury, poisoning and procedural complications. Additionally, the Applicant reviewed post-marketing adverse events of interest and calculated the following postmarketing exposure incidence rates as of the cut-off date of October 22, 2016:

- **Mortality:** The current USPI for belimumab IV contains a Warning and Precaution regarding an increase in deaths associated with the product that was observed in the safety database submitted in support of its marketing. According to the Applicant, the incidence rate of belimumab post-marketing mortality in SLE patients was 0.31/100 subject years with a 95% confidence interval (CI) [0.26, 0.37] which is lower than has been reported in the literature for SLE patients (1.63/100 patient-years) by Bernatsky et al 2005.
- **Infections:** There is also a Warning and Precautions regarding the increase risk for serious and fatal infections in the USPI for belimumab IV. The post-marketing incidence rate of opportunistic infections (excluding herpes zoster and tuberculosis) was 0.06/100 subject years; 95% CI [0.04, 0.08] which is again lower than the range of rates reported in the literature for SLE patients (1.3-1.9/100 patient-years) (Fernandez-Nebro et al and Gladman et al). The postmarketing incidence rate for herpes zoster (disseminated or recurrent) it was 0.02/100 subject years; 95% CI [0.01, 0.03] which is also lower than the range reported in the literature for SLE patients (0.32/100 subject years) (Manzi et al). (Note: As there was only one spontaneous case of tuberculosis reported in the belimumab postmarketing safety database, the Applicant did not provide a postmarketing incidence rate for tuberculosis.) The Applicant also provided the spontaneous rate of death due to infection for belimumab which they estimate to be 0.06/100 subject years; 95% CI [0.04, 0.09] which is lower than the range of rates for SLE patients reported in the literature (0.17-1.66/100 patient-years) (Alarcon et al, Cervera et al 2003, Cervera et al 2009, Fernandez-Nabro et al, Mok et al, and Terrier et al).
- **PML:** In 2014, a Warning and Precautions regarding the occurrence of PML in SLE patients who had received belimumab IV in addition to concomitant immunosuppressive agents was added to the product's USPI. Based on exposure of 56,998 subject-years, the estimated rate of clinical trial and spontaneous reports of PML is 7.02/100,000 subject years; 95% CI [1.91, 17.97].
- **Psychiatric Events:** As a result of a depression and suicidality signal noted on review of the safety database submitted in support of the IV formulation of belimumab, a Warning and Precautions regarding suicidality and depression was included in the product's USPI. According to the Applicant, there has been only one spontaneous postmarketing report collected for completed suicide for

belimumab. Their estimated postmarketing incidence rate for suicide is 2.20/100,000 subject years; 95% CI [0.06, 12.26]. The postmarketing incidence rate of total suicidality (suicidal behavior + suicidal ideation + completed suicides) for belimumab is 101/100,000 patient years; 95% CI [74, 135] which is consistent with background rates for completed suicide (10.0-2182/100,000 patient years) (Cervera et al 2009, Li-Yu et al) and for suicide or suicide attempts (117/100,000 patient years; 95% CI [46.9, 240] that have been reported for SLE patients in observational studies (Karassa et al).

- Malignant neoplasm: The incidence rate for malignancies (excluding NMSC) for postmarketing belimumab SLE cases was 0.12 per 100 subject years; 95% CI [0.09, 0.16] which does not exceed the rate reported in the literature for SLE patients (0.53/100-subject years) (Bernatsky 2013, and Bernatsky 2005).
- Post-Infusion/Injection Systemic Reactions: The Warnings and Precautions section for hypersensitivity reactions including anaphylaxis in the belimumab USPI was updated in 2012 and 2103 to reflect postmarketing cases of these types of events. According to the Applicant, the incidence of postmarketing hypersensitivity/infusion reactions for belimumab in SLE patients was 0.30/100 subject years; 95% CI [0.25, 0.35]. Since most of these adverse event reports were adjudicated by the Applicant to hypersensitivity reactions, the incidence of postmarketing hypersensitivity reactions for belimumab in SLE patients was 0.21/100 subject years; 95% CI [0.17, 0.25].

The Applicant's postmarketing safety update suggests that the safety profile of belimumab IV appears to be consistent with that reviewed in support of its marketing approval and no strengthening of the current Warnings and Precautions in the current USPI is indicated, however, the estimated incidences of the various adverse events of interest should be reviewed with caution due to the known occurrence of underreporting of spontaneous events.

The Office of Surveillance and Epidemiology (OSE) in conjunction with this review division completed a 915-New Molecular Entity (NME) Postmarket Safety Summary Analysis of the IV formulation of belimumab (BLA 125370) on October 11, 2016 that included an overview of spontaneous postmarketing case reports of adverse events associated with belimumab contained in the FDA Adverse Event Reporting System (FAERs) that did not identify any new safety concerns associated with the product.

Review of the safety data contained in the 120-day safety update as of the cut-off date October 22, 2016 collected from the six ongoing phase 3 and 4 studies of IV belimumab conducted by the Applicant as well as two interventional investigator sponsored studies of the IV formulation supported by the Applicant, and two postmarketing observational registries for safety and pregnancy conducted by the Applicant, resulted in no new safety concerns identified.

9 Appendices

9.1 Literature Review/References

The Applicant submitted the results of an updated literature search as of the cut-off date of October 22, 2016 in the 120-day safety update that utilized Medline and/or Embase.com for literature citations and abstracts, and Searchlight for conference abstracts. As per the Applicant, the results of this exercise did not identify any new safety information for belimumab. The Office of Surveillance and Epidemiology (OSE) in conjunction with this review division completed a 915-New Molecular Entity (NME) Postmarket Safety Summary Analysis of the IV formulation of belimumab (BLA 125370) on October 11, 2016 that included a literature review for adverse events associated with belimumab utilizing the search engine PubMed. A total of two case reports of progressive multifocal leukoencephalopathy (PML) that occurred in SLE patients treated with belimumab in addition to concurrent immunosuppressive agents were identified in that literature search. (Note: Since April 2014, the USPI for IV belimumab has contained a Warning and Precautions regarding the risk for PML to occur in patients treated with the product and concomitant immunosuppressives.) An updated literature search was conducted by this medical officer on June 2, 2017 utilizing PubMed and the same search parameters as did the 915-NME Postmarketing Safety Summary Analysis which identified two new publications as follows: one article described the results from Study C1115 and the other described the results from a randomized open label study investigating the effect of belimumab on pneumococcal vaccination in patients with SLE. (Note: The results of the vaccination study had been submitted previously by the Applicant to belimumab's IND and were summarized in this application in support of the SC formulation.) No new potential safety signals for belimumab were identified as a result of this updated literature review.

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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 (b) (4)® is acceptable. It has been deemed acceptable by both DMEPA and the Division.
2. Benlysta (b) (4)® 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 same Warnings and Precautions as listed in the USPI for belimumab IV should be included in the labeling for belimumab SC
4. (b) (4)
5. Under Section 14 Clinical Studies information regarding belimumab SC's marginal effectiveness in black patients needs to be included

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this application in view of the well documented safety profile IV belimumab and the lack of any new or unexpected safety signal identified during the review of the safety database submitted in support of belimumab SC.

10 Individual Study Reviews

10.1 Study Report for Study 200339

Title: An Open-Label Single Arm Study to Evaluate the Reliability of an Autoinjector that Administers Belimumab Subcutaneously in Subjects with Systemic Lupus (SLE) Erythematosus (SLE)

Dates Conducted: This trial was started on May 20, 2014 and completed on April 13, 2015.

Study Sites: A total of 27 centers in the U.S.

Objectives:

Primary Objective:

- Evaluate the suitability of the autoinjector (AI) for self-administration of belimumab by subjects with SLE

Secondary Objective:

- Evaluate the use of the AI inside the clinic setting
- Evaluate the use of the AI outside the clinic setting

Other Objectives:

- Assess any injection failures related to use of device performance
- Assess the safety and tolerability of belimumab administered via the AI
- Determine the change in belimumab trough concentrations when switching from IV to SC administration

Overall Design:

This was to have been an open-label, multicenter, single-arm, multi-dose study to assess the suitability (including usability and robustness) of the AI for self-administration of 200 mg of belimumab subcutaneously (SC) once weekly for 8 weeks in 95 subjects with SLE. In order to be eligible to participate in this trial, potential study subjects were required to have received treatment with IV belimumab and/or completed the open-label portion of the phase 3 study C1115 that evaluated the SC formulation via prefilled syringe (PFS). All subjects were to have been trained by study site personnel at Screening and Day 0 to self-administer belimumab SC into the thigh or abdomen using the AI. The training they were to have received at these study visits was to have been representative of the instruction and training materials that will be used in the post-marketing setting and were to have included a walk-through of the instructions for use for the AI and filling out the study diaries. All subjects were additionally required to perform a supervised practice injection using a practice device and injecting into a practice pad at these training sessions. Four of the eight weekly doses were to have been administered under observation in the clinic while the remaining four doses were to have been administered outside the clinic without observation. Subjects were to have

reported on the success of the injection and recorded their experience with the device (including information regarding device performance) by completing a patient diary after each injection while study personnel were to have recorded observations regarding the injections completed at the study clinic. All subject diary entries were to have been reviewed by study personnel who were also required to complete an Interview Guide for each self-administered injection performed outside of clinic. In order to permit root-cause investigation and overall assessment of device usability and reliability, both diary and Interview Guide entries for unsuccessful injections were to have included a description of the error that occurred. For the purposes of this study, a self-administered injection was considered successful if the following 3 criteria had been achieved: use of the correct injection site (abdomen or thigh); proper actuation of the device while on the injection site (i.e., gold needle guard flush with injection site and fully depressed to start injection); and device held in place on the injection site until the full dose is delivered (i.e., until the purple indicator has stopped moving at the bottom of the viewing window).

Upon completion of the eight SC doses via the AI, subjects were to have resumed or initiated treatment with IV belimumab within a 2-3 week target window after the last dose of belimumab SC for the administration of the first dose of IV belimumab. The protocol mandated that subjects who completed the 8 doses of belimumab SC and were either resuming or initiating treatment with IV belimumab had to return for an Exit Visit between Weeks 10 and 12. Subjects who were not resuming or initiating treatment with IV belimumab were to have been scheduled to return for an Exit Visit at Week 12.

Study Entry Criteria: The entry criteria for this study were similar to those of study C1116 except subjects were also required to have been on a SLE treatment regimen that included IV belimumab every 28 days for at least three 28-day cycles or completed the open-label portion of the phase 3 study C1115 that evaluated the SC formulation via prefilled syringe (PFS).

Treatment: This study utilized the PFS presentation of the liquid formulation of belimumab for subcutaneous administration (200 mg/mL) contained in a single use, disposable AI designed for automatic delivery of the drug via a powered spring mechanism. (Refer to the preceding Section 2.1 for additional information regarding the liquid formulation of belimumab for SC administration.) The AIs used in this study were to have been stored at 2-8°C and protected from light. Practice AIs used in this study were for demonstration and training purposes only and were not used to administer treatment.

Concomitant Medications: The protocol permitted study subjects to continue their concomitant SLE treatment regimens with the exception IV belimumab. The same prohibitions regarding the use of concomitant medications utilized in study C1115 were applied in this trial.

Study Procedures: The following Table 77 and Table 78 are tabular flow charts of the scheduled study visits as well as protocol specified procedures and evaluations to have been performed over the course of this 8 week study.

Table 77 – Schedule of Events and Procedures for Study 200339

	Screening Day-35 to -1	Day 0 (Week 1)	Week 2 ± 1 day	Week 3	Week 4 ± 1 day	Week 5	Week 6	Week 7	Week 8 ± 1 day	Week 12 Exit Visit/ Early Withdrawal ^f	Follow-up (16-weeks post last SC dose) ^{h,i}
Procedures Visit number	V1	V2	V3		V4				V5	V6	V7
Informed consent	X										
Demographics	X										
Medical history	X										
Inclusion/Exclusion criteria	X										
Training session ^a	X	X ^a									
SC belimumab administration in clinic		X	X		X				X		
SC belimumab administration outside of clinic ^a				X		X	X	X			
Laboratory:											
Pregnancy test ^b	S	U ^a			U				U	U	U
Hematology/Chemistry ^c	X	X ^a			X ^a				X ^a	X	
Serum immunoglobulin (IgA, IgM, IgG)	X	X			X				X	X	
Hepatitis B and C serology and HIV	X										
Drug and alcohol screen	X	X									
Urinalysis ^c	X	X ^a			X ^a				X ^a	X	
Anti-dsDNA/ANA	X										
PK		X ^a	X ^a		X ^a				X ^a		
Immunogenicity ^d		X ^a							X ^a	X	
ALT, AST, Total bilirubin											X ⁱ
Physical/Clinical:											
Vital signs ^e	X	X ^{a,k}	X ^{a,k}		X ^a				X ^a	X	
12-lead ECG	X										
Physical examination	X	X ^{a,l}			X ^a				X ^a	X	
Weight	X	X ^a			X				X	X	
Dispense patient diary and study drug for self-administration outside of clinic			X		X						
Return patient diary and study drug for self-administration outside of clinic					X				X	X ^m	
Complete patient diary including pain		X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a		

Source: Sponsor's Table 3; p. 37 study protocol

Table 78 – Schedule of Events and Procedures for Study 200339 (cont.)

	Screening Day-35 to -1	Day 0 (Week 1)	Week 2 ± 1 day	Week 3	Week 4 ± 1 day	Week 5	Week 6	Week 7	Week 8 ± 1 day	Week 12 Exit Visit/ Early Withdrawal ^f	Follow-up (16-weeks post last SC dose) ^{h,i}
Procedures Visit number	V1	V2	V3		V4				V5	V6	V7
assessment											
Autoinjector use assessment		X	X	X	X	X	X	X	X		
Record AEs and concomitant meds	X ^a	X	X ^a		X ^a				X ^a	X	

a. Dosing should be weekly ± 1 day. Subjects will be instructed to contact clinical study staff if they have concerns or questions regarding self-administration. They will have the option of returning to the clinical site for further training or assistance with self-administration. Requirement for additional training or assistance will be documented.
b. S = Serum; U = urine. Serum pregnancy test is required at Screening. The pregnancy test (urine) result on Day 0, Week 4, and Week 8 must be available prior to dosing and must be negative for the subject to receive belimumab.
c. Refer to Section 6.5.3 of the protocol for a listing of laboratory assessments to be completed.
d. If a subject discontinues and IV dosing will be resumed prior to Week 8, every attempt should be made to collect an immunogenicity sample prior to the infusion on the day that IV dosing is restarted.
e. Vital signs include temperature, sitting blood pressure, respiratory rate and pulse.
f. If the subject completes all 8 SC doses per protocol and is resuming treatment with IV belimumab, the last visit must not be before Week 10 but can be before Week 12. At the last visit for these subjects, Week 12 assessments, including labs and recording of AEs, will be performed prior to receipt of the IV belimumab infusion. If the subject does not resume treatment with IV belimumab before Week 12, the last visit will be Week 12.
g. The Exit Visit will occur at the time of discontinuation for any subject who withdraws prior to Week 12 (for instructions for treatment after last SC dose, see Section 5.11).
h. Perform prior to belimumab administration.
i. A home pregnancy test will be provided to female subjects of childbearing potential. These subjects will be contacted by phone approximately 16 weeks after the last dose of SC belimumab to obtain the results of the test. SAEs will not be actively solicited, but SAE(s) reported by the subject during this call will be reported to the Drug Safety designee on the SAE worksheet.
j. A follow-up visit to collect ALT, AST, and Total bilirubin 16 weeks post-dose is required for any subject who does not resume IV belimumab and whose last dose of belimumab was an SC dose.
k. Perform at 3 hours post belimumab administration.
l. A symptom-driven physical examination will be performed.
m. For any subject who withdraws prior to Week 12, patient diary and study drug for self-administration outside of clinic will be returned at this visit.
n. Pain at the injection site will be assessed using a visual analog scale immediately after injection, 1 hour after injection and 24 hours (± 4 hours) after injection and recorded.
o. Any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All other AEs/SAEs are recorded from the start of study treatment through 4 weeks following administration of the last dose of belimumab (Week 12/Exit visit).
p. Injection site reactions (e.g., induration, erythema, edema, rash, pruritus) are to be recorded on the AE CRF.

Source: Sponsor's Table 3; p. 38 study protocol

Outcome Measures:

Primary efficacy Endpoint:

- The proportion of subjects successfully able to self-administer their observed first and second doses in Weeks 1 and 2

Secondary Efficacy Endpoints:

- Proportion of subjects successfully able to self-administer their observed their doses inside the clinic at Weeks 4 and 8
- Proportion of subjects who report they were successfully able to self-administer their doses outside the clinic setting in Weeks 3, 5, 6, and 7.

Additional efficacy endpoints included: root-cause analysis and evaluation of each unsuccessful injection related to either use-error or device performance.

Statistical Analysis: Data from this study was to have been analyzed via descriptive statistics.

Study Conduct: There was one amendment to the protocol on February 18, 2014 that resulted in the following major protocol changes: the eligibility criteria were change to permit the enrollment of subjects who had completed the open-label portion of the phase 3 belimumab SC study C1115, and a revision in the sample size assumptions.

RESULTS:

A total of 95 subjects were enrolled into this trial, out of which 91 (96%) subjects completed the study. Of the 4 (4%) subjects who prematurely withdrew from the trial, 3 (3%) subjects withdrew due to an adverse event while the remaining 1 subject (1%) was lost to follow-up. Baseline demographics were generally comparable to those of study C1115. The study population was overwhelmingly white (73%) and female (93%). Mean age was 44.8 years and mean BMI was 31.4 kg/m². Ninety-eight percent (98%) of subjects had previously received treatment with IV belimumab while the remaining 2% had previously received treatment with belimumab SC prior to enrolling in the study. The most common concomitant medications used by subjects in this study were hydroxychloroquine (63%), prednisone (41%), and vitamin D (23%).

Efficacy:

A total of 90 subjects were able to successfully self-administer the first two study injections under observation. This included 5 subjects who required assistance for successful second attempts with their injections at Week 1 but who were subsequently able to administer all remaining injections inside and outside of the clinic without assistance. As a result, a high proportion (89/90; 90%) of subjects in this study met the primary efficacy endpoint of being successfully able to self-administer their observed first and second doses of belimumab 200 mg SC using the AI at Weeks 1 and 2. A high proportion of subjects were also able to successfully self-administer their observed dose of belimumab 200 mg SC via AI at Weeks 4 and 8 (85/87; 98%) as well as outside the clinic setting at Weeks 3, 5, 6, and 7 (81/87; 93%), thus meeting both of the study's secondary efficacy endpoints. Overall, 98% (720/736) of the attempted injections during

the study were successful. A total of 9 subjects had unsuccessful injections (inside clinic = 3 subjects versus outside clinic = 6 subjects). A root cause analysis of the 16 injections reported to be unsuccessful or incomplete revealed 14 (4 from a single subject) were associated with use errors, 13 of which were concluded to be related to not holding the AI in place until the injection was completed. These use errors were not repeated by any subject with the exception of 1 subject, suggesting that the subjects self-corrected and there are no chronic usability issues with the AI. Based on this analysis, the reported use errors in this study were attributed to initial inexperience of the user with the device. Additional data regarding usability of the AI was provided by qualitative feedback from subjects regarding the handling and ergonomics of the device. Favorable ratings $\geq 97\%$ were given to operations related to cap removal, hand-held comfort, and injection time, however, the ability to press the AI down to activate at the first attempted injection received a lower rating of 89% which improved to 99% with subsequent injections. Since the root cause analysis of the remaining 2 unsuccessful/incomplete injections resulted in one malfunction being substantiated as an actual device error (defective syringe component on examination of returned device), the AI received an overall functional performance rating of 99.9% in this study.

Safety:

Overall, 39 (41%) of the subjects in this study experienced ≥ 1 adverse events (AEs). The proportions and patterns of AEs were similar to those observed in other belimumab studies with the highest rates of AEs occurring in the infections and infestations (19%), musculoskeletal and connective tissue (13%), and general disorders and administration site conditions (11%) system organ classes (SOCs). The most commonly reported AEs in this study were nausea (6%), arthralgia (4%), bronchitis (3%), sinusitis (3%) and diarrhea (3%). There were 3 subjects who discontinued study medication due to AEs that included postoperative abscess (1 subject), nausea and vomiting with pyrexia (1 subject) and herpes zoster (1 subject). No deaths occurred during this study and the overall rate of treatment-emergent serious AEs (SAEs) was low (4%) and included pneumonia with pyrexia, neutropenia, and anemia (1 case); postoperative abscess (1 case), pulmonary embolism (1 case) and deep venous thrombosis (1 case). In terms of AEs of special interest (AESI), no malignancies or cases of depression/suicidality/self-injury were reported over the course of the study. Explorations for hypersensitivity spectrum reactions including anaphylaxis and injection site reactions revealed a total of 4 subjects (4%) who reported injection site reactions, the majority of which occurred post abdominal injection and included erythema, pruritus, and rash at the injection site. Injection site pain was low overall, and most subjects considered it to be acceptable. Review of the lab safety data collected over the course of the study did not reveal any new or unexpected safety signals. The results from immunogenicity testing for this trial were also negative.

PK Results:

The median belimumab serum concentration at Week 8 was 113 $\mu\text{g/mL}$ suggesting the average steady-state exposure for 200 mg of belimumab administered SC once weekly

via AI was similar to the C_{avg} of 110 µg/mL for 10 mg/kg belimumab IV every 4 weeks. Overall, steady state levels of belimumab were observed following the third weekly dose in this study. Subjects with IV to SC switching time intervals of 2-4 weeks had Week 1 concentrations of belimumab close to their steady-state concentration. Subjects with switching time intervals less than 2 weeks had Week 1 belimumab concentration between their IV C_{max} and eventual SC steady-state concentration.

Conclusions: The overall high rate (98%) of successful injections with the belimumab autoinjector support the device's usability and reliability in terms of function and performance when used for self-administration of belimumab via the subcutaneous route. Demonstration that the majority of subjects who required assistance or misused the device were also able to learn how to correctly use it provided additional support for this device. At the dose (200 mg) and dosing regimen (subcutaneous injection into the thigh or abdomen once weekly) evaluated in this trial, treatment with the belimumab autoinjector appeared to be safe and well tolerated with no new or unexpected safety signals observed. Pharmacokinetic data generated from this study also support a 1-4 week switching interval between the intravenous and subcutaneous routes of administration of belimumab.

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/s/

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