CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/BLA #	BLA 761043
Drug Name:	Benlysta (b) (4) Belimumab (SC administration)
Indication(s):	Systemic Lupus Erythematosus (SLE)
Applicant:	GlaxoSmithKline LLC
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BLA Review, Subgroup Analysis, Logistic Regression, Odds Ratio, Adverse Events, Sensitivity Analysis.

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1 EXECUTIVE SUMMARY

GlaxoSmithKline (GSK) has submitted a BLA for the approval of a new subcutaneous (SC) formulation of belimumab (fixed dose 200 mg weekly) for patients with SLE. The SC formulation aims to provide a convenient option for SLE patients. The program consists of a Phase 3 trial investigating belimumab SC (BEL112341) and two supporting studies using belimumab IV (BEL110751, BEL110752). The two IV studies were previously reviewed as part of the original BLA for the IV formulation of belimumab. The applicant also submitted the details of five supportive studies to evaluate safety, bioavailability, PK, quality and tolerability.

BEL112341 was a randomized, multicenter, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab administered via SC injection in adult subjects with active SLE. Data from the study adequately demonstrated that the proportion of patients who obtained an SRI response at Week 52 was significantly greater for the belimumab 200 mg group (61.37%) compared to the placebo group (48.39%), with an odds ratio of 1.675 (95% CI: 1.245, 2.254; p-value: 0.0006). The results from the analyses of the subcomponents of the SRI were generally consistent with those of the primary analysis.

Analysis of the secondary endpoint, time to first severe SLE flare, showed a significant improvement for the patients in the belimumab group over the placebo group. However, the difference in the average prednisone dose reduction between the two groups was not statistically significant (p-value: 0.0732). Subgroup analyses found no meaningful difference across gender, race, age group, and baseline disease characteristics.

FDA generally requires evidence of effectiveness from at least two Phase 3 clinical studies to support new drug approval. However, in the current submission, evidence from the single SC study is persuasive, and the two previous IV studies can be considered to provide supportive evidence of effectiveness. These studies demonstrated drug effectiveness and were reviewed under the application, BLA 125370. Thus, the overall package provides substantial evidence of efficacy for the proposed SC administration of belimumab (fixed dose 200 mg weekly) for the treatment of SLE.

2 INTRODUCTION

2.1 Overview

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disorder characterized by abnormal B cell activation and differentiation. SLE is more prevalent in women (~90% of patients) with childbearing potential. Major symptoms of SLE are; skin rashes, discoid lesions, arthritis/arthralgia, nephritis, cardiac and pulmonary disease. Standard therapies for SLE include corticosteroids, anti-malarial agents, non-steroidal anti-inflammatory drugs (NSAIDs), cytotoxic agents and immunosuppressive agents.

Belimumab is a human monoclonal antibody that inhibits B-lymphocyte stimulator (BLyS) and thereby inhibits survival of B cells. In 2011, FDA approved Benlysta, the intravenous (IV) formulation of belimumab, for the treatment of SLE.

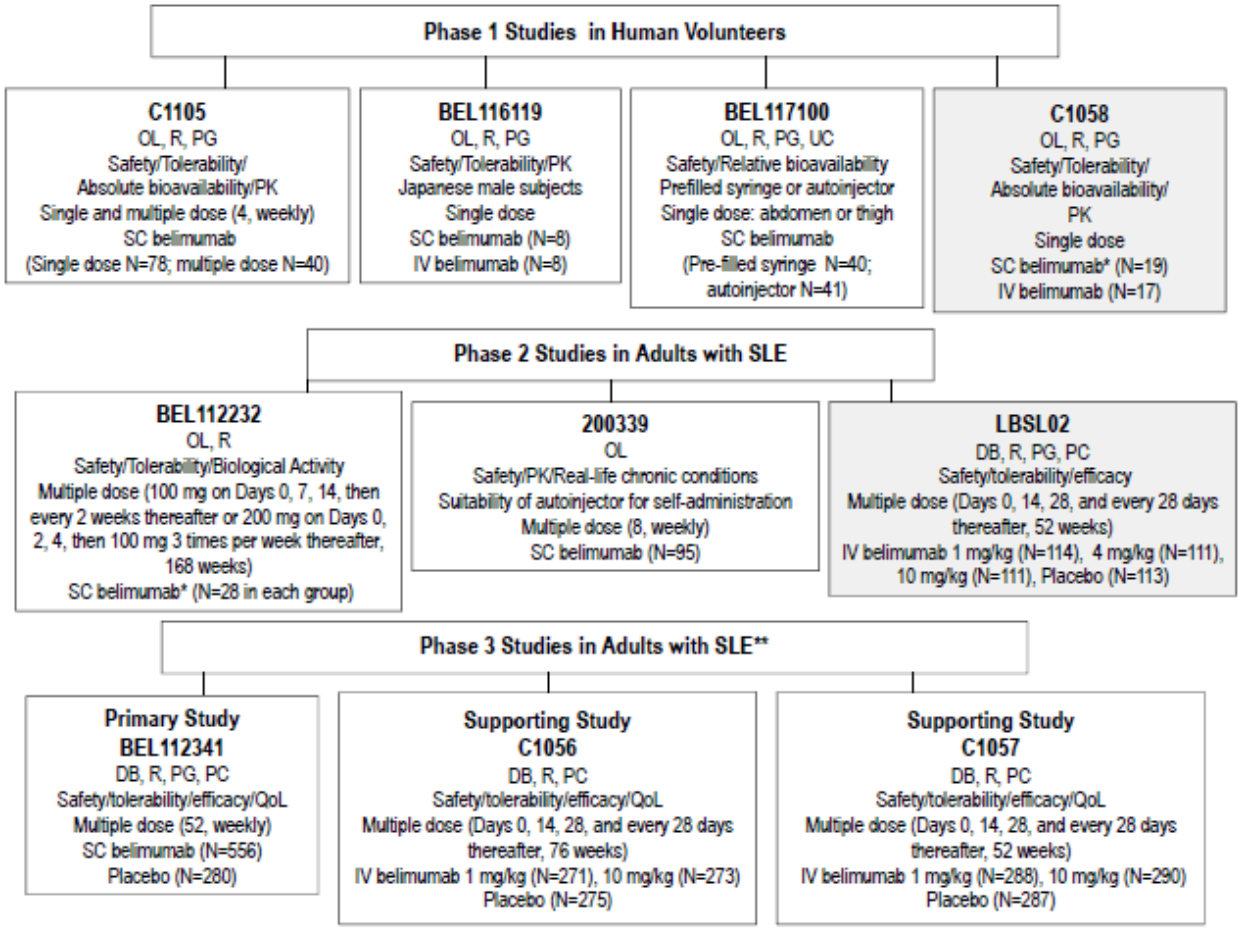
In this submission for the approval of the subcutaneous (SC) administration of belimumab, the pivotal study is referred to as BEL112341. This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab administered subcutaneously to subjects with SLE. There were 839 randomized subjects in the study.

2.2 History of Drug Development

The approval of IV administration of belimumab was based on two pivotal IV Phase 3 studies (C1056 and C1057) completed in 2009. In these Phase 3 IV studies, belimumab 10 mg/kg demonstrated superiority over placebo plus standard of care. On March 9, 2011, FDA approved the IV formulation of belimumab for the treatment of adult patients with active, autoantibody-positive SLE who are receiving standard therapy.

The clinical program of belimumab SC consisted of several studies conducted in various phases of the drug development. There were four Phase 1 studies in human volunteers (C1105, BEL116119, BEL117100, C1058), and three Phase 2 studies in adults with SLE (BEL112232, 200339, LBSL02).

Figure 1: Clinical Studies overview



Source: Applicant

Relevant Correspondence with Applicant: On 02 December 2004, FDA agreed with the applicant's proposed comparability study design for Phase 2 vs Phase 3 bulk drug substance and drug product. Later, in the pre-Phase 3 meeting on 07 July 2011, FDA confirmed that a Phase 3 pivotal efficacy and safety study in ~816 patients was adequate, if positive, to support a BLA. The following is an excerpt from the meeting minutes:

> *According to your meeting package, you are proposing to conduct a Phase 3, 52-week, multicenter, international, randomized, double-blind, placebo-controlled trial in approximately 816 patients with active, seropositive SLE to assess the efficacy and safety of belimumab when administered as a SC injection. Overall, the proposed study design is similar to that of the\ pivotal Phase 3 trials reviewed in support of the IV administration of belimumab in this population with notable changes to the trial's entry criteria (baseline SELENA SLEDAI score >8 and exclusion of subjects*

with history of suicidal behavior), randomization (2:1 randomization to active treatment vs. placebo stratified for SELENA SLEDAI score [8-9 vs. > 10], baseline complement [low C3 or C4 vs. other] and race [black vs. other], and the non-prohibited use of statins and ACE inhibitors/ARBs that are based on the results from the pivotal studies.

We agree in principle that positive results from your proposed study should be adequate to support the filing of a sBLA for the new formulation of belimumab delivered via pre-filled syringe. However, we have a number of concerns related to the design of the proposed study. We question the clinical appropriateness of conducting a placebo-controlled trial in patients with active SLE now that there is an approved product for this disease. In view of this potential ethical issue, provide a rationale for conducting a placebo-controlled study in this population. The second concern is based on your projected regional enrollments of patients for this international Phase 3 study. The generalizability of the proposed study's data as it relates to demographic subgroups (e.g., black patients with SLE) will be a review issue.

These issues were clarified in follow-up correspondence with FDA and there was agreement that the Phase 3 study would be placebo controlled without inclusion of an IV comparator.

In the pre-BLA meeting held on 08 September 2015, FDA agreed with the applicant's proposal on content, analysis approach, and data presentation, and submission of data analysis programs and macros. Moreover, FDA responded that the applicant's proposed analyses for flare rate assume that censored data are missing-at-random, a strong and unverifiable assumption, and that supportive tipping point analyses should be conducted to address the impact of missing flare rate data after censoring. FDA agreed that unadjusted tipping point analyses would be acceptable.

Phase 3 Studies: Among the three studies in Phase 3, BEL112341 was the pivotal study which evaluated the efficacy, safety and tolerability of belimumab SC compared to placebo. BEL112341 was a multi-center, international, double-blind, placebo-controlled, 52 week study in 839 randomized SLE patients who were receiving standard therapy. There were two supporting studies (C1056 and C1057) previously conducted in adults with active, autoantibody positive SLE to evaluate the safety and efficacy of belimumab IV compared to placebo. These studies were reviewed under the application, BLA 125370. For additional details on the design and efficacy results, we refer to the statistical review by Ruthanna C. Davi submitted on December 9, 2010. The following table (Table 1) summarizes various studies included in this application.

Table 1: List of all studies included in this application

Trial ID	Phase	Treatment Period	Follow-up Period	# of Subjects	Study Population
BEL112341	Phase 3	52 Weeks	6 months	RND = 839 TRT = 836	Adults with SLE
C1056	Phase 3	76 Weeks	8 Weeks	RND = 826 TRT = 819	Adults with SLE
C1057	Phase 3	52 Weeks	4 Weeks	RND = 867 TRT = 865	Adults with SLE
BEL 112232	Phase 2	24 Week	-	RND = 56 TRT = 56	Adults with SLE
200339	Phase 2	8 Weeks	-	RND = 95 TRT = 91	Adults with SLE
LBSL02	Phase2	52 Weeks	24 Weeks	RND = 475 TRT = 449	Adults with SLE
C1105	Phase 1	70 Days	-	Single Dose: RND = 78, TRT = 74 Double Dose: RND = 40, TRT = 32	Healthy Subjects
BEL1161119	Phase 1	71 Days	-	RND = 16 TRT = 16	Healthy Subjects
BEL117100	Phase 1	-	-	RND = 81 TRT = 79	Healthy Subjects

Source: Applicant | RND- Randomized, TRT- Treated

2.3 Specific Studies Reviewed

This review focuses on the Phase 3 study, BEL112341. The applicant has submitted statistical analyses and a study report to demonstrate the efficacy and safety of belimumab SC in adults with active SLE.

2.4 Data Sources

The applicant submitted the BLA 761043 electronically on September 22, 2016. The application includes protocols, statistical analysis plans, study reports, and all referenced literature. The data and final study report for the electronic submission were archived under the network path location \\CDSESUB1\evsprod\BLA761043\761043.enx

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data submitted by the sponsor has sufficient quality for review, and I was able to replicate the primary and major secondary analyses from the analysis data model (ADaM) datasets. The

applicant provided adequate documentation for the datasets and the analysis methods were explained in the statistical analysis plan.

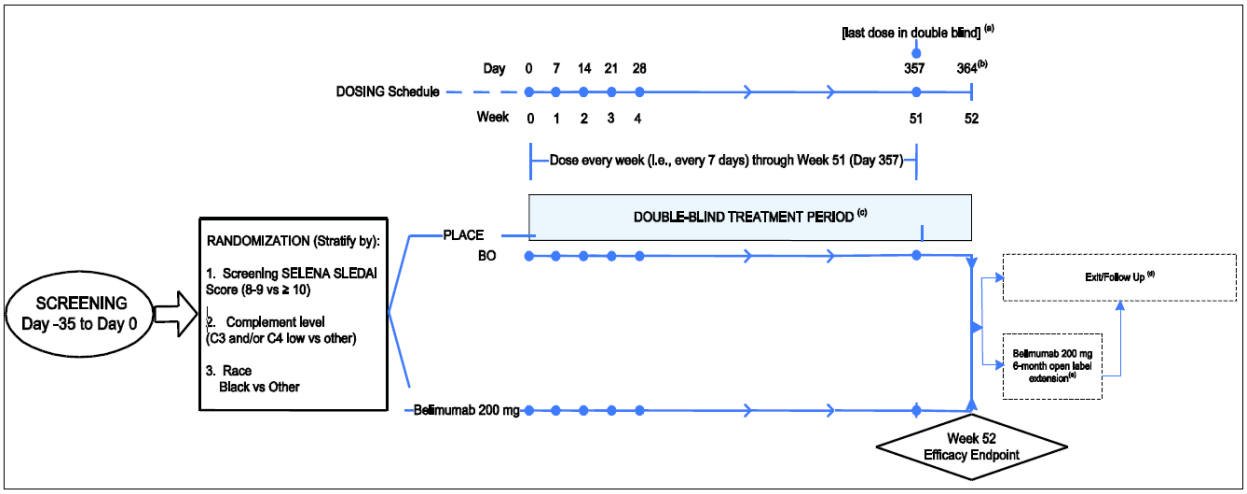
3.2 Evaluation of Efficacy

The efficacy and safety of belimumab SC was evaluated in a single study BEL112341. This was a Phase 3, randomized, parallel group, double-blind study to evaluate the efficacy and safety of 200 mg belimumab administered SC weekly, and compared with placebo over a 52-week treatment period in subjects with active SLE (defined by a Safety of Estrogen in Lupus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA SLEDAI) score ≥8).

3.2.1 Study Design and Endpoints

BEL112341 was a randomized, multicenter, double-blind, placebo-controlled, 52-week study with 839 randomized subjects conducted at 177 centers in 30 countries in North America, Central America, South America, Western Europe, Eastern Europe, and Asia. There were 836 subjects randomized in 2:1 ratio- 556 in the belimumab 200 mg SC group and 280 in the placebo group. Randomization was stratified by patients' screening SELENA SLEDAI score (8-9 vs. ≥10), complement level (C3 and/or C4 low vs. other), and race (Black vs. Other). The study agent was administered every week from Week 0 through Week 51. Subjects who completed the 52-week, double-blind phase entered into an open-label extension phase where they received belimumab 200 mg SC weekly.

Figure 2: Study Schematic



Source: Applicant

The objectives of the study were:

- To evaluate the efficacy of belimumab administered SC in adult subjects with SLE
- To evaluate the safety and tolerability of belimumab administered SC in adult subjects with SLE.

The primary endpoint of the study was the SRI response at Week 52, defined as

- ≥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 at the time of assessment (Week 52).

SELENA SLEDAI was a cumulative index with 24 items assessing 9 organs/systems to measure disease activity in SLE patients. It captured the subject's condition over the 10 days prior to the visit. Physician's Global Disease Assessment (PGA) scale ranged from 0 to 3, with 0 representing no disease activity, 1 representing mild disease activity, 2 representing moderate disease activity and 3 representing the most severe lupus disease imaginable. British Isles Lupus Assessment Group (BILAG) index was a clinical measure of lupus disease activity based upon the physician's intention to treat. These three components of the primary efficacy endpoint were analyzed separately to support the primary analysis.

There were two major secondary endpoints in the study:

1. *Time to first severe flare over 52 Weeks:* Severe flare was defined based on the Modified SELENA SLEDAI SLE flare index.. Severe fares that were triggered only by an increase in SELENA SLEDAI score to >12 were excluded in the analysis. Only post-baseline severe flares were considered in these analyses.
2. *Percent of subjects with average prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during week 40 through week 52:* A responder was defined as a subject who experienced an average prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52. Subjects who used prednisone > 7.5 mg/day at baseline were included in the analysis.

The applicant included several additional endpoints related to disease activity, flares, organ-specific measures, and prednisone use in the study. A patient-reported outcome measure, the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score was evaluated in the study (b) (4). The FACIT-Fatigue score is obtained from a questionnaire about patients' fatigue. It contains 13 items with values ranging from 0 to 4 (0 represents "Not at all" and 4 represents "Very much"). Higher item

values indicate greater severity in 11 items and the reverse is true for the other two items. All the test scores except these two measures were reversed to compute the total FACIT-F score.

3.2.2 Sample Size Calculation

The applicant targeted a sample size of at least 816 subjects (544 in belimumab group and 272 in placebo group) which would provide at least 90% power at a two-sided 5% level of significance to detect a minimum of 12% absolute improvement in the response rate for the belimumab group relative to the placebo group at Week 52.

3.2.3 Statistical Methodologies

The intent-to-treat (ITT) population was defined as all subjects who were randomized and treated with at least one dose of study treatment and the Per Protocol population contained all subjects who were randomized and treated with at least one dose of study treatment excluding subjects with major protocol deviations. A total of 836 subjects were included in the intent-to-treat set with 556 subjects in the belimumab group and 280 subjects in the placebo group. The per-protocol group contained 789 subjects of whom 677 subjects completed all 52 weeks of the planned double-blind treatment period. Subjects were assigned to treatment groups according to the actual treatment administered to the subject; all patients received their assigned treatment in the study.

The key efficacy analyses were carried out in the ITT population. A logistic regression model was used to estimate the odds of a response for belimumab vs. placebo for binary efficacy endpoints, including the primary endpoint, and for each component of the primary endpoint. The independent variables in the model included 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). For the analysis of the PGA component, baseline PGA score was also included as a covariate in the model. For the analysis of the BILAG component, baseline BILAG organ domain involvement (at least 1A/2B vs. at most 1B) was included as a covariate in the model.

A Cox proportional hazards model was used for the analysis of time to first flare, adjusting for baseline SELENA SLEDAI score, baseline complement levels, and race. The SFI flare endpoint was defined as the number of days from treatment start date until the subject experienced the severe flare event (event date – treatment start date +1). If a subject withdrew from the study or completed the study up to Week 52 without a severe SFI flare, time to the first severe SFI flare was censored at the time of the last observation in the time period being analyzed. If a subject received a protocol-prohibited medication meeting treatment failure criteria, the subject was considered as having a severe flare at the time the medication was started.

A logistic regression model was used to analyse the average prednisone reduction endpoint. In these analyses, 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) were used as covariates. Subjects who withdrew from the study prior to the Week 52 visit and/or received a dose of protocol prohibited/restricted medication that resulted in a treatment failure designation prior to the Week 52 visit were considered as non-responders for this analysis.

Treatment comparisons for FACIT-Fatigue score were performed using an ANCOVA model with treatment group, baseline FACIT-Fatigue Scale score, baseline SELENA SLEDAI score ($\leq$ 9 vs. $\geq$ 10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (black vs. other) as covariates. Last observation carried forward (LOCF) was used for missing data.

In the primary efficacy analysis and the analyses of the components of the primary endpoint, subjects who started prohibited medications or therapies at any time during the study were considered treatment failures for analysis. Subjects who dropped out of the study or were classified as treatment failures were considered as non-responders. The applicant also used the following methods to handle the different data scenarios at Week 52:

- If a subject had at least 1 visit within ±28 days of Day 364 visit, the data from the visit closest to Day 364 was used for the Week 52 primary efficacy analysis.
- If a subject had 2 visits with equal distance within ±28 days of Day 364 visit, the data from the visit prior to Day 364 was used for the Week 52 primary efficacy analysis.
- If a subject had a visit within the required window, but partial data of the primary efficacy endpoint were missing (including individual items of any component of the primary endpoint), LOCF was used for the missing item or component, i.e., the last observed value for that item at a previous visit was carried forward.

The applicant conducted sensitivity analyses using different analyses such as a logistic regression analyses without adjustment for covariates, an analysis with LOCF for missing data, and analyses restricted to completers and to the per-protocol population. However, none of these sensitivity analyses comprehensively evaluate the potential effect of missing data on the reliability of the efficacy results. Consequently, we recommended the inclusion of tipping point analyses that vary assumptions about the missing outcomes on the two treatment arms. The tipping point approach was a method that estimates the treatment effect under varying assumptions about the outcomes of the dropouts in each treatment group. The analysis was two-dimensional, which allowed assumptions about the missing outcomes on the two arms to vary independently, and included scenarios where dropouts on belimumab had worse outcomes than dropouts on control.

3.2.4 Multiple Comparisons and Multiplicity

To control the overall type-1 error rate, a step-down sequential testing procedure was used in the analysis of primary and major secondary endpoints. The endpoints were evaluated for statistical significance (2-sided alpha=0.05) based on the following pre-specified sequence: (1) SRI response rate at Week 52, (2) time to first severe SLE flare, and (3) percent of subjects with average prednisone dose that has been reduced by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52.

Efficacy endpoints other than the primary and major secondary endpoints were not included in the multiple testing hierarchy. All reported p-values were 2-sided and all reported confidence intervals were at the 95% level.

3.2.5 Patient Disposition, Demographic and Baseline Characteristics

The applicant screened a total of 1427 subjects to obtain 839 randomized subjects, of whom 836 subjects received at least 1 dose of study agent. The subjects enrolled in the study were randomized in a 2:1 ratio to belimumab or placebo, stratified by their screening SELENA SLEDAI score, complement level, and race. There were 237 (28%) subjects from the United States.

From the baseline patient characteristics given in the table below (Table 2), the two treatment arms were generally comparable and had similar patient profiles. Patients in the placebo group were slightly older than in the belimumab group. As SLE is more prevalent in females of child bearing potential, the majority of the study population was female (94.38%) and of age younger than 45 years (71.29%). Around 60% of patients were whites. There were no large imbalances in demographic and disease characteristics between the two study groups.

Table 2: Subject Demographics

	Placebo N=280		Belimumab 200 mg N=556		Total N=836	
Age	39.57	12.61	38.10	12.10	38.59	12.29
Age group						
<=45 years	193	68.93	403	72.48	596	71.29
>45 to <65 years	80	28.57	141	25.36	221	26.44
>=65 to <75 years	7	2.5	11	1.98	18	2.15
>=75 years	0	0	1	0.18	1	0.12
Sex						
Female	268	95.71	521	93.71	789	94.38
Male	12	4.29	35	6.29	47	5.62
Race						
White	166	59.29	335	60.25	501	59.93
American Indian	18	6.43	39	7.01	57	6.82
Asian	63	22.5	119	21.4	182	21.77
African American	30	10.71	55	9.89	85	10.17
Multiple	3	1.07	6	1.08	9	1.08
Native Hawaiian or Other Pacific Islander	0	0	2	0.36	2	0.24

Source: Reviewer
Cell contents are mean and standard deviation for Age and frequency and percent for other characteristics

The disposition of subjects in the study was slightly imbalanced across the two study arms, with higher patient dropout in the placebo arm than the belimumab arm (Table 3). Up to Week 52, 159 (19.0%) patients had withdrawn from the study: 93 (16.7%) patients from belimumab and 66 (23.6%) patients from placebo. Adverse events and subject request were the major reasons for withdrawal from the study. Withdrawal from the study due to adverse events was similar in the two study arms. However, a greater proportion of patients in the placebo arm withdrew from the study by subject request (5.36% vs. 2.16%).

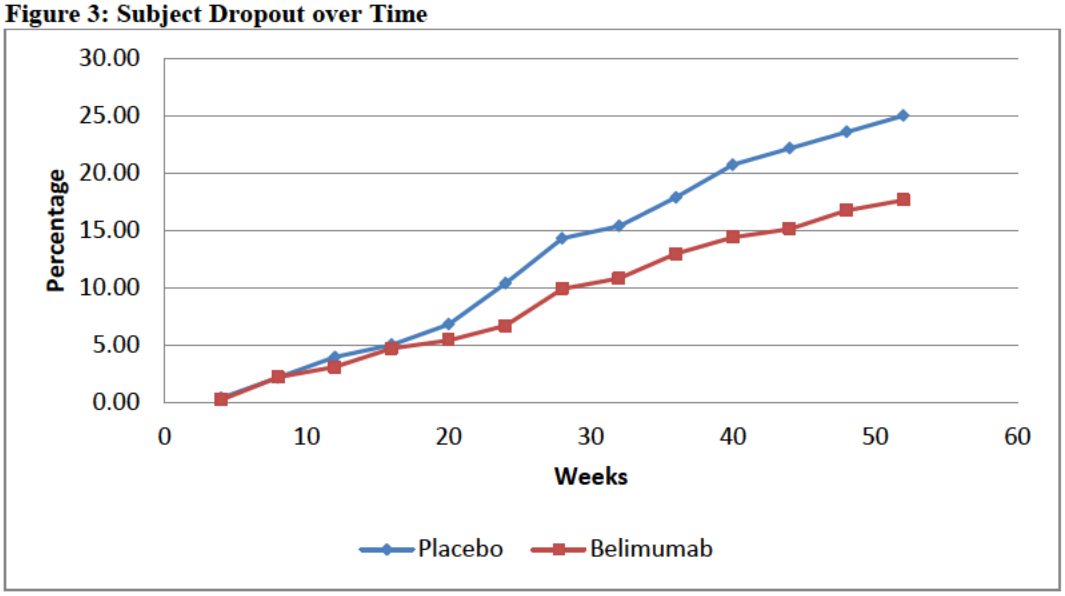
Table 3: Subject Disposition

	Actual Treatment				Total (N=836)	
	Placebo (N=280)		Belimumab 200 mg (N=556)			
	N	%	N	%	N	%
Completed Week 52 visit	214	76.43	463	83.27	677	121.76
Withdrawn prior to Week 52	66	23.57	93	16.73	159	19.02
Adverse Event	25	8.93	40	7.19	65	7.78
Disease Progression/Lack of Efficacy	10	3.57	15	2.70	25	2.99
Investigator Decision	5	1.79	1	0.18	6	0.72
Lack of Compliance	2	0.71	1	0.18	3	0.36
Lost to Follow-up	2	0.71	6	1.08	8	0.96
Other	4	1.43	14	2.52	18	2.15
Protocol Violation	3	1.07	4	0.72	7	0.84
Subject Request	15	5.36	12	2.16	27	3.23

Source: Reviewer

The following figure (Figure 3) shows the proportion of subjects withdrawing from the study over time. Withdrawal in the belimumab group was less than the placebo group and the difference in the proportions withdrawing increased over time.

Figure 3: Subject Dropout over Time



Source: Reviewer

3.2.6 Results and Conclusions

3.2.6.1 Primary Efficacy Analysis

All primary efficacy analyses were conducted using the statistical procedures specified in the Reporting and Analysis Plan. Results for the primary endpoint, SRI response at Week 52, show that the belimumab group had a statistically significant higher response rate than the placebo group (Table 4). In particular, the proportion of patients who obtained an SRI response at Week 52 was 61.37% in the belimumab 200 mg group as compared to 48.39% in the placebo group, with an odds ratio comparing belimumab to placebo of 1.675 (95% CI: 1.245, 2.254; p-value=0.0006).

Table 4: SRI Response at Week 52

Treatment Arm	Response n/n (%)	Observed Difference	Odds ratio (95% CI)	p-value
Placebo (N=280)	135/279 (48.39)	12.98	1.675 (1.245, 2.254)	0.0006
Belimumab 200 mg (N=556)	340/554 (61.37)			

Source: Reviewer

Reasons for lack of response in the primary analysis in both the groups were further explored in the following table (Table 5). Less than a 4-point reduction in SELENA SLEDAI was the major

reason for non-response, and was the biggest contributor to the treatment difference shown in the primary analysis. Differences in the proportions of patients dropping out and meeting treatment failure criteria also contributed to observed treatment effect on SRI response.

Table 5: Disposition of SRI non-responders

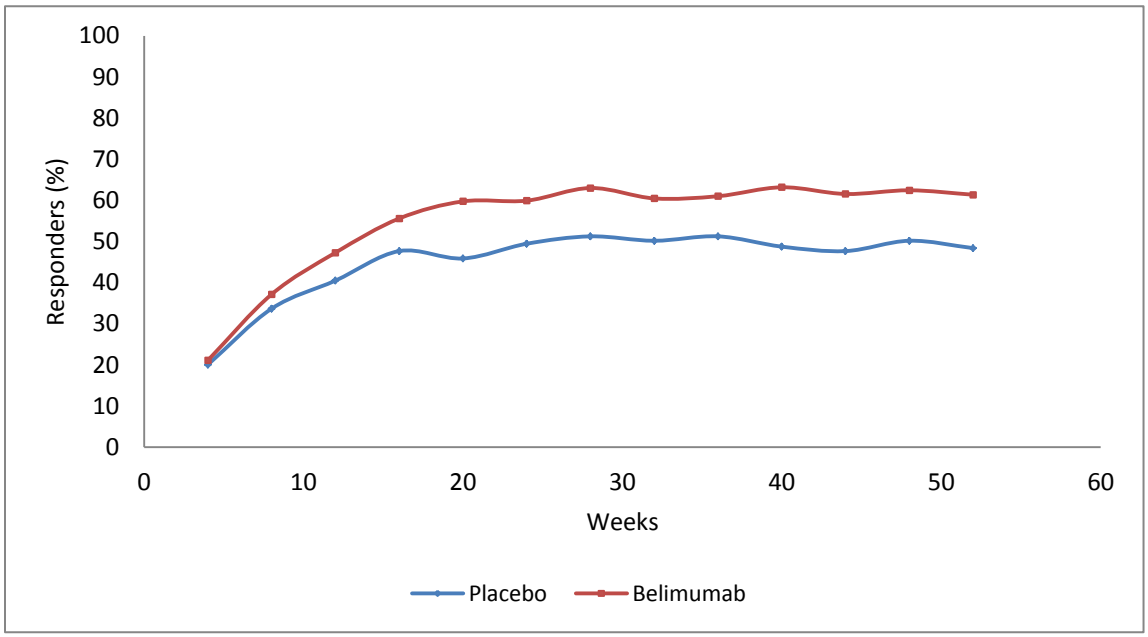
	Actual Treatment			
	Placebo (N=280)		**Belimumab 200 mg (N=556)**	
	N	**%**	**N**	**%**
SRI Responder	135	48.4	340	61.4
SRI Non-Responder	144	51.6	214	38.6
Treatment Failure	27	9.7	42	7.6
Drop Out	42	15.1	55	9.9
SELENA SLEDAI <4 point reduction*	73	26.2	112	20.2
SELENA SLEDAI >=4 point reduction	2	0.7	5	0.9
PGA worsening only	0	0.0	1	0.2
BILAG new 1A/2B only	1	0.4	4	0.7
Both PGA worsening and BILAG new 1A/2B	1	0.4	0	0.0

Source: Reviewer

*Does not include dropouts or subjects who took protocol−prohibited or restricted medication or dose.

The time-response plot (Figure 4) displays the proportion of SRI responders in the two groups over time. The plot shows that the response rates on the belimumab group and the placebo group began to separate within a few months, and the difference was sustained through Week 52.

Figure 4: SRI Response by Visit (Double-Blind Phase)



Source: Reviewer

3.2.6.2 Component analysis of primary endpoint

Each component in the composite primary endpoint was analyzed using logistic regression adjusted for baseline stratification factors in the ITT population and the results showed statistically significant results, with a higher percentage of responders in the belimumab group compared to the placebo group.

Comparing the SLE Disease Activity Index (SELENA SLEDAI) which captured the subject's condition over the 10 days prior to the visit, the belimumab group showed a significantly higher response rate (4 point reduction) than the placebo group (Table 6). The odds ratio was found to be 1.690 with a 95% confidence interval of (1.257, 2.274).

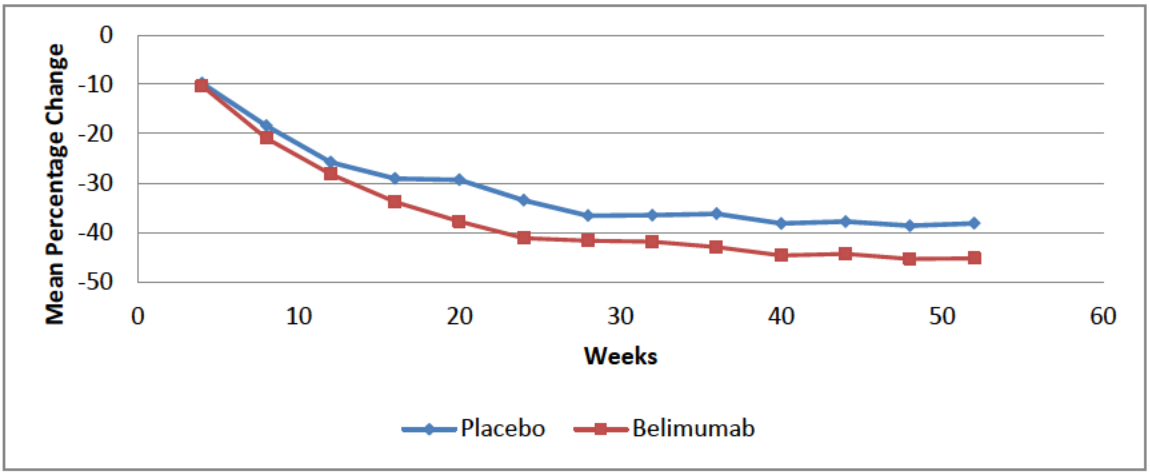
Table 6: Primary Component Analysis - 4 Point reduction in SELENA SLEDAI

Treatment Arm	Response n/n (%)	Observed Difference	Odds ratio (95% CI)	p-value
Placebo (N=280)	137/279 (49.10)	13.17	1.690 (1.257, 2.274)	0.0005
Belimumab 200 mg (N=556)	345/554 (62.27)			

Source: Reviewer

Figure 5 shows that the SELENA SLEDAI percent change from baseline decreased on average over time for both the placebo and belimumab 200 mg SC group, with greater decrease in the belimumab group. At Week 52, the adjusted mean percent change from baseline was -33.22% in the placebo group and -39.96% in the belimumab group (95% CI for difference: -13.91, 0.45; p=0.0660).

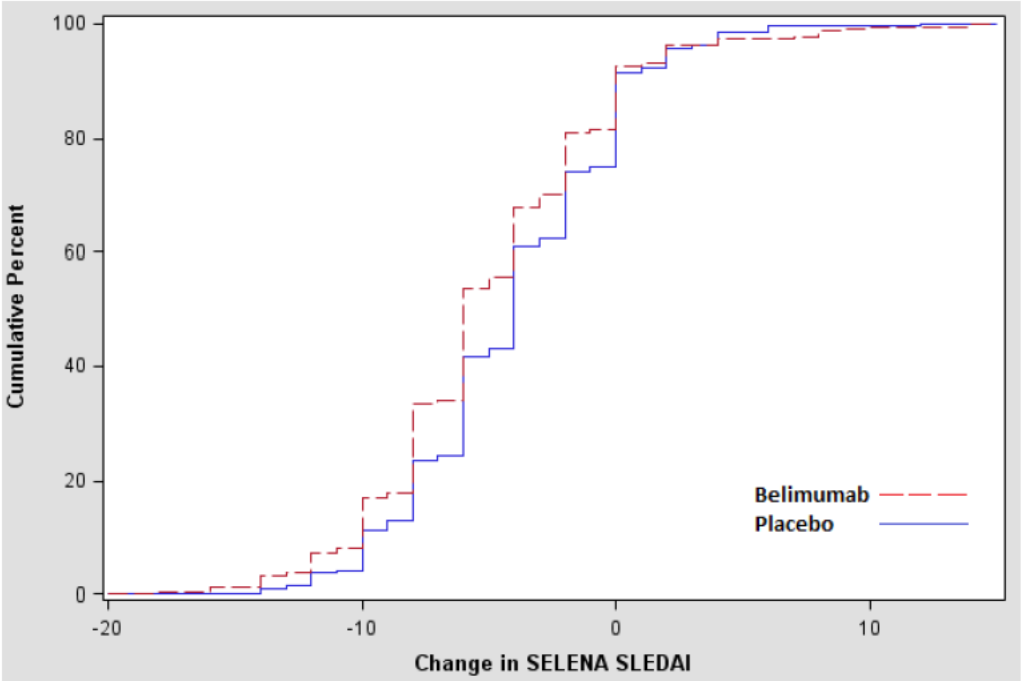
Figure 5: SELENA SLEDAI Percent Change from Baseline by Visit



Source: Reviewer

The empirical distribution plot (Figure 6) shows that a greater proportion of patients in the belimumab group experienced reductions in SELENA SLEDAI score from baseline across the range of thresholds that could be used to define response.

Figure 6: Cumulative Distribution Function of Change in SELENA SLEDAI



Source: Reviewer

The physician global assessment score captures the improvement in the disease activity measured in a visual analog scale scored from 0 to 3 (1=mild, 2=moderate, 3=severe). Results from a logistic regression analysis of PGA score in Table 7 showed that the proportion with no worsening in disease activity was higher in the belimumab group (81.23%) compared to placebo (72.76%).

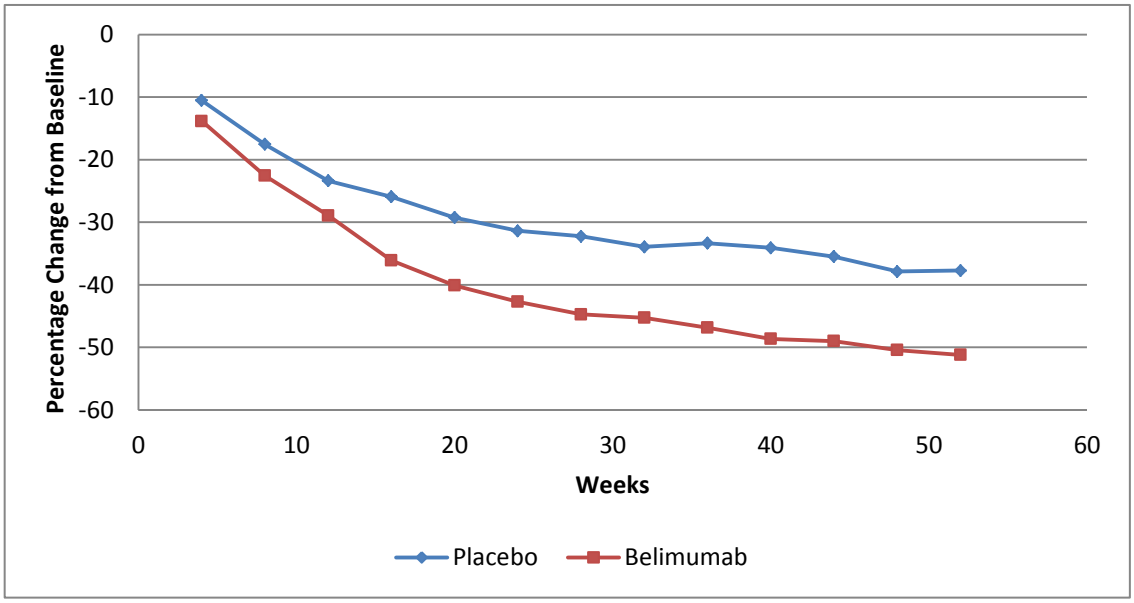
Table 7: Primary Component Analysis - No worsening in PGA

Treatment Arm	Response n/n (%)	Observed Difference	Odds ratio (95% CI)	p-value
Placebo (N=280)	203/279 (72.76)	8.47	1.618 (1.150, 2.277)	0.0057
Belimumab 200 mg (N=556)	450/554 (81.23)			

Source: Reviewer

Reduction in PGA percent change from baseline was observed in both the treatment arms (Figure 7). However, the reduction was greater in the belimumab group compared to the placebo group and the difference was significant ($p<0.0001$).

Figure 7: PGA Percent Change from Baseline by Visit



Source: Reviewer

The BILAG is an organ-based transitional activity instrument which provides disease activity scorings across eight organ systems on an ordinal scale. The odds of not having a new BILAG

score was significantly greater (p-value: 0.0057) for subjects in the belimumab group compared to placebo with an odds ratio of 1.464 and 95% CI of (1.036, 2.068) (Table 8).

Table 8: Primary Component Analysis - No New BILAG Score

Treatment Arm	Response n/n (%)	Observed Difference	Odds ratio (95% CI)	p-value
Placebo (N=280)	207/279 (74.19)	6.68	1.464 (1.036, 2.068)	0.0057
Belimumab 200 mg (N=556)	448/554 (80.87)			

Source: Reviewer

3.2.6.3 Secondary Efficacy Analysis

Time to first severe flare and prednisone reduction were the two major secondary efficacy endpoints in the study.

3.2.6.3.1 Time to first severe flare over 52 Weeks

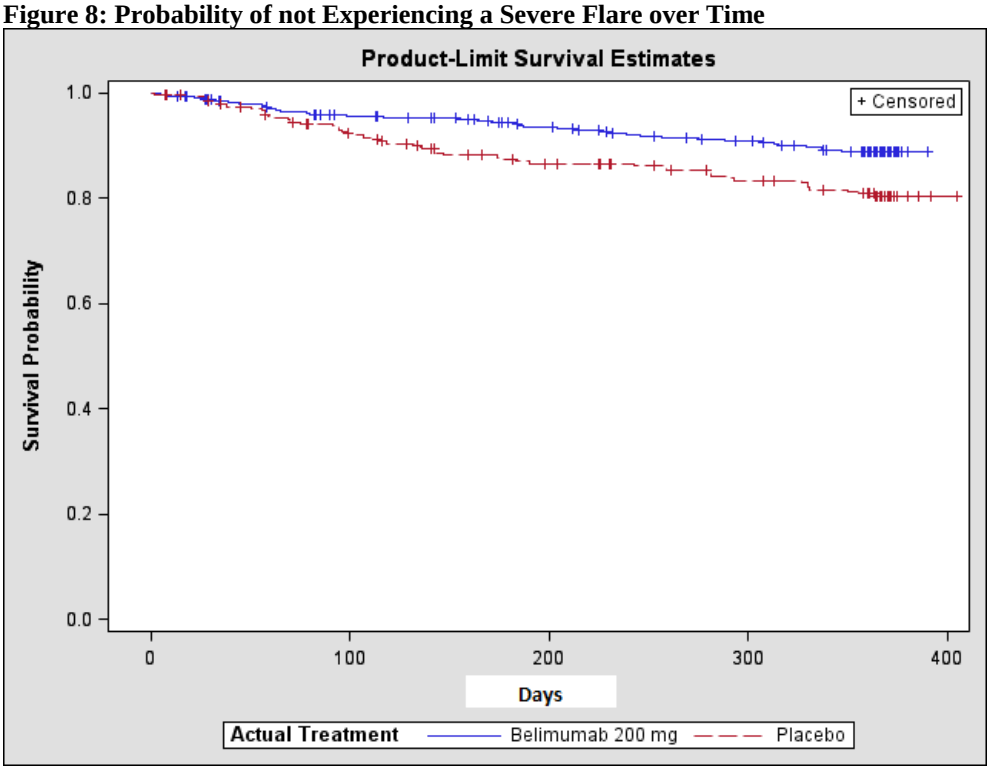
The time to first severe flare measurement was analyzed using a Cox proportional hazards model. The results showed that the subjects in the belimumab group had a 49% lower risk of experiencing a severe flare compared with the placebo group (Table 9). The hazard ratio obtained was 0.510, with a 95% CI of (0.350, 0.743).

Table 9: Time to first severe flare over 52 Weeks

Treatment Arm	Severe Flare No of subjects (%)	Difference	Hazard ratio (95% CI)	p-value
Placebo (N=280)	51 (18.2)	7.6	0.510 (0.350, 0.743)	0.0004
Belimumab 200 mg (N=556)	59 (10.6)			

Source: Reviewer

Figure 8: Probability of not Experiencing a Severe Flare over Time



Source: Reviewer

3.2.6.3.2 Average Prednisone Dose Reduction

The secondary endpoint analyzed in this section is the percentage of subjects whose average prednisone dose was reduced by ≥25% from baseline to ≤7.5 mg/day during Week 40 through Week 52. This analysis was restricted to subjects who were receiving greater than 7.5 mg/day at baseline, who comprised 60.2% of the overall study population.

The estimated proportion of subjects who reduced their prednisone dose was greater in the belimumab group (18.21%) compared to placebo (11.90%), but this difference was not statistically significant (p-value=0.0732) (Table 10). The odds ratio was obtained as 1.647 with a 95% CI of (0.954, 2.841).

Table 10: Average Prednisone Dose Reduction

Treatment Arm	Response n/n (%)	Observed Difference	Odds ratio (95% CI)	p-value
Placebo (N=280)	20/168 (11.90)	6.3	1.647 (0.954, 2.841)	0.0732
Belimumab 200 mg (N=556)	61/335 (18.21)			

Source: Reviewer

3.2.6.4 FACIT-Fatigue

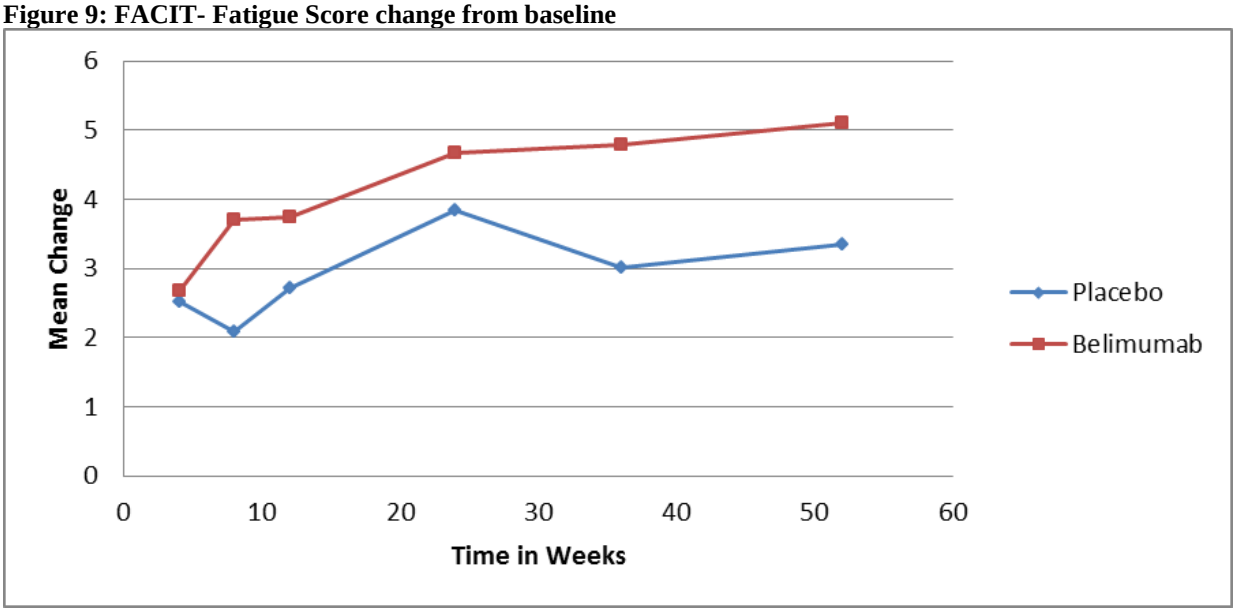
Results given in Table 11 show that the subjects in the placebo and belimumab groups had an increased (improved) mean FACIT-Fatigue Scale score over time; the improvement was slightly greater for subjects in the belimumab group, with nominal statistical significance at a few time points, including Week 52 (mean difference: 1.62; p-value=0.01). However, this analysis was not included in the multiple testing procedure to control the type1 error rate.

Table 11: FACIT-Fatigue Score Absolute Change from Baseline by Visit

	Actual Treatment	
	Placebo (N=280)	**Belimumab 200 mg (N=556)**
Week 4		
LS Mean	2.86	2.95
Treatment differences vs. Placebo (95% CI)		0.09 (-0.89, 1.08)
P-value		0.85
Week 8		
LS Mean	1.58	3.06
Treatment differences vs. Placebo (95% CI)		1.48 (0.39,2.57)
P-value		0.01
Week 12		
LS Mean	2.51	3.40
Treatment differences vs. Placebo (95% CI)		0.09 (-0.29,2.06)
P-value		0.14
Week 24		
LS Mean	3.68	4.38
Treatment differences vs. Placebo (95% CI)		0.70 (-0.54,1.93)
P-value		0.27
Week 36		
LS Mean	2.26	3.89
Treatment differences vs. Placebo (95% CI)		1.63 (0.40,2.86)
P-value		0.01
Week 52		
LS Mean	2.75	4.4
Treatment differences vs. Placebo (95% CI)		1.62 (0.34,2.90)
P-value		0.01

Source: Reviewer

Figure 9: FACIT- Fatigue Score change from baseline



Source: Reviewer

3.2.7 Sensitivity Analysis

3.2.7.1 Sensitivity analyses using different analysis sets

In the study, 159 (19%) subjects withdrew prior to Week 52. Sensitivity analyses using different analyses methods provided similar results to the primary analysis (Table 12). However, such analyses largely evaluate results under similar or single, alternative assumptions to those of the primary analysis and therefore do not comprehensively evaluate the potential effect of violations in missing data assumptions on the reliability of the results. Therefore, we focus on the tipping point analysis results.

Table 12: Sensitivity Analyses

	Placebo	Belimumab
Unadjusted Analysis		
Response	48.39	61.37
Observed difference vs. placebo		12.98
Odds ratio (95% CI) vs. placebo		1.689 (1.261, 2.261)
p-value		0.0004
LOCF Analysis (adjusted)		
Response	57.71	67.87
Observed difference vs. placebo		10.16
Odds ratio (95% CI) vs. placebo		1.531 (1.127, 2.080)
p-value		0.0064
Completers Analysis (adjusted)		
Response	63.08	72.94
Observed difference vs. placebo		9.86
Odds ratio (95% CI) vs. placebo		1.538 (1.075, 2.202)
p-value		0.0185
Per Protocol Analysis (adjusted)		
Response	48.31	61.92
Observed difference vs. placebo		13.61
Odds ratio (95% CI) vs. placebo		1.750 (1.291, 2.373)
p-value		0.0003

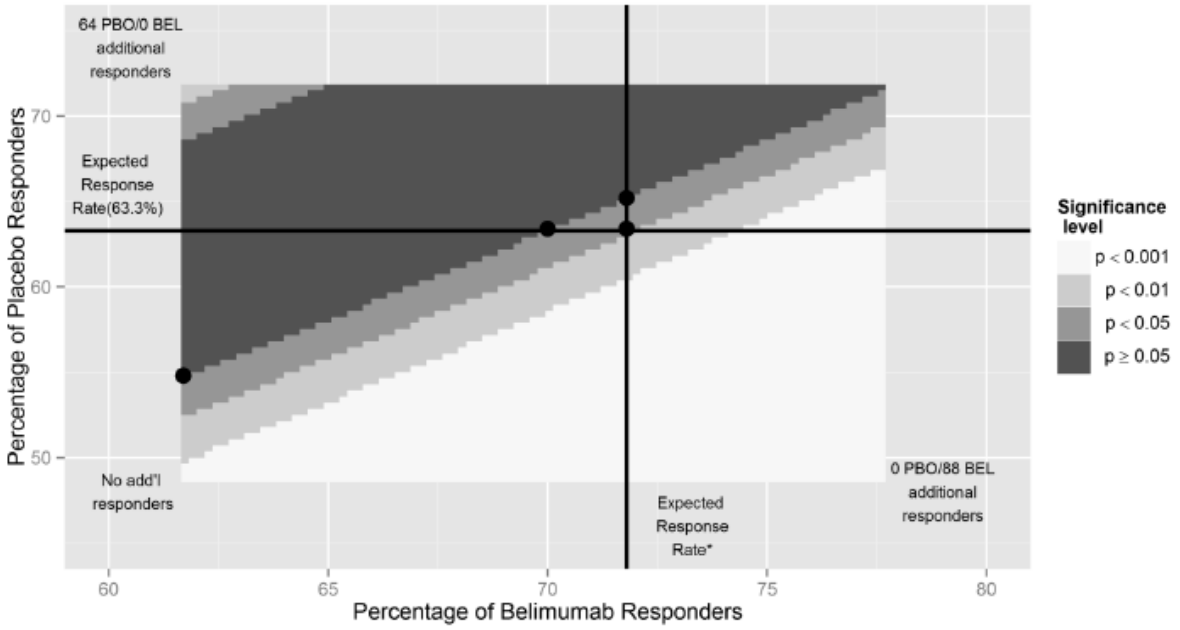
Source: Reviewer

3.2.7.2 Tipping Point Analysis

The tipping point analyses targeted the de facto estimand, i.e., the difference in SRI response in all randomized patients regardless of adherence, and therefore included all observed data regardless of treatment adherence.

Results from the tipping point analysis are shown in Figure 10. One potential assumption is that the subjects who dropped out on both arms would have a response similar to the observed response rate among placebo completers (63.3%). Under this scenario, the overall estimated response rate for the belimumab group was 71.8%, with a treatment difference versus placebo of 8.4% and a significant p-value (0.0134). This scenario is represented by the intersection of the black lines in Figure 10. In order to tip the results, i.e., for there to no longer be evidence of a treatment effect, the dropouts from the belimumab group would have had to have a moderately lower 52-week response rate than the dropouts on the placebo arm (e.g., ~51% in belimumab dropouts compared to 63.3% in placebo dropouts) . These scenarios are considered less plausible than scenarios with similar response rates between dropouts on the two arms, such that the results generally support the efficacy of belimumab despite the missing data. This has been verified by the reviewer's analysis.

Figure 10: Tipping point analysis



* Belimumab response rate: 342/466(73.4%) observed + 63.6% for dropouts based on placebo response rate = 71.8% overall.

Source: Applicant

3.3 Evaluation of Safety

Table 13 provides an overall summary of adverse events reported during the study. 84.29% of subjects in the placebo group experienced at least one adverse event compared to 80.76% in the belimumab group. Two deaths in the placebo group and three in the belimumab group were reported during the study period.

Table 13 : Adverse Events Summary

At least one event	Placebo		Belimumab 200 mg	
	(N=280)	%	(N=556)	%
Adverse Event	236	84.29%	449	80.76%
Related AE	73	26.07%	173	31.12%
Serious AE	44	15.71%	60	10.79%
Severe AE	40	14.29%	55	9.89%
AE resulted in study agent discontinuation	27	9.64%	43	7.73%
Deaths	2	0.71%	3	0.54%

Source: Reviewer

Dr. Rosemarie Neuner, the Medical Reviewer, conducted the complete safety evaluation. The details of the safety evaluation can be found in Dr. Neuner's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses compared efficacy results across different subgroups defined by sex, region, age, race, baseline BMI values, SELENA SLEDAI score, anti-dsDNA status, C3 or C4 levels, and prednisone use. The consistency of the treatment effect on the primary efficacy endpoint across subgroups was analyzed using logistic regression with main effects for treatment and subgroup, and treatment-by-subgroup interactions. Subgroup analyses were performed without adjusting for any covariates.

4.1 Analysis of black race subgroup

Recent studies show that SLE is more common in the black population[1]. When belimumab IV was approved for SLE, there were questions raised during the review about the effectiveness in patients of black race due to subgroup analysis results. Therefore, FDA asked for a post-marketing commitment (PMC) from the applicant to further study the safety and effectiveness of belimumab in black patients. In the belimumab SC study, BEL112341, there were 92 (11%) patients in the black subgroup and 744 (89%) in other racial categories. The subgroup analysis (Table 14) showed that the belimumab group exhibited a higher response rate (44.83%) compared to placebo (39.39%) with an observed difference of 5.44%, although the difference was not significant, with an odds ratio comparing belimumab to placebo of 1.250 (95% CI: 0.524, 2.981; p-value=0.6148). The relatively small number of black subjects in this study leads to considerable uncertainty around the treatment comparison and makes it difficult to reach meaningful conclusions based on these results. Hence, the ongoing post marketing study remains important in assessing the effect of belimumab in the black population.

Table 14: Analysis of Black subgroup

Treatment Arm	Response n/n (%)	Difference	Odds ratio (95% CI)	p-value
Placebo	13/33 (39.39)	5.44	1.250 (0.524, 2.981)	0.6148
Belimumab 200 mg	26/58 (44.83)			

Source: Reviewer

Six subjects in the Black subgroup were identified as 'American Indian or Alaska Native' and not 'African American' in the Race subgroup variable used in Sections 3.2.5 and 4.2.

[1] Emily C Somers, Wendy Marder, Patricia Cagnoli, Emily E Lewis, Peter DeGuire, Caroline Gordon, Charles G Helmick, Lu Wang, Jeffrey J Wing, J Patricia Dhar, James Leisen, Diane Shaltis and W. Joseph McCune. Population-based incidence and prevalence of systemic lupus erythematosus: The Michigan Lupus Epidemiology & Surveillance (MILES) Program. Arthritis and Rheumatism, October 2013

4.2 Other demographic and baseline disease characteristics

Plots of odds ratios for the primary endpoint, SRI response at Week 52, by various subgroups are presented in Figure 11 and

Figure 12. The odds ratio obtained from the primary efficacy analysis in the overall study population is represented by the dark vertical line and the red vertical line represents an odds ratio of 1, which indicates no difference between belimumab 200 mg SC and placebo. Points to the right of the line indicate higher responses for belimumab relative to placebo and points to the left of the line indicate lower responses for belimumab relative to placebo. No significant treatment-by-subgroup interactions were observed for any of the subgroup analyses, and estimates were largely consistent across the subgroups.

Figure 11: Estimated Odds Ratio Comparing Belimumab and Placebo with Respect to SRI Response at Week 52, Stratified by Selected Subgroups.

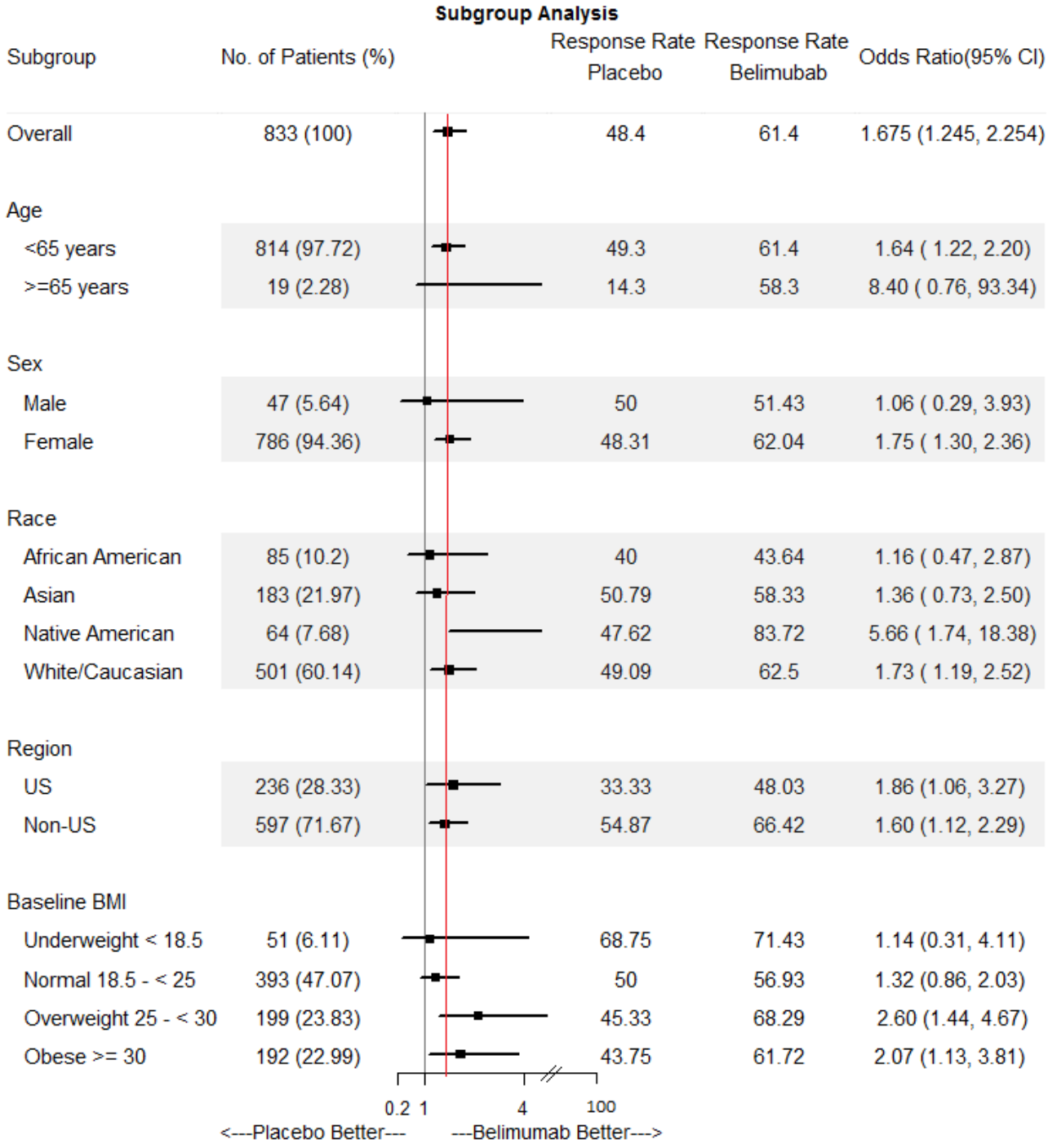
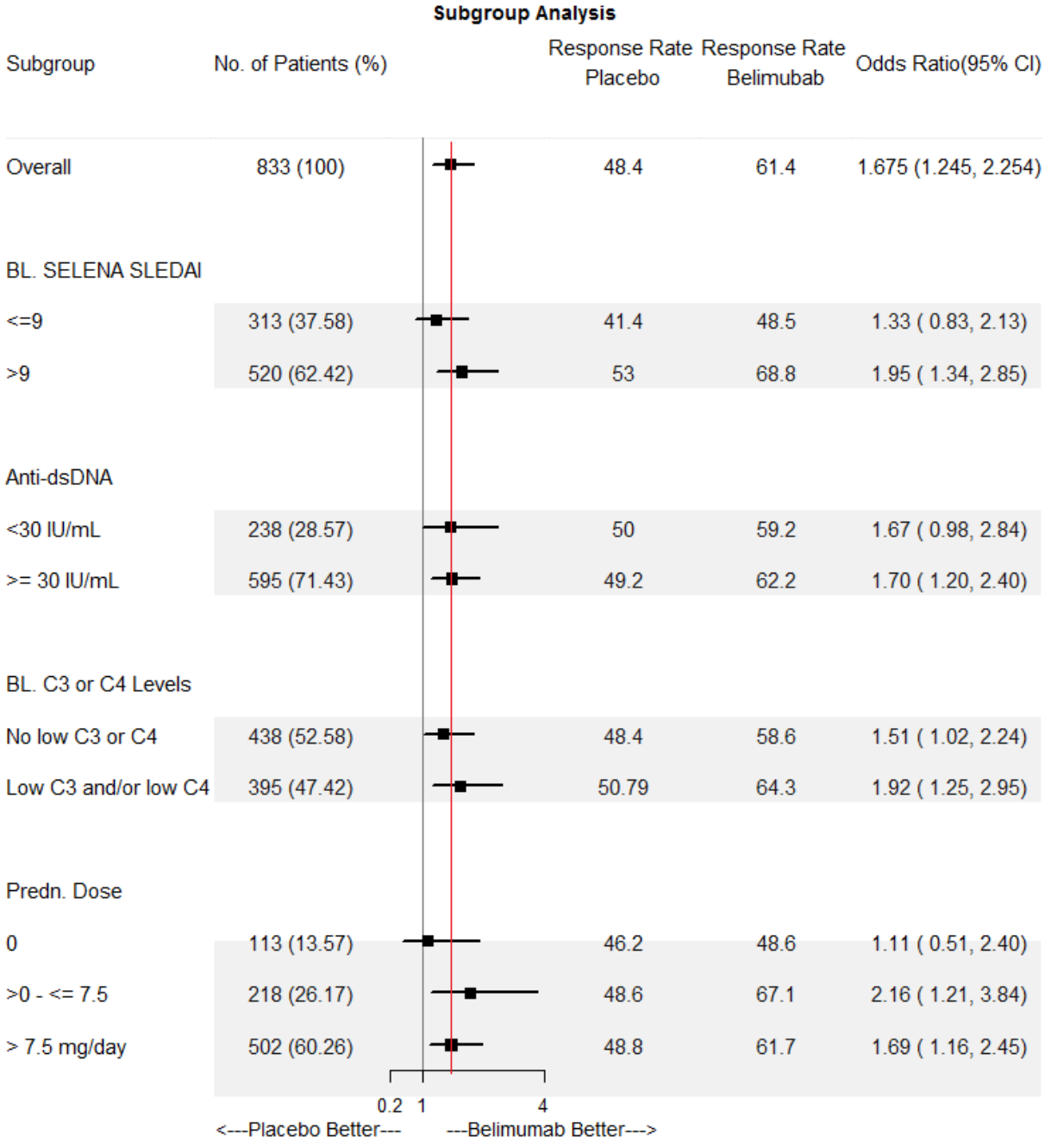


Figure 12: Estimated Odds Ratio Comparing Belimumab and Placebo with Respect to SRI Response at Week 52, Stratified by Selected Subgroups.



5 SUMMARY AND CONCLUSIONS

This BLA submission is for the approval of a new subcutaneous formulation of belimumab (fixed dose 200 mg weekly) for patients with SLE. The program consists of a Phase 3 trial investigating belimumab SC (BEL112341) and two supporting IV studies (BEL110751, BEL110752). The two IV studies were previously reviewed as part of the original BLA for the IV formulation of belimumab.

5.1 Statistical Issues

The following statistical issues have been identified during the review process.

5.1.1 Potential effect of missing data on the reliability of efficacy results

Patient dropout in the placebo arm was higher than that of the belimumab arm. Up to Week 52, 159 (19.02%) patients had withdrawn from the study: 93 (16.73%) patients from belimumab and 66 (23.57%) patients from placebo. This led to substantial missing data in important analyses, such as the evaluations of SRI response at Week 52 in all randomized patients regardless of adherence. The applicant performed a variety of sensitivity analyses using different analysis methods, such as a logistic regression analyses without adjustment for covariates, an analysis with LOCF for missing data, and analyses restricted to completers and to the per-protocol population. However, none of these sensitivity analyses comprehensively evaluate the potential effect of missing data on the reliability of the efficacy results. Therefore, primary focus was given to tipping point analysis to evaluate the potential effect of missing data on the reliability of efficacy results. Tipping point analyses were performed to gauge the extent to which the demonstration of a treatment effect was dependent on the non-responder imputation. In this study, tipping point sensitivity analyses largely support the findings of the key efficacy analyses.

5.1.2 Multiple Comparisons and Multiplicity

The applicant used a step-down sequential testing procedure to control the overall type 1 error rate for the analysis of the primary and the major secondary efficacy endpoints. The primary and two major secondary endpoints evaluated for statistical significance in this sequence were: (1) SRI response rate at Week 52, (2) time to first severe SLE flare, and (3) percent of subjects with average prednisone dose that has been reduced by $\geq 25\%$ from baseline to ≤ 7.5 mg/day during Weeks 40 through 52. The analysis of the primary and one of the secondary (time to first severe SLE flare) endpoints were found statistically significant. However, the analysis of the other major secondary endpoint (average prednisone dose reduction) was not statistically significant (p-value=0.0732).

Analyses of efficacy endpoints other than the major secondary efficacy endpoints were not subject to any multiple comparison procedure. In addition, given that an analysis in the multiple

testing hierarchy (of prednisone reduction) did not provide evidence of an effect, additional analyses are generally considered exploratory in nature. (b) (4) Furthermore, while the FACIT-F analysis showed nominal statistical significance at Week 52, the totality of the results (e.g., at various time points and considering the amount of missing data and the use of LOCF) from this single study were not highly persuasive. (b) (4)

5.2 Collective Evidence

The proportion of patients who obtained an SRI response at Week 52 was found to be significantly greater for the belimumab 200 mg group (61.37%) compared to the placebo group (48.39%), with an odds ratio of 1.675 (95% CI: 1.245, 2.254; p=value=0.0006). The results from the analyses of the subcomponents of the SRI and secondary endpoints were generally supportive of those of the primary analysis. There was considerable missing data in important analyses, but tipping point sensitivity analyses largely support the key efficacy results in the study. Thus, the collective evidence from the randomized, multicenter, double-blind, placebo-controlled, 52-week study supports the efficacy of belimumab administered SC injection in adult subjects with active SLE.

5.3 Conclusions and Recommendations

In summary, there was evidence of efficacy for SC belimumab from this study. These results are also supported by the results from the two IV studies that were reviewed under the application, BLA 125370. Therefore, the overall package provides substantial evidence of efficacy for the proposed SC administration of belimumab (fixed dose 200 mg weekly) for the treatment of SLE.

5.4 Labeling Recommendations (as applicable)

The focus of the labeling review will be on Section 14 Clinical Studies. Edits to the labeling are pending. (b) (4)

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/s/

GINTO J POTTACKAL
06/19/2017

GREGORY P LEVIN
06/19/2017

Table 1: Summary of Phase 3 Trials of Belimumab SC and IV

Trial ID	Design*	Treatment/ Sample size by Group Entered/ Completed	Endpoint/Analysis	Preliminary Findings
BEL112341/ HGS1006-C1115	MC, R, DB, PG, PC	Placebo: 280/214 Belimumab 200 mg: 556/463	**Primary:** SRI Response at Week 52 (≥4 point reduction from baseline in SS score and no worsening in PGA and no new BILAG 1A/2B) **Secondary:** Time to first severe SLE flare, and percent of subjects with average prednisone dose that has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52.	Reduction in disease activity: belimumab 200 mg SC plus standard therapy achieved a significantly greater SRI at Week 52 compared with placebo plus standard therapy.
HGS1006-C1056/ BEL110751	MC, R, DB, PC	Placebo: 275/205 IV Belimumab 1 mg : 271/216 10 mg: 273/209	**Primary:** SRI Response at Week 52 (≥4 point reduction from baseline in SS score and no worsening in PGA and no new BILAG 1A/2B)	Belimumab (IV) 10 mg/kg demonstrated significant improvement over placebo for the response component of 4-point reduction in SELENA SLEDAI
HGS1006-C1057/ BEL110752 m5	MC, R, DB, PC	Placebo: 287/226 IV Belimumab 1 mg : 288/240 10 mg: 290/241	**Primary:** SRI Response at Week 52 (≥4 point reduction from baseline in SS score and no worsening in PGA and no new BILAG 1A/2B)	Belimumab (IV) demonstrated a dose ordered trend for significant improvement over placebo for all 3 response components of 4-point reduction in SELENA SLEDAI, no worsening in PGA, and no new 1A or 2B BILAG domain scores

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**No interim Analysis was planned in the study protocol**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**Yes**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Yes**

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\cdsesub1\evsprod\BLA761043\0000\m5\datasets\bel112341
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	ADSRI, ADBILAG, ADPGA, ADSLEDAI, ADTF
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No

Content Parameter	Response/Comments
Safety data are organized to permit analyses across clinical trials in the BLA.	NA

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	✓			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	✓			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	✓			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

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GINTO J POTTACKAL
11/14/2016

GREGORY P LEVIN
11/14/2016