CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125370

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA	125370	*Submission Dates*	0000 (06/09/2009)
Brand Name		BENLYSTA® (proposed)	
Generic Name		Bilimumab	
Reviewer		Ping Ji, Ph.D.	
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Pharmacometrics Reviewer		Ping Ji, Ph.D.	
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Genomics Team Leader		Mike Pacanowski, Pharm.D., M.P.H.	
OCP Division		Division of Clinical Pharmacology-II	
OND Division		Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)	
Sponsor		Human Genome Sciences, Inc	
Relevant IND(s)		BB-IND 9970	
Submission Type; Code		351(a)	P
Formulation; Strength(s)		Single-use vials of belimumab lyophilized powder with 120 mg/5-mL vial and 400 mg/20-mL vial	
Indication		(b) (4) in adult patients with active, autoantibody positive, systemic lupus erythematosus who are receiving standard therapy.	
Proposed Dosing Regimen		Recommended dosage regimen is 10 mg/kg at 2 week intervals for the first 3 doses and at 4 week intervals thereafter as an intravenous infusion over one hour.	

Belimumab Signature Page

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1 Executive Summary

1.1 Recommendations

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Comments to Clinical Team

Based on the apparent lack of demonstrated efficacy in black subjects enrolled in trials C1056 and C1057, the sponsor proposes in the AC meeting background package that future studies will be designed to enroll greater numbers of black patients so that clinical outcomes in black patients can be better elucidated. We agree and recommend that the proposed trial be designed to assess treatment effects in black subjects with varying levels of disease activity.

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Belimumab, a monoclonal anti-BLyS antibody, is proposed for the indication of treating adult patients with active, autoantibody positive systemic lupus erythematosus (SLE) who are receiving standard therapy. Belimumab is a recombinant, fully human, IgG1λ monoclonal antibody that binds and antagonizes the biological activity of soluble B lymphocyte stimulator (BLyS) protein, a member of the tumor necrosis factor (TNF) ligand superfamily that promotes the survival of B lymphocytes. The proposed commercial final drug product (FDP) is a lyophilized powder to be reconstituted with sterile water for injection, for intravenous (IV) infusion. The proposed dosing regimen is 10 mg/kg every 2 weeks for the first 3 doses, then every 4 weeks thereafter.

The PK of IV administered belimumab were evaluated in 4 clinical studies in SLE subjects (LBSL01, LBSL02, C1056 and C1057), 1 clinical study in RA subjects (LBRA01), and 1 clinical study in healthy subjects (C1058). The 2 Phase 1 studies, LBSL01 in SLE subjects and C1058 in healthy subjects, evaluated the full PK profile of belimumab, while sparse sampling methods were employed in the Phase 2 (LBSL02) and 3 studies (C1056 and C1057) in SLE as well as in the Phase 2 study in RA (LBRA01). Long-term safety evaluation of belimumab continues in open-label continuation trials of the Phase 2 (LBSL99) and Phase 3 trials (C1066 and C1074).

Pharmacokinetics in Healthy Subjects

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

Pharmacokinetics in SLE patients

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

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

Pharmacokinetics in special populations

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

Sex
Gender did not significantly influence belimumab pharmacokinetics in the largely (94%) female study population. The number of male subjects was small.

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

Weight
As weight increased, the systemic clearance of belimumab also increased. This effect was adjusted by the body-weight based dosing regimen.

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

Hepatic Impairment
No formal studies were conducted to examine the effects of hepatic impairment on belimumab PK. Belimumab has not been studied in patients with severe hepatic impairment. Population PK analysis showed that baseline AST, ALT, and belirubin levels were not a significant covariate for belimumab CL.

Renal Impairment
No formal studies were conducted to examine the effects of renal impairment on belimumab PK. Population PK analysis showed that belimumab exposure was similar in patients with different baseline creatinine clearance.

Pharmacodynamics

Belimumab reduces IgG, anti-dsDNA, and various B cell populations, and increases complement (C3 and C4) and T-lymphocytes. More belimumab-treated subjects had normalization of these biomarkers than placebo. These changes were observed as early as week 8 and were sustained through Week 52. Changes in C3, C4, and naïve B-cells, were significantly correlated with response to belimumab, but did not adequately predict belimumab treatment responses.

Dose (exposure)-Response Relationship

No clear dose (exposure) response relationship for belimumab was shown in the Phase 1 and 2 trials. For the primary efficacy endpoint of the response rate at Week 52, the belimumab 10 mg/kg dose achieved statistically significant superiority over placebo in both Phase 3 trials, while the 1 mg/kg dose was significantly superior to placebo in Study C1057 only.

Immunogenicity

The incidence of anti-belimumab antibodies was low across various clinical studies. For the two pivotal Phase 3 trials, anti-belimumab antibodies were detected in 13.1% of SLE patients administered with 1 mg/kg belimumab and 0.9% of SLE patients administered with 10 mg/kg belimumab. The trough belimumab concentration for antibody positive patients was within the range of those for antibody negative patients. The presence of positive anti-belimumab antibodies did not appear to affect the safety and effectiveness of belimumab. However, no definitive conclusion can be made as the incidence of anti-belimumab antibodies was low. The immunogenicity assay in the Phase 1 and 2 studies was not robust and the assay was also sensitive to belimumab concentrations.

2 Question-Based Review

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Belimumab, a monoclonal anti-BLyS antibody, is proposed for the indication of treating adult patients with active, autoantibody positive systemic lupus erythematosus (SLE) who are receiving standard therapy. Belimumab is a recombinant, fully human, IgG1λ monoclonal antibody that binds and antagonizes the biological activity of soluble B lymphocyte stimulator (BLyS) protein, a member of the tumor necrosis factor (TNF) ligand superfamily that promotes the survival of B lymphocytes. The proposed commercial final drug product (FDP) is a lyophilized powder to be reconstituted with sterile water for injection, for intravenous (IV) infusion. The proposed dosing regimen is 10 mg/kg every 2 weeks for the first 3 doses, then every 4 weeks thereafter.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Belimumab is a fully human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

Belimumab is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for intravenous infusion. Upon reconstitution with Sterile Water for Injection, USP, each single-use vial delivers 80 mg/mL belimumab in 0.16 mg/mL citric acid, 0.4 mg/mL polysorbate 80, 2.7 mg/mL sodium citrate, and 80 mg/mL sucrose, with a pH of 6.5.

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

Belimumab is a fully human IgG1λ monoclonal antibody that binds to soluble human B-lymphocyte stimulator (BLyS; also known as B cell activating factor belonging to the TNF family [BAFF] and TNFSF13B) and inhibits its biological activity. BLyS, a member of the tumor necrosis factor (TNF) ligand superfamily, is a B cell survival factor. BLyS inhibits B cell apoptosis and stimulates the differentiation of B cells into immunoglobulin-producing plasma cells. BLyS is overexpressed in patients with systemic lupus erythematosus (SLE) and other autoimmune diseases and constitutive over expression of BLyS by transgenic mice results in autoimmune-like disease. BLyS can bind to 3 receptors, BLyS receptor 3 (BR3), transmembrane activator–1 and calcium modulator and cyclophilin ligand–interactor (TACI), and B-cell maturation antigen (BCMA), but the phenotype of BLyS and BR3 deficient mice suggests that the biological effect of BLyS is predominantly mediated through BR3. Inhibition of BLyS activity with soluble BLyS receptors (TACI-Fc or BR3-Fc) administered to New Zealand Black/New Zealand White (NZB/NZW) F1 mice, which develop a lethal, SLE-like autoimmune syndrome, slowed disease progression and improved survival. In patients with SLE followed for

2 years, BLyS levels correlated with changes in lupus disease activity as well as with elevated anti-dsDNA antibody titers, and worsening disease activity was predicted by rises in serum BLyS concentrations. Together, these data suggested an important role for BLyS in SLE pathogenesis and accordingly a role for an antagonist of BLyS, such as belimumab, as a therapeutic agent for SLE.

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

2.1.4 What are the proposed dosage(s) and route(s) of administration?

The proposed treatment regimen is 10 mg/kg belimumab administered by intravenous (IV) infusion over 1 hour every 2 weeks for the first 3 infusions, then every 4 weeks thereafter. The proposed commercial final drug product (FDP) is a lyophilized formulation to be reconstituted with sterile Water for Injection (WFI) and further diluted to a final volume of 250 mL in normal saline for IV infusion.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The PK of IV administered belimumab were evaluated in 4 clinical studies in SLE subjects (LBSL01, LBSL02, C1056 and C1057), 1 clinical study in RA subjects (LBRA01), and 1 clinical study in healthy subjects (C1058). The 2 Phase 1 studies, LBSL01 in SLE subjects and C1058 in healthy subjects, evaluated the full PK profile of belimumab, while sparse sampling methods were employed in the Phase 2 and 3 studies in SLE as well as in the Phase 2 study in RA. The aforementioned studies are included in this review.

Table 1: List of studies reviewed.

Study	Objectives
LBSL01	Safety, tolerability, PK, immunogenicity in SLE subjects
LBSL02	Efficacy, safety, tolerability, PK, and immunogenicity in SLE subjects
C1056	Efficacy, safety, tolerability, PK, and immunogenicity in SLE subjects
C1057	Efficacy, safety, tolerability, PK, and immunogenicity in SLE subjects
C1058	PK, safety, tolerability, and immunogenicity in healthy subjects
LBRA01	Safety, tolerability, PK, immunogenicity in RA subjects. Sparse PK

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The selection of the response endpoints were in line with the recommendations from the "Guidance for Industry: Developing Medical Products for Treatment of Systematic Lupus Erythematosus."

The primary efficacy endpoint in the Phase 3 trials was a SLE responder index (SRI), an evidence-based tool identified from the results of a belimumab Phase 2 SLE clinical trial (LBSL02). This primary efficacy endpoint included an objective measure of the reduction in global disease activity (reduction in SELENA SLEDAI score ≥ 4) for efficacy and 2 measures to ensure that the improvement in disease activity was not offset by worsening of the subject's condition overall (i.e., no worsening [increase of < 0.30 points] in the PGA) or by worsening in any BILAG specific organ domain (i.e., no new BILAG A or 2 B flares). The primary efficacy analysis was at Week 52 in both trials. This primary endpoint was agreed with regulatory authorities prior to initiation of the Phase 3 trials and is consistent with the recommendations in the Draft Guidance for Industry: Systemic Lupus Erythematosus-Developing Drugs for Treatment (June 2010).

Currently, none of the known biomarkers (e.g., anti-dsDNA levels, complement levels) in SLE has been validated as a surrogate endpoint, and therefore no biomarker can substitute for a direct assessment of clinical benefit in clinical trials.

2.2.3 What are the PK characteristics of belimumab?

a) What are the single dose and multiple-dose PK characteristics?

The single dose PK of belimumab was studied in SLE subjects in study LBSL01. The serum belimumab concentration-time profiles following single or double IV doses given as 2-hour infusion is shown below.

Figure 1: The Serum belimumab concentration-time profiles following single or double IV doses given as 2-hour infusion.

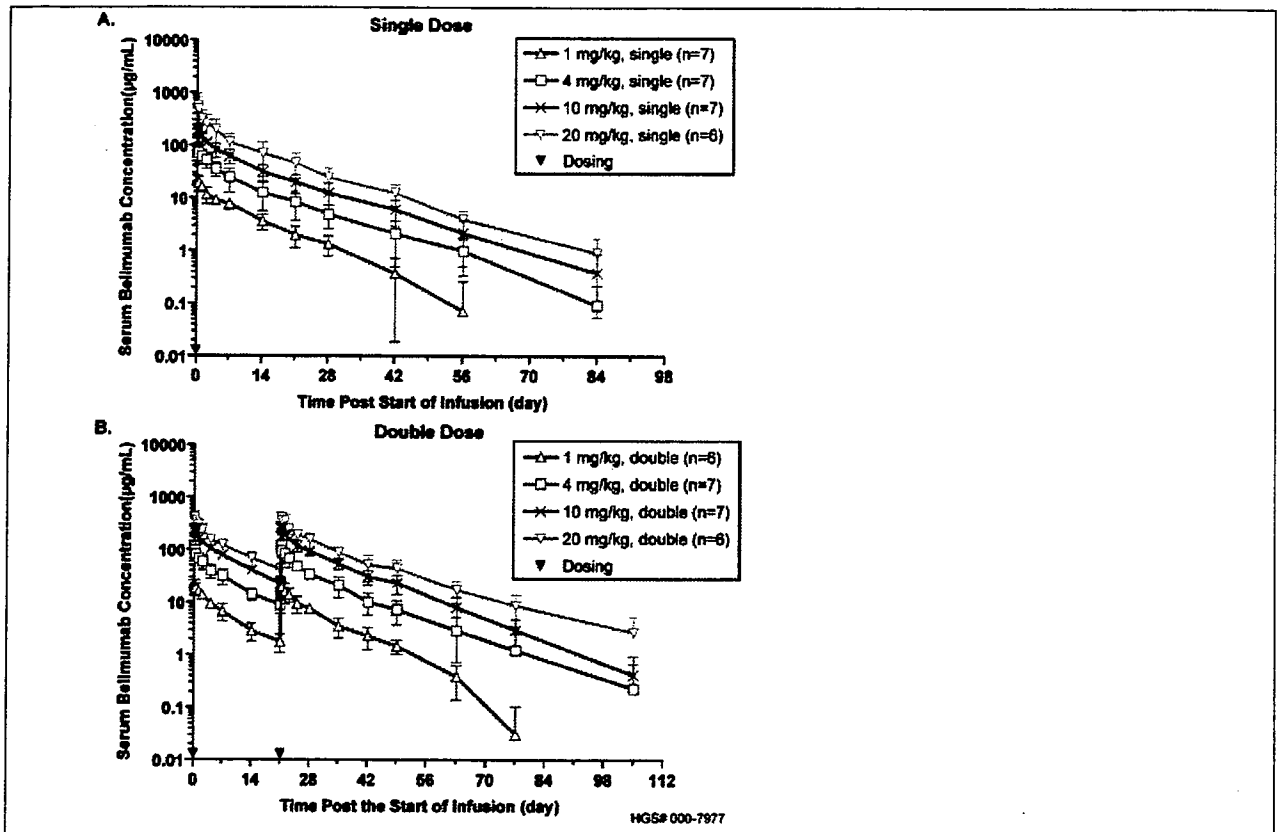


Figure 2.7.2-1 Serum belimumab concentrations (mean ± SD) following single or double (Days 0 and 21) IV doses given as 2-hour infusion (LBSL01)

Following single IV administration, serum belimumab concentrations declined in a bi-exponential manner, with a mean distribution half-life ($t_{1/2,\alpha}$) of 1.0 to 1.8 days and a mean terminal elimination half-life ($t_{1/2,\beta}$) of 8.5 to 11.3 days. The mean volume of distribution for the central compartment (V_1) ranged from 45 to 53 mL/kg, approximating the plasma volume (43 mL/kg). The mean steady-state volume of distribution (V_{ss}) ranged from 73 to 112 mL/kg, about twice the mean V_1 and one-fourth to one-half of the extracellular fluid volume (~260 mL/kg, Davies and Morris, 1993), suggesting that belimumab localizes primarily in the plasma compartment and the interstitial fluid spaces of more permeable tissues. The CL of belimumab after a single IV dose ranged from 6.9 to 7.3 mL/day/kg across the single cohorts, which is much less than the glomerular filtration rate (2571 mL/day/kg,), indicating that renal clearance is not a major component of belimumab clearance. The mean residence time (MRT) ranged from 11.1 to 14.0 days across the single dose cohorts.

Following IV administration of 2 doses of belimumab given 21 days apart, the mean $t_{1/2,\alpha}$ ranged from 1.0 to 2.2 days, while the mean $t_{1/2,\beta}$ ranged from 9.6 to 14.1 days. The mean V_1 (40 to 57 mL/kg), V_{ss} (69 to 102 mL/kg), CL (5.6 to 7.0 mL/day/kg), and MRT (11.0 to 16.1 days) were similar to the corresponding values in single dose cohorts. Drug accumulation for the maximum serum drug concentration (C_{max}) averaged 9% when 2 doses of 4, 10 or 20 mg/kg were administered 21 days apart, which was as expected based on the $t_{1/2,\beta}$ for those cohorts.

There were no statistically significant differences in PK parameters between single and double dose cohorts. Overall, belimumab exposures were dose-proportional across the 1 to 20 mg/kg dose range in this study.

b) How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The exposure of belimumab was comparable in SLE patients (C1056&C1057) and those in healthy subjects (C1058) as well as in RA patients (LBRA01).

The PK of belimumab in healthy subjects in study C1058 was compared to that in SLE patients in study C1056&1057 as all these three studies utilized the same analytical method. A comparison of the PK variables of belimumab is shown in the table below.

Table 2: The PK variables of belimumab in healthy and SLE patients after single intravenous administration.

PK	Healthy (Study C1058, 100 mg)	SLE (Study C1056&C1057, 10 mg/kg)*
Cmax/dose (μg/mL/μg/kg)	0.028 (0.0048)	0.031
AUC/dose (μg day/mL/μg/kg)	0.32 (0.062)	0.31
CL (mL/day/kg)	3.3 (0.58)	3.0
Vss (mL/kg)	63 (10.7)	76
T1/2 (Day)	13.5 (3.2)	19.4

*based on model prediction.

The mean dose-normalized C_{max} and $AUC_{0-\infty}$ values and CL in SLE patients were comparable to those in healthy subjects. The estimated volume of distribution in healthy subjects appeared slightly less than those in SLE subjects. The mean terminal elimination half-life of belimumab was 13.5 days in healthy subjects, which compared to the estimated half-life of 19.4 days in SLE patients.

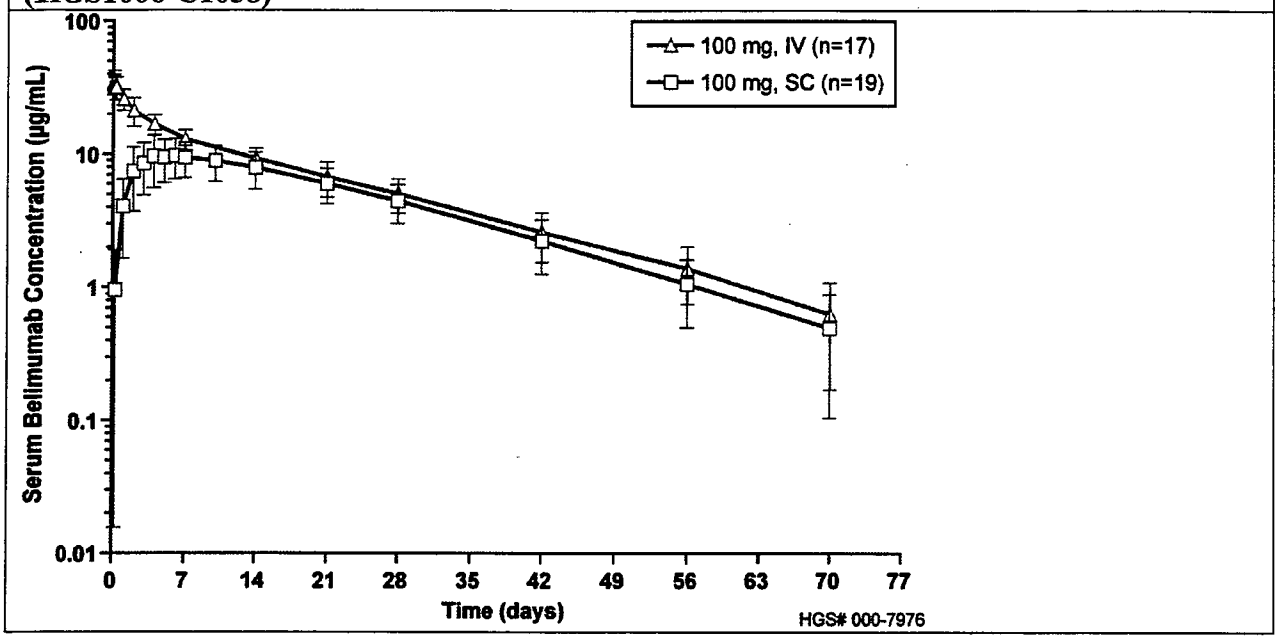
The sparse PK sampling was also conducted in the Phase 2 study in RA patients (LBRA01). Serum belimumab concentrations in subjects with RA in this study (Cmax: 0.025 μg/mL/μg/kg) were generally comparable to the healthy subjects and SLE patients.

c) What are the characteristics of drug absorption?

The absolute bioavailability of a 100 mg SC dose is 67%. The mean peak plasma concentration of belimumab is reached in about 5 days after SC administration.

Following SC administration, the C_{max} was reached at a median time of 5.0 days postdose. The bioavailability (F) of SC administration was 67.2%. Mean serum belimumab concentrations-time profiles are presented in the figure below.

Figure 2. Serum belimumab concentration (mean ± SD) following single IV or SC dose (HGS1006-C1058)



d) What are the characteristics of drug distribution?

The volume of distribution of belimumab at steady state is 56-80 mL/kg.

Belimumab, as a macromolecule, is expected to distribute to plasma and extracellular compartments with limited distribution to tissues. Consistent with PK parameters from other monoclonal antibodies, the volume of distribution of belimumab at steady-state was 56-80 mL/kg.

e) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The exposure of belimumab is approximately dose proportional over the dose range of 1 to 20 mg/kg investigated.

The single dose PK of belimumab in SLE patients over the range of 1 to 20 mg/kg was investigated in study LBS01. The exposure of belimumab is approximately dose proportional over the dose range of 1 to 20 mg/kg. The dose-normalized Cmax was 0.0223 kg/mL at 1 mg/kg, 0.0203 kg/mL at 4 mg/kg, 0.0192 kg/mL at 10 mg/kg, and 0.0262 kg/mL at 20 mg/kg. The dose-normalized AUC was 0.1561 kg.day/mL at 1 mg/kg, 0.1572 day.kg/mL at 4 mg/kg, 0.1510 kg.day/mL at 10 mg/kg, and 0.1692 kg.day/mL at 20 mg/kg.

f) What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

The coefficient of variation (CV%) ranged from 18 to 56% for Cmax, and from 29-42% for AUC. The other parameters are shown in the Table 3 below.

Table 3: Mean (±SD) PK parameters following a single IV dose of belimumab at 1, 4, 10 and 20 mg/kg given at a 2-hour infusion.

	Cohort 1 1 mg/kg (n = 7)[a]	Cohort 2 4 mg/kg (n = 7)	Cohort 3 10 mg/kg (n = 7)	Cohort 4 20 mg/kg (n = 6)[b]
C_{max} (μg/mL)	22.3 ± 4.2	81.2 ± 24.6	192.4 ± 34.9	523.9 ± 293.7
C_{max}/Dose (kg/mL)	0.0223 ± 0.0042	0.0203 ± 0.0061	0.0192 ± 0.0035	0.0262 ±0.0147
$AUC_{0-\infty}$ (day•μg/mL)	156 ± 46	629 ± 258	1510 ± 315	3384 ± 1424
$AUC_{0-\infty}$/Dose (day•kg/mL)	0.1561 ± 0.0456	0.1572 ± 0.0646	0.1510 ± 0.0315	0.1692 ± 0.0712
$t_{1/2,\alpha}$ (day)	0.96 ±0.61	1.49 ± 0.76	1.84 ± 0.89	1.27 ± 0.43
$t_{1/2,\beta}$ (day)	8.46 ± 2.21	9.88 ± 2.18	10.63 ± 2.89	11.34 ± 3.02
V_1 (mL/kg)	44.90 ± 7.12	52.69 ± 18.59	52.91 ± 10.20	53.17 ± 40.89
V_{ss} (mL/kg)	73.29 ± 13.64	82.33 ± 22.31	86.30 ± 16.77	111.67 ± 95.72
CL (mL/day/kg)	7.15 ± 3.18	7.20 ± 2.48	6.90 ± 1.57	7.33 ± 4.38
MRT (day)	11.13 ± 3.08	12.18 ± 3.22	13.03 ± 3.59	14.01 ± 4.17

2.2.4 Exposure-response

2.2.4.1 Is there evidence of dose and response relationship for efficacy?

No clear dose (exposure) response relationship for belimumab was shown in the Phase 1 and 2 trials. For the primary efficacy endpoint of the response rate at Week 52, the belimumab 10 mg/kg dose achieved statistically significant superiority over placebo in both Phase 3 trials, while the 1 mg/kg dose was significantly superior to placebo only in Study C1057.

The Phase 1 Study LBSL01 evaluated belimumab over a range of doses including 1, 4, 10 and 20 mg/kg as a single dose or 2 doses 21 days apart. No clear dose response for biomarker effects was found.

Figure 3: Dose-response relationship in study LBSL01.

Biomarker response

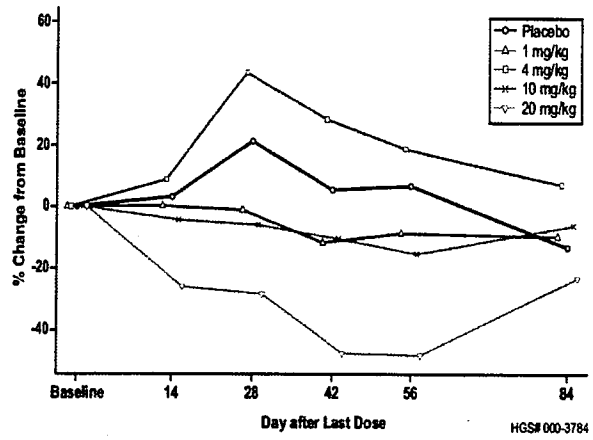


Figure 8 Mean percent change in anti-dsDNA levels for subjects with baseline values ≥ 10 IU/mL (n = 31) by dose level

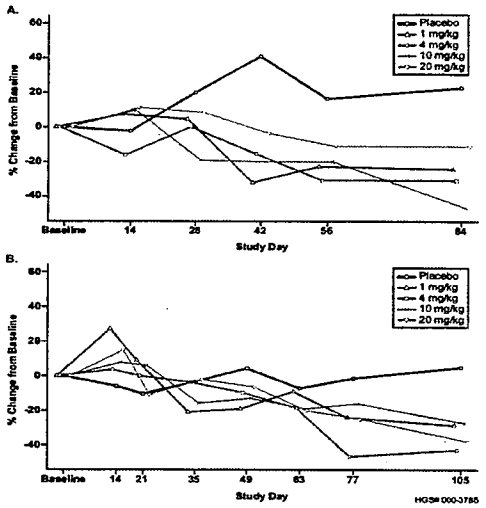


Figure 9 Median percent change in CD20⁺ cells - single dose (A) and double dose (B) cohorts

Disease activity response

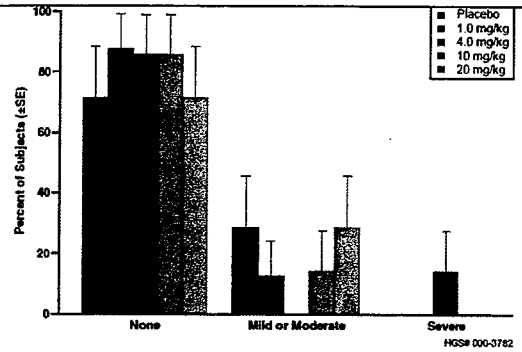
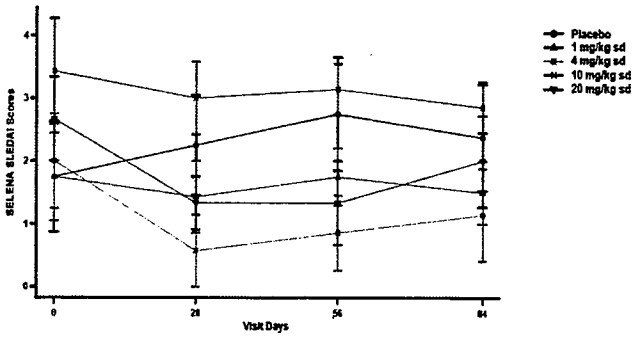


Figure 6 Worst SLE Flare Index result - single dose cohorts

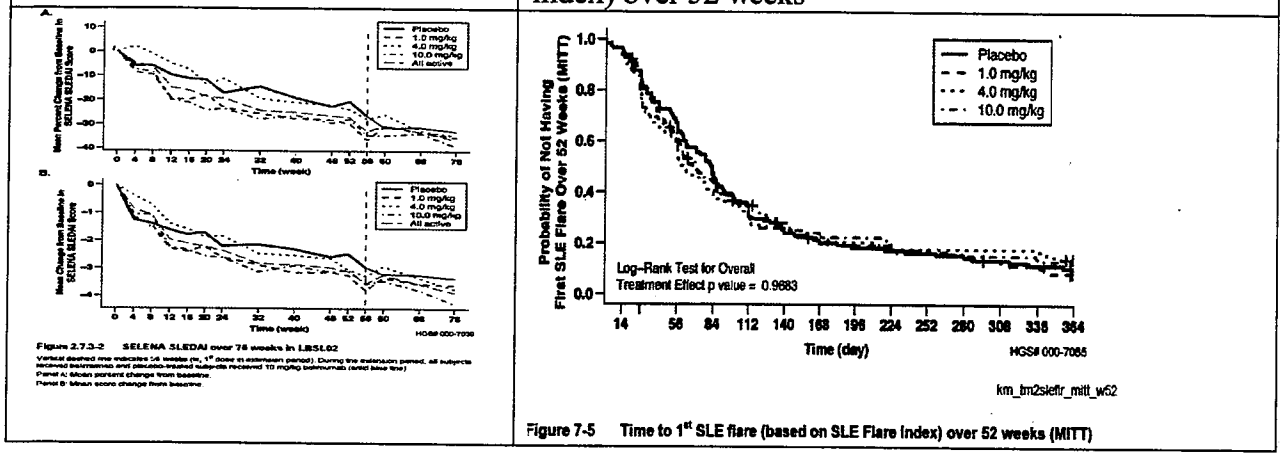


F11A Mean +/- SE scores for SELENA SLEDAI – single dose cohorts

The Phase 2 studies LBRA01 and LBSL02 explored belimumab doses of 1, 4 and 10 mg/kg. Again, in these studies, no consistent dose response was observed.

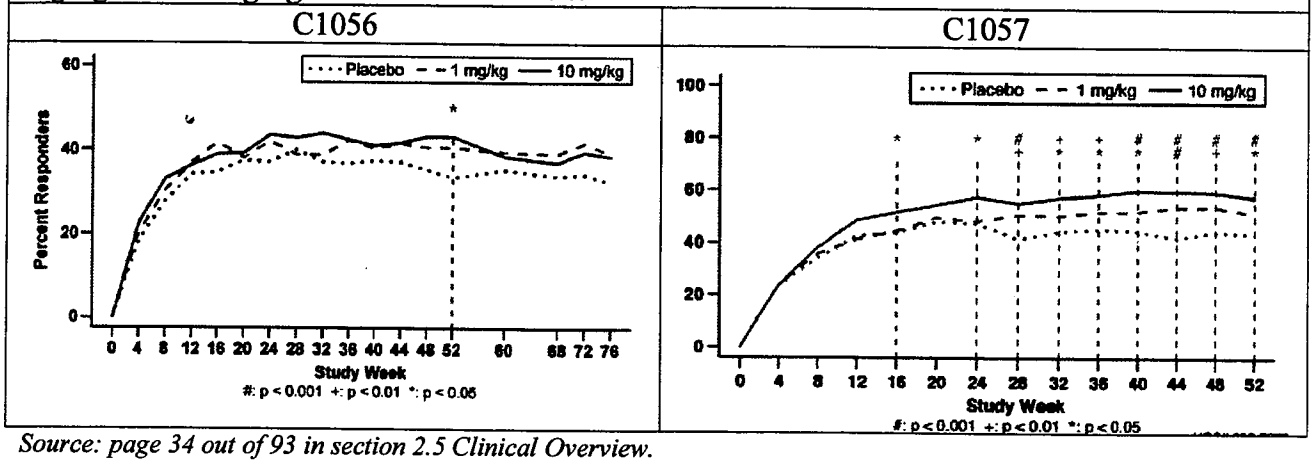
Figure 4: Dose-efficacy response in study LBSL02.

SELENA SLEDAI score at 24 wk	Time to 1st mild/moderate or severe flare (SLE flare index) over 52 weeks



The two pivotal Phase 3 studies investigated the belimumab doses of 1 and 10 mg/kg. For the primary efficacy endpoint of the response rate at Week 52, the belimumab 10 mg/kg dose achieved statistically significant superiority over placebo in both Phase 3 trials, while the 1 mg/kg dose was significantly superior to placebo only in Study C1057. Furthermore, the time to response that was sustained to Week 52 was statistically significantly faster with 10 mg/kg belimumab in both trials compared with placebo. Both primary response rates and time to sustained response were numerically better with 10 mg/kg belimumab than with 1 mg/kg, but not statistically significant.

Figure 5. The percent response for primary endpoint analysis at various weeks for placebo, 1 mg/kg and 10 mg/kg in the Phase 3 trials.

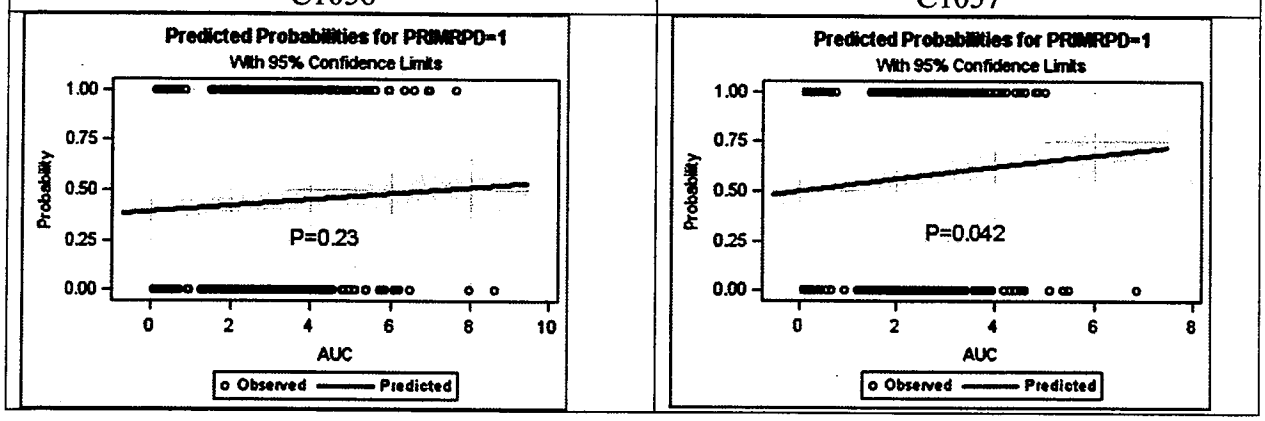


Source: page 34 out of 93 in section 2.5 Clinical Overview.

Note: The primary endpoint was response at Week 52 with response defined as a ≥ 4 point reduction from baseline in SELENA SLEDAI score, 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.

Consistent with the dose-response relationship for belimumab in the Phase 3 trials, the logistic analysis for the primary endpoint (SRI at week52) showed that the exposure-response relationship was significant in C1057, but not significant in C1056.

Figure 6. The logistic analysis for the primary endpoint at week 52 versus predicted AUC for the Phase 3 trials.



2.2.4.2 What are the characteristics of the dose-response relationships for safety?

There was no increase in the incidence or severity of AEs with dose.

In the 3 placebo-controlled SLE studies, belimumab in combination with standard of care therapies for SLE had an overall safety profile that was similar to placebo plus standard of care with regard to frequency, severity, and types of AEs. Over 90% of subjects experienced at least 1 AE. SAEs were experienced by 19% and 17% in the 1 mg and 10 mg belimumab dose groups, respectively, compared with 16% in the placebo group. Severe adverse events occurred at similar rates across the treatment groups.

Table 4. Number of subjects with AEs.

	Placebo N = 675	1 mg/kg N = 673	4 mg/kg N = 111	10 mg/kg N = 674
At least 1 AE	624 (92.4%)	626 (93.0%)	107 (96.4%)	625 (92.7%)
At least 1 serious AE	107 (15.9%)	125 (18.6%)	15 (13.5%)	117 (17.4%)
At least 1 severe[2] AE	104 (15.4%)	104 (15.5%)	26 (23.4%)	103 (15.3%)
At least 1 serious and/or severe[2] AE	145 (21.5%)	155 (23.0%)	32 (28.8%)	152 (22.6%)
At least 1 AE resulting in study agent discontinuation	48 (7.1%)	42 (6.2%)	4 (3.6%)	45 (6.7%)
Deaths	3 (0.4%)	5 (0.7%)	-	6 (0.9%)

Studies LBSL02, C1056, and C1057.

[1] Related is define as possibly, probably or definitely related to study agent.

[2] Severe refers to Grade 3 and Grade 4.

Source: Page 64 out of 93 in Section 2.5 Clinical Overview.

For detailed information regarding the safety information of belimumab, please refer to the medical review.

2.2.4.3 Does this drug prolong the QT or QTc interval?

A designated thorough QT study was not conducted for belimumab. For detailed information regarding the cardiac signals in the Phase 2 and 3 trials, please refer to the medical review.

2.2.5 Immunogenicity

2.2.5.1 What is the incidence of immunogenicity after single and multiple doses of belimumab?

Immunogenicity was observed relatively infrequently. In the 2 Phase 3 studies, 73 out of 559 (13.1%) subjects in the 1 mg/kg group and 5 out of 563 (0.9%) subjects in the 10 mg/kg group tested positive for anti-belimumab antibodies at at least 1 timepoint (ie, both persistent and transiently positive). The immunogenicity assay in the Phase 1 and 2 studies was not robust (please see the immunogenicity assay review for details).

Table 5. The incidence of anti-belimumab antibody.

Study	Study Design	Immunogenicity sampling	Positive anti-belimumab antibody	Neutralizing antibody
LBS01	Single and double dose study N=57	Single dose: Predose, Days 14, 28, 42, 56, and 84/exit Double dose: predose, Days 14, Day 21 prior to dosing, Days 35, 49, 63, 77, and 105/ext	2	1 (1 mg/kg single dose)
LBS02		Predose; prior to dosing at Weeks 2, 8, 24, and 52; and at follow-up visits Week 8 and 24. Extension period: prior to dosing at Weeks 56, 64, and 76; and at follow-up visits Week 8 and 24.	1 (1 mg/kg)	1
C1056	Placebo n=275	Predose, and Weeks 8, 24,	1 (placebo)	1 (placebo)

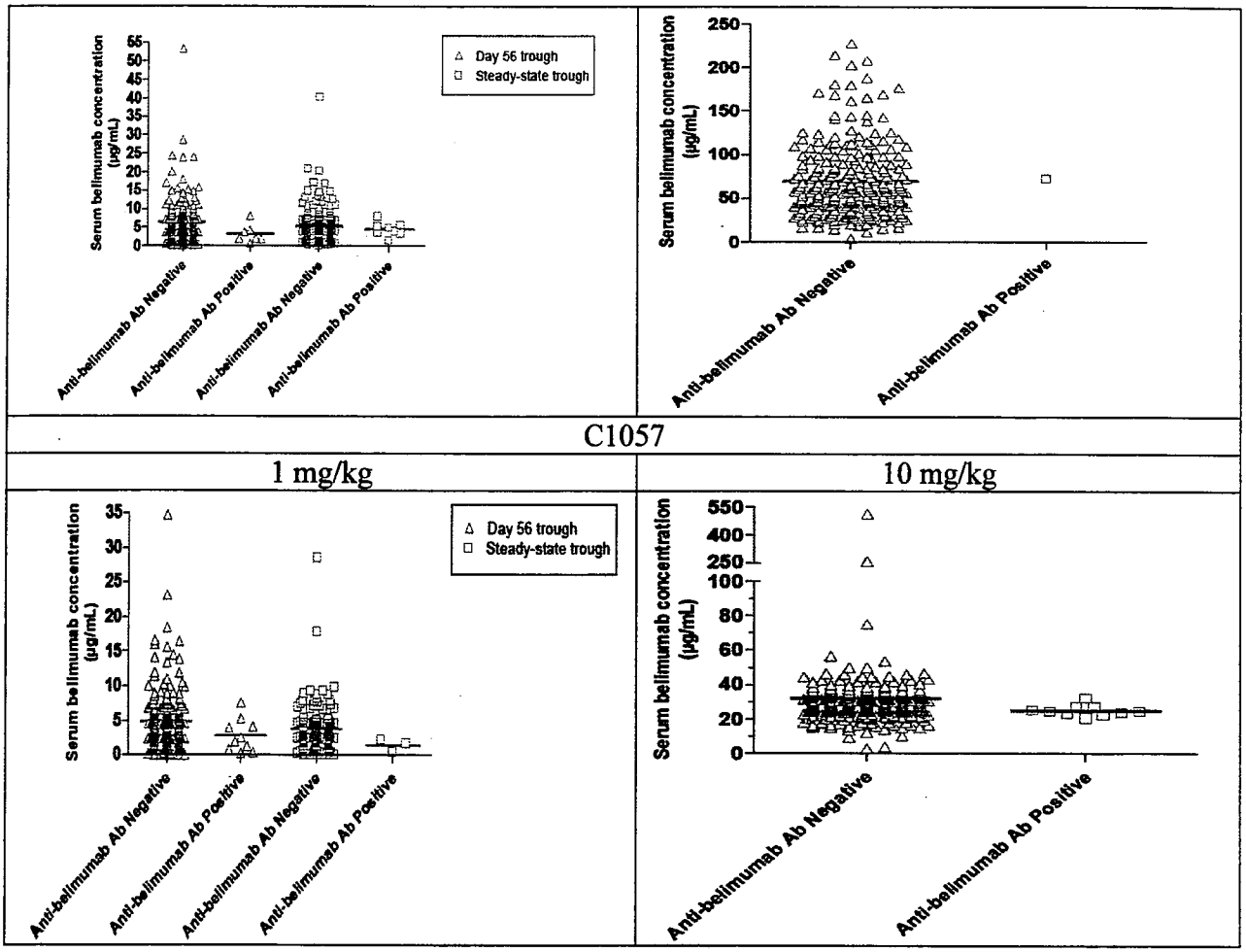
Table 5. The incidence of anti-belimumab antibody.				
	1 mg/kg n=271 10 mg/kg n=273	52/Exit and Week 76/Exit, as well as 8-week follow-up (for subjects discontinuing treatment and not entering the extension period of the study).	39 (1 mg/kg) 2 (10 mg/kg)	2 (1 mg/kg) NA (10 mg/kg)
C1057	Placebo n=287 1 mg/kg n=288 10 mg/kg n=290	Predose, Weeks 8, 24, 52/Exit, and 8-week follow-up (for subjects discontinuing treatment and not entering the extension period of the study).	10 (placebo) 34 (1 mg/kg) 3 (10 mg/kg)	6 (placebo) 2 (1 mg/kg) 0 (10 mg/kg)
LBRA 01	Phase 2 study N=85	prior dose on Day 0, predose at Weeks 2, 8, 24/Exit, and at the 8-week and 24-week follow-up visits.	none	none
C1058	BA study in healthy subjects IV (n=17) SC (n=19)	predose on Day 0 and postdose on Days 14, 21, 28, 42, 56, and 70 or, for subjects who withdrew from the study, at the Exit visit.	2	none

2.2.5.2 What is the effect of immunogenicity on PK, safety and efficacy?

Limited immunogenicity data showed that Immunogenicity did not appear to significantly affect the PK, safety and efficacy of belimumab, however, no definitive conclusion can be made.

In the Phase 3 SLE studies, samples for immunogenicity assessment were drawn on Day 0, and Weeks 8, 24, 52/Exit and Week 76/Exit (in Study C1056), as well as 8-week follow-up (for subjects discontinuing treatment and not entering the extension period of the study). For subjects who had a positive anti-belimumab antibody response at the 8-week follow-up, a serum sample was obtained, if possible, at least 6 months after the last dose of study agent or upon completion and/or unblinding of the study, whichever was later. In the two Phase 3 studies C1056 and C1057, 13.1% of SLE patients in 1 mg/kg and 0.9% of SLE patients in 10 mg/kg showed positive immunogenicity response. The trough belimumab concentration for antibody positive patients was within the range of those for antibody negative patients. The population analysis did not show a statistically significant effect of anti-belimumab antibodies on clearance. The immunogenicity assay in the Phase 1 and 2 studies was not robust (please see the immunogenicity assay review for details). Therefore, the immunogenicity results from these studies are not discussed here.

Figure 7: Trough serum belimumab concentrations following IV infusions of belimumab summarized by anti-belimumab antibody status.	
C1056	
1 mg/kg	10 mg/kg



The immunogenicity status for subjects in Phase 3 studies (where immunogenicity was most reliably measured) who experienced infusion and hypersensitivity reactions is listed in Table 6. Of 76, 88, and 84 Phase 3 subjects in the placebo, 1 mg/kg and 10 mg/kg groups, respectively, that experienced an infusion or hypersensitivity reaction, 4 subjects (1 in the placebo group, 2 in the 1 mg/kg group, and 1 in the 10 mg/kg group) also had persistent positive immune responses to belimumab. Eight subjects in the 1 mg/kg group that had an infusion or hypersensitivity reaction had transient immune responses to belimumab, and the remaining subjects who experienced an infusion or hypersensitivity reaction did not have detectable anti-belimumab antibodies.

Table 6. Immunogenicity summary in Phase 3 studies among subjects with infusion reactions and hypersensitivity reactions.

TA145 Immunogenicity Summary in Phase 3 Studies among subjects with infusion reactions and hypersensitivity reactions

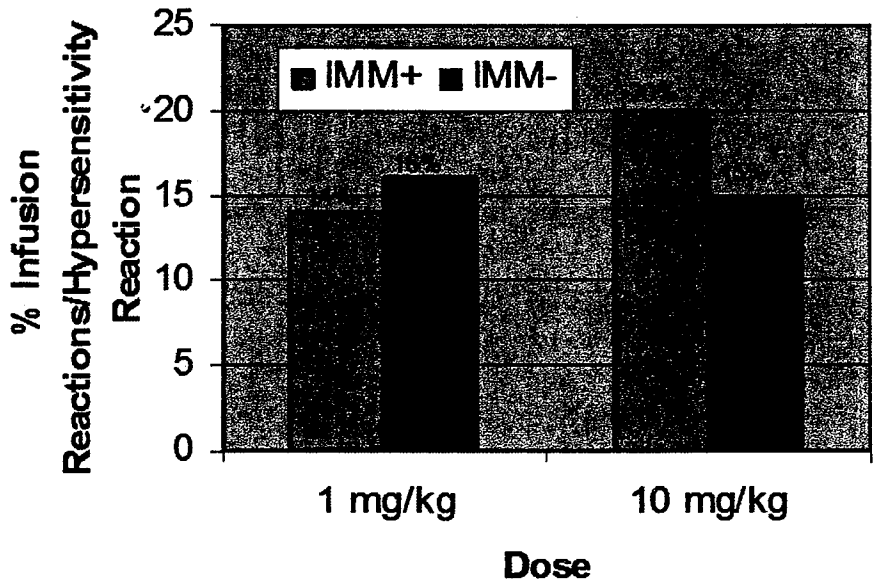
	Placebo N=562	1 mg/kg N=559	10 mg/kg N=563
n	76	88	84
Persistent Positive[1]	1 (1.3%)	2 (2.3%)	1 (1.2%)
NA/Negative —> positive	1 (1.3%)	2 (2.3%)	1 (1.2%)
Median max Assay B signal[3] (range)	619.0 (619, 619)	1071.5 (952, 1191)	1056.0 (1056, 1056)
Max Assay B signal > 1000 ECL	0/ 1 (0.0%)	1/ 2 (50.0%)	1/ 1 (100%)
Max Assay B signal > 10,000 ECL	0/ 1 (0.0%)	0/ 2 (0.0%)	0/ 1 (0.0%)
Neutralizing any time post baseline [4]	1/ 1 (100%)	0/ 1 (0.0%)	0/ 1 (0.0%)
Transient Positive[2]		8 (9.1%)	
NA/Negative —> positive		7 (8.0%)	
Positive —> negative		1 (1.1%)	
Median max Assay B signal[3] (range)		1337.5 (586, 9386)	
Max Assay B signal > 1000 ECL		4/ 8 (50.0%)	
Max Assay B signal > 10,000 ECL		0/ 8 (0.0%)	
Neutralizing any time post baseline [4]		1/ 3 (33.3%)	
Negative	75 (98.7%)	78 (88.6%)	83 (98.8%)

[1]Persistent positive refers to positive immunogenic response at 2 or more assessments or at the final assessment.
[2]Transient positive refers to positive immunogenic response at only 1 assessment and negative at final.
[3]Maximum Assay B signal (without inhibitor) observed per subject among confirmed positive assay B samples.
[4]Neutralizing any time post-baseline among subjects with neutralization assay results available.

Source: Page 4118 of 4999 in the Section 2.7.4 Summary of Clinical Safety Appendices.

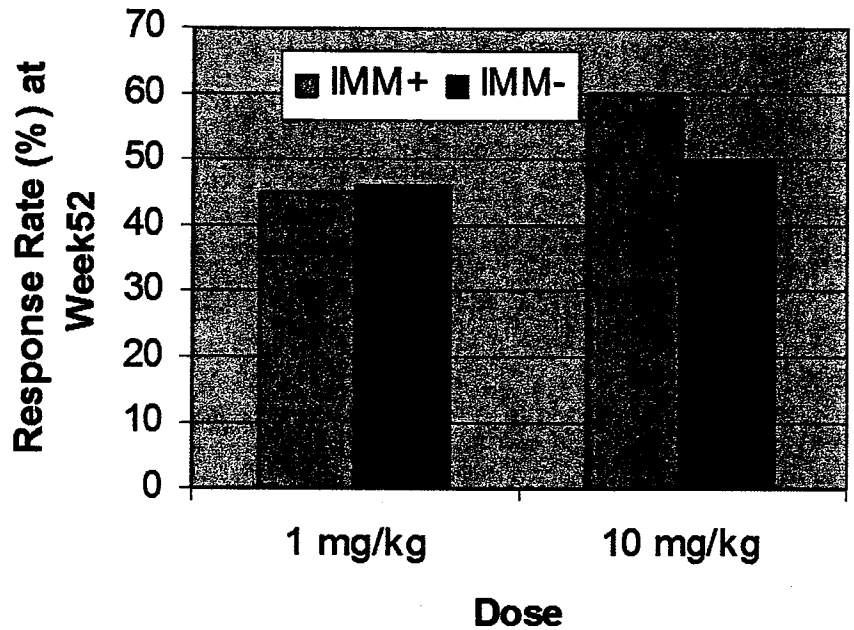
As summarized in Figure 7, for antibody positive patients in 1 mg/kg, the percent infusion reactions/hypersensitivity reaction was 14%; whereas for antibody negative patients in 1 mg/kg, the percent infusion reactions/hypersensitivity reaction was 16%. Similarly, for antibody positive patients in 10 mg/kg, the percent infusion reactions/hypersensitivity reaction was 20%; whereas for antibody negative patients in 10 mg/kg, the percent infusion reactions/hypersensitivity reaction was 15%. Therefore, the percent infusion reactions/hypersensitivity reaction was comparable between antibody positive patients and antibody negative patients.

Figure 8: The effect of anti-belimumab antibody status on the incidence of infusion reactions/hypersensitivity reaction for the Phase 3 trials.



The presence of anti-belimumab antibody did not appear to affect effectiveness of belimumab (Figure 9). In the two Phase 3 studies, for anti-belimumab antibody positive patients, the percent responders at week 52 based on primary endpoint analysis was 60% (3/5) at 10 mg/kg and 45% (33/73) at 1 mg/kg. For anti-belimumab antibody negative patients, the percent responders at week 52 based on primary endpoint analysis was 50% (282/558) at 10 mg/kg, and 46% (225/486) at 1 mg/kg.

Figure 9: The effect of anti-belimumab antibody status on the response rate at week 52 for the Phase 3 trials.



It is of note that as the incidence of immunogenicity is uncommon and the immunogenicity assay was sensitive to biologic concentrations, no definitive conclusion can be made on the effect of immunogenicity on PK, safety, and efficacy.

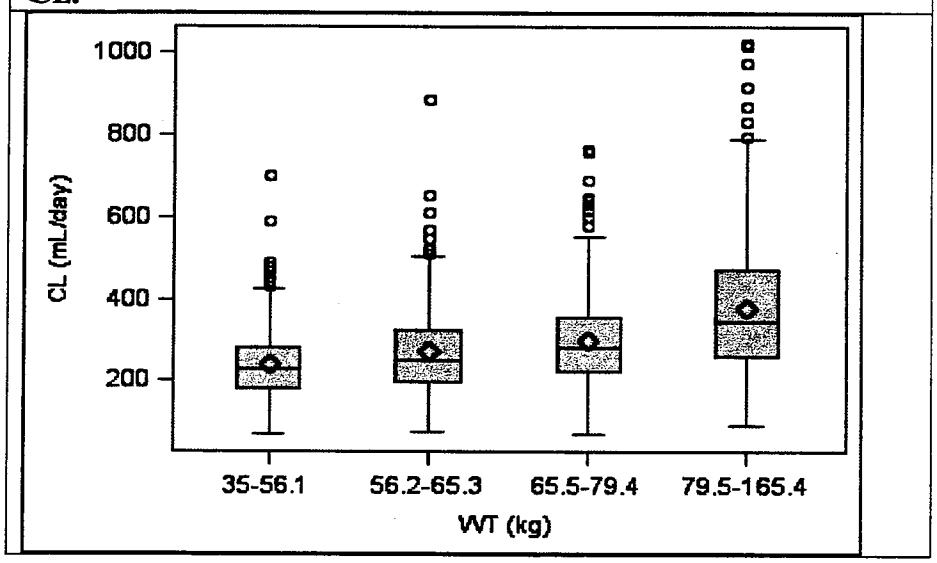
2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

a) Weight

As body weight increases, the systemic clearance of belimumab also increases.

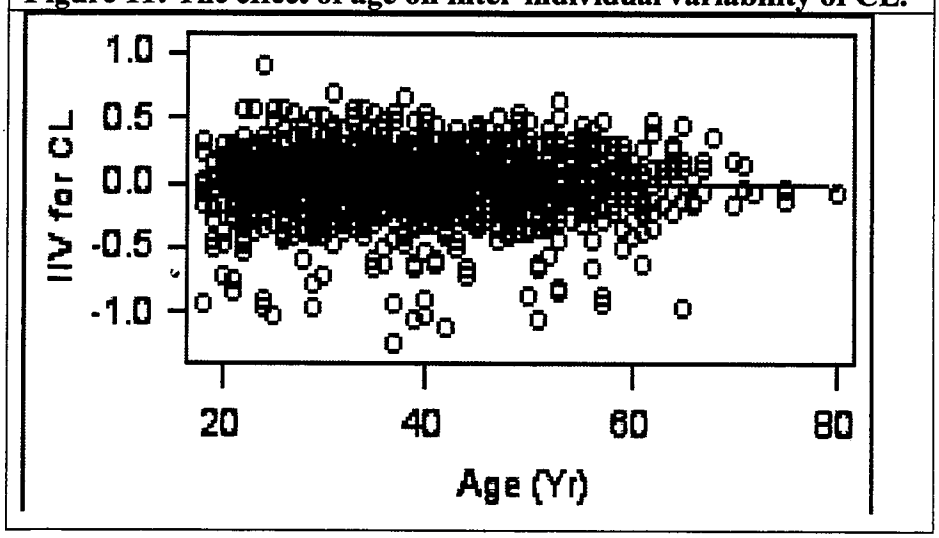
Figure 10: The effect of weight on inter-individual variability of CL.



b) Age

In the overall study population (age range 18 to 80 years) in which, 70% of subjects were 45 or younger and 1.4% of subjects were 65 years or older, age had no statistically significant impact on belimumab PK in the study population.

Figure 11: The effect of age on inter-individual variability of CL.



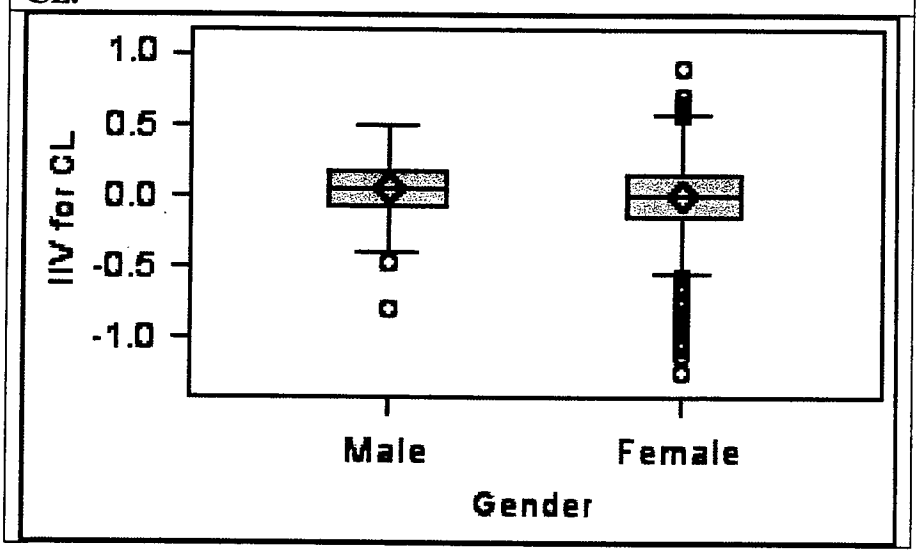
c) Pediatric patients

Belimumab was not evaluated in the pediatric patients in this submission.

d) Gender

The study population comprised about 94% female and 6% male subjects. Sex did not have a statistically significant impact on belimumab PK in the population analysis. However, the number of males in the studies was small.

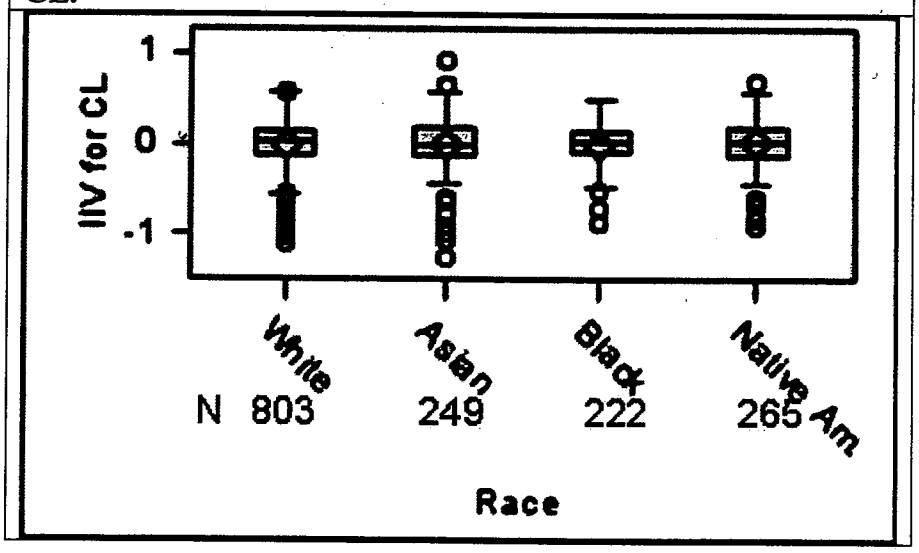
Figure 12: The effect of gender on inter-individual variability of CL.



e) Race

Race (53% white, 16% Asian, 16% Alaska Native or American Indian and 14% black) did not have a statistically significant impact on belimumab PK in the population analysis.

Figure 13: The effect of race on inter-individual variability of CL.



Primary efficacy endpoint response rates in C1056 & C1057 were lower in black subjects

receiving belimumab as compared to placebo (P-interaction=0.06), as shown in the table below. Imbalances in baseline disease activity were observed in subjects of black race (e.g., SLICC damage index 1.18 vs 0.73, low C4 45% vs. 57%). In addition, discontinuation was considered as a treatment failure in the primary endpoint, and blacks tended to have higher discontinuation rates on belimumab than non-blacks (respective discontinuation rates on belimumab 1 mg/kg or 10 mg/kg and placebo were 34% vs. 22% in blacks and 8% vs. 12% in non-blacks). However, similar trends toward lack of efficacy were noted in subjects completing 52 weeks of treatment. Among blacks, the most predictive baseline covariate for response (overall and in the placebo arm) was C4. Among black (and non-black) subjects, those with normal/high C4 at baseline tended to demonstrate no beneficial treatment effect relative to placebo, whereas those with low C4 tended to have a positive response to belimumab at the 10 mg/kg dose relative to placebo. Due to the small sample size, heterogeneity in treatment effects as a function biomarker levels could not be definitively concluded for the black population. The relationship between baseline biomarker levels and BILAG responses to treatment, which does not include serologic measures, was similar.

Table 7 : Response rates and treatment effects by race and baseline C4 status (C1056+C1057)

Population	Primary Endpoint Rate – Week 52						Treatment Comparisons			
	Placebo		1 mg/kg		10 mg/kg		1 mg/kg vs. Placebo	10 mg/kg vs. Placebo	P	P-int
	n	%	n	%	n	%	OR (95%CI)	OR (95%CI)		
Non-Black										
All	196	38.3	24	47.6	267	52.1	1.46 (1.13-1.88)	1.79 (1.39-2.30)	<0.0001	
C4 Normal/high	102	44.7	116	52.5	110	52.4	1.36 (0.93-1.99)	1.37 (0.93-2.02)	0.1898	0.1125
C4 Low	94	33.1	127	43.8	157	51.8	1.60 (1.13-2.26)	2.29 (1.63-3.22)	<0.0001	
Black										
All	22	44.0	15	31.2	18	36.0	0.60 (0.26-1.39)	0.75 (0.33-1.70)	0.4870	
C4 Normal/high	18	58.1	11	45.8	9	34.6	0.69 (0.22-2.13)	0.41 (0.13-1.30)	0.3173	0.1037
C4 Low	4	21.1	4	16.7	9	37.5	0.67 (0.13-3.27)	1.89 (0.46-7.79)	0.3013	

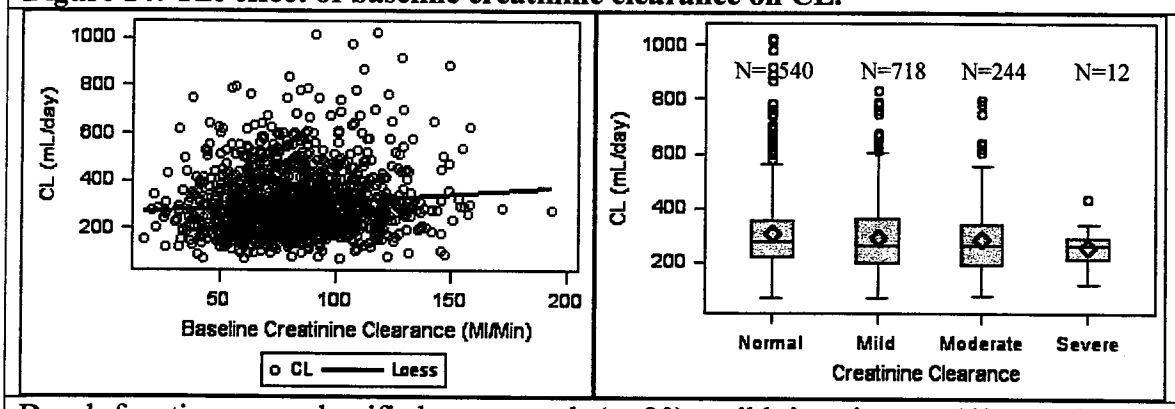
n is the number of responders based on composite endpoint
Odds ratios (OR), 95% confidence intervals (95%CI) adjusted for stratification variables (baseline SLEDAI, proteinuria, race), and trial; MITT population
C4: Normal/High (≥16 mg/dL); Low (<16 mg/dL)
P-values based on Wald test for global effect

Taken together, the lack of efficacy in blacks appears to be driven in part by different disease characteristics that modify placebo response. Belimumab appears to be efficacious in certain subgroups of the black population (specifically those with higher levels of disease activity as reflected by SLEDAI scores or low complement levels).

f) Renal impairment

No formal study was conducted to assess the effect of renal impairment on the belimumab PK. The population PK analysis showed that baseline creatinine clearance was a covariate of CL. However, the median value of CL in normal, mild, moderate, and sever renal impairment patients were similar and were 277, 259, 260, and 264 mL/day, respectively.

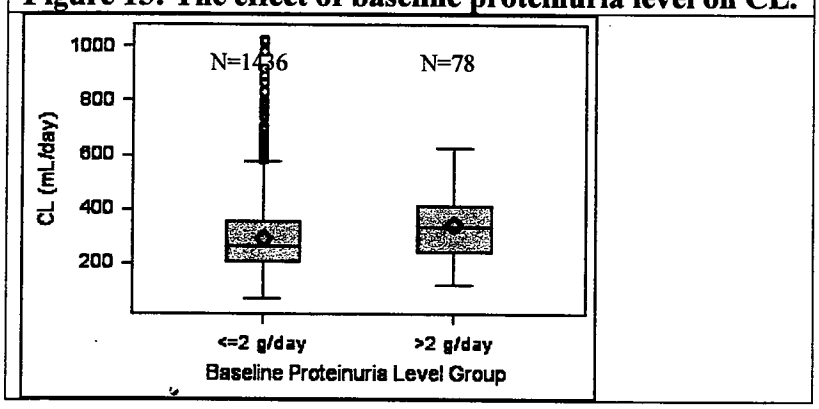
Figure 14: The effect of baseline creatinine clearance on CL.



Renal function was classified as normal (≥ 90), mild impairment (60 to <90), moderate impairment (30 to <60), and severe impairment (< 30).

Baseline protenuria level was also a population covariate of CL. The CL was slightly higher (16%) in patients with baseline proteinuria level greater than 2 g/day as compared to less then or equal to 2 g/day. However, the difference in CL is not likely to be clinically significant and no dose adjustment is needed.

Figure 15: The effect of baseline proteinuria level on CL.

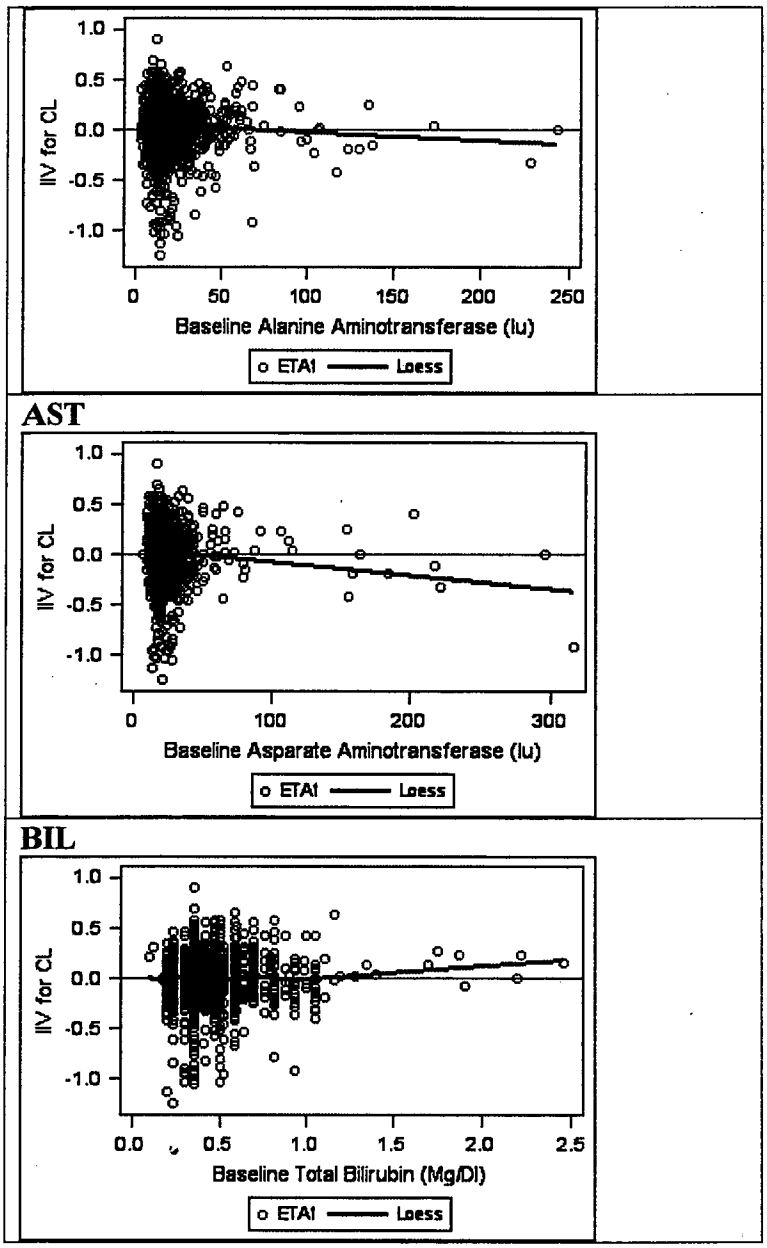


g) Hepatic impairment

No formal study was conducted to assess the effect of hepatic impairment on the belimumab PK. Belimumab has not been studied in patients with severe hepatic impairment. The population PK analysis showed that the inter-individual variability of CL cannot be explained by the baseline value of alanine aminotransferase (ALT), aspirate aminotransferase (AST), and total bilirubin level (BIL).

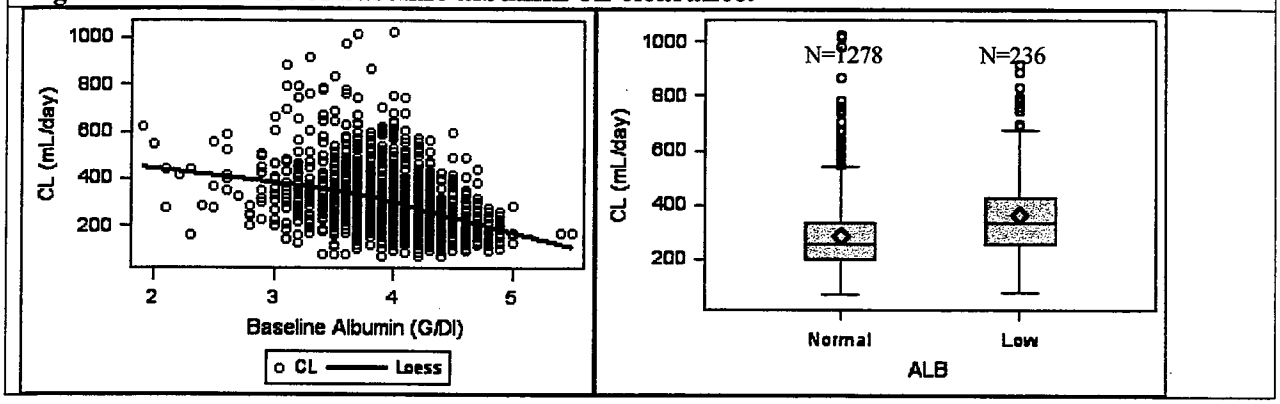
Figure 16: The effect of baseline AST, ALT and BIL on the inter-individual variability of CL.

ALT



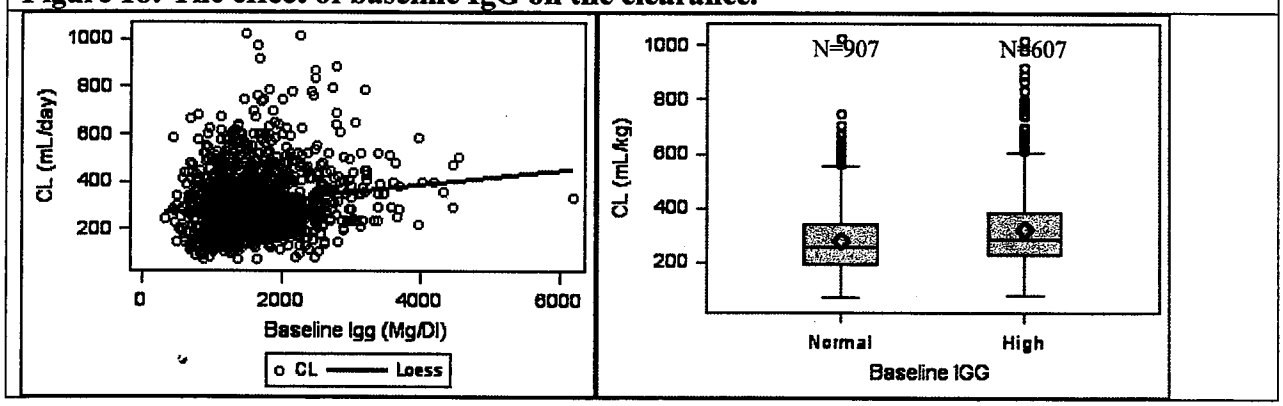
A moderate increase in clearance (30%) was observed for patients with low levels albumin compared to normal patients. The median albumin level in the low group was 3.3 g/dL which is close to normal level of (3.5 g/dL and above). The median value of albumin in the normal groups was 4.1 g/dL. Median values of clearance in the low and normal groups are 258 and 335 mL/day, respectively. The increase in clearance in patients with the low level of albumin is not likely to be clinically significant and no dose adjustment is needed.

Figure 17: the effect of baseline albumin on clearance.



A slightly increase in clearance (10%) was observed for patients with high levels IgG compared to normal patients. The median IgG level in the high group was 2010 mg/dL, and the median IgG level in the normal group was 1230 mg/dL (the cutoff value was 1816 mg/dL). The median value of albumin in the normal groups was 4.1 g/dL. Median values of clearance in the normal and high groups are 256 and 281 mL/day, respectively. The increase in clearance in patients with the high level of IgG is not likely to be clinically significant and no dose adjustment is needed.

Figure 18: The effect of baseline IgG on the clearance.



h) Genetic polymorphism

Not evaluated.

i) What pregnancy and lactation use information is there in the application?

NA.

j) Other factors that are important to understanding the drug's efficacy and safety

Differential efficacy was noted based on baseline levels of C3 and C4, suggesting greater benefit

of belimumab in subjects with higher levels of serologic activity. C3 and C4 levels appeared to interact significantly with treatment, such that subjects with low C3 and C4 had substantially greater treatment effects relative to placebo. This is consistent with greater efficacy in individuals who have higher disease activity (based on SLEDAI scores).

Table 8: Primary efficacy endpoint by baseline biomarker status and treatment (C1056+C1057)

Population	Primary Endpoint Response Rate						Treatment Comparisons			
	Placebo		1 mg/kg		10 mg/kg		1 mg/kg vs. Placebo	10 mg/kg vs. Placebo	P	P-int
	n	%	N	%	n	%	OR (95%CI)	OR (95%CI)		
Overall	218	38.8	258	46.2	285	50.6	1.36 (1.07-1.73)	1.65 (1.30-2.10)	0.0002	
Anti-dsDNA										
Positive	136	35.8	178	45.4	203	51.1	1.52 (1.13-2.04)	1.96 (1.46-2.63)	<0.0001	0.1689
Negative	82	44.8	80	47.9	82	49.4	1.16 (0.75-1.78)	1.19 (0.77-1.84)	0.6905	
C3										
Normal/high	139	44.3	159	51.1	152	50.5	1.35 (0.98-1.86)	1.31 (0.95-1.81)	0.1343	0.0475
Low	79	31.8	99	39.9	133	50.8	1.47 (1.01-2.15)	2.32 (1.61-3.36)	<0.0001	
C4										
Normal/high	120	46.3	127	51.8	119	50.4	1.26 (0.88-1.81)	1.20 (0.83-1.73)	0.4134	0.0325
Low	98	32.3	131	41.7	166	50.8	1.53 (1.09-2.13)	2.24 (1.61-3.11)	<0.0001	

n is the number of responders based on composite endpoints.
Odds ratios (OR), 95% confidence intervals (95%CI) adjusted for stratification variables (baseline SLEDAI, proteinuria, race), and trial; MITT population
P-values based on Wald test for global effect

Changes in C3, C4, and naïve B-cells, were significantly correlated with response to belimumab. However, these biomarkers were not robust surrogates of response.

2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The exposure of belimumab is not affected by age, gender, race, and immunogenicity. No dose modification is needed. The effect of body weight on belimumab exposure was adjusted by the body weight based dosing regimen.

2.4 Extrinsic Factors

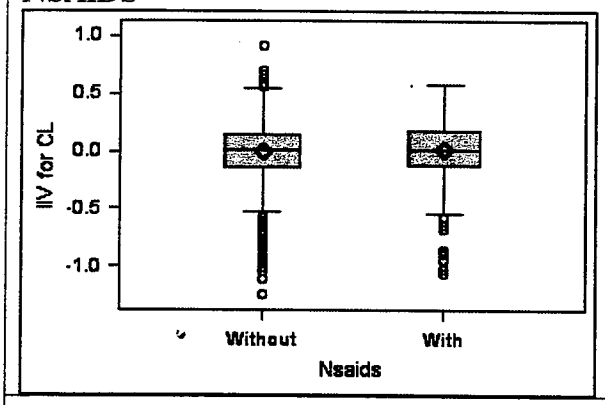
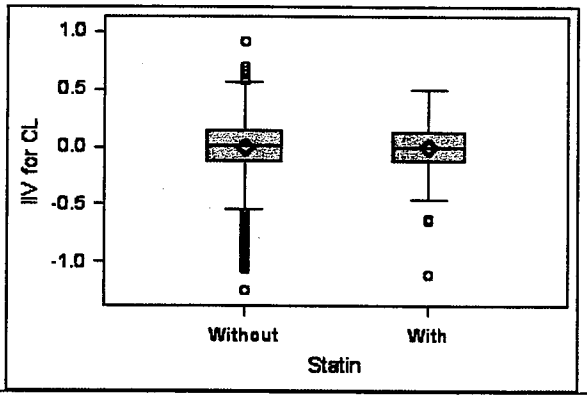
2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

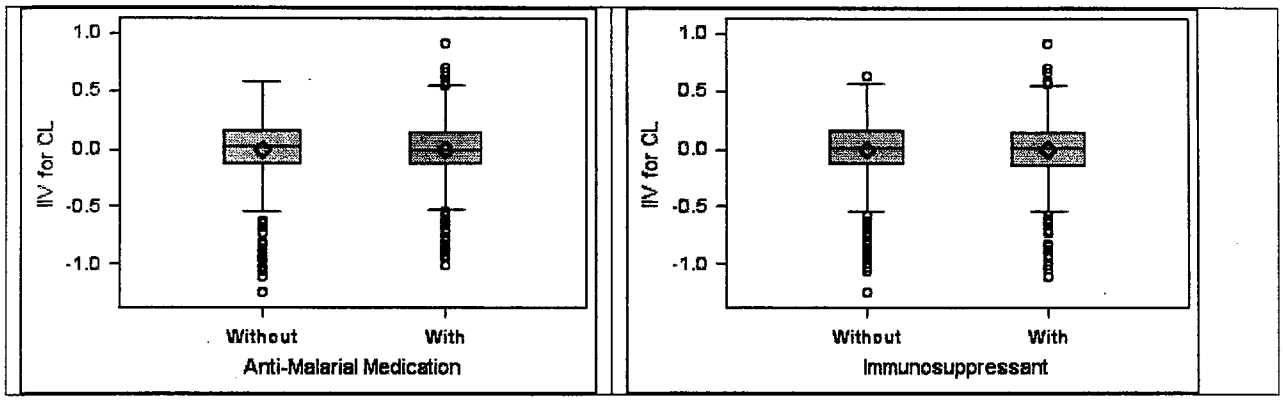
NA.

2.4.2. Drug-Drug Interactions

No formal drug-drug interaction studies were conducted in this submission. IgG antibodies are not metabolized by P450s. Therefore, direct pharmacokinetic interaction via the CYP pathway is not expected between belimumab and co-administered small molecular weight drugs. POP-PK analysis evaluated the commonly co-administered drugs in SLE patients including corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including azathioprine, methotrexate, and mycophenolate), angiotensin pathway antihypertensives, HMG-CoA reductase inhibitors (statins), and NSAIDs. The coadministration of NSAIDS, statins, anti-malarial medications and immuosuppressants did not affect the belimumab PK.

Figure 19: The effect of concomitant medication on inter-individual variability of CL based on population analysis.

NSAIDS	Statins
	
Anti-malarial medications	Immunosuppressant medications



Only steroids and ACE inhibitors has statistically significant effects on belimumab exposure (6% and 9% increase in central clearance, respectively), which were small and not of clinical concern.

The effect of belimumab on the exposures of coadministered drugs was not evaluated.

2.4.3. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

NA.

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

NA.

2.5.2. What is the *in vivo* relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Commercial formulation (06-B) was also used in the Phase 3 studies. The proposed commercial manufacturing processes (M10-15) were used in the Phase 3 studies. No clinical comparability studies were needed.

2.6 Analytical Section

2.6.1 What bioanalytical methods were used to assess belimumab concentrations?

Serum belimumab concentrations were measured using either an enzyme-linked immunosorbent assay (ELISA) or an electrochemiluminescence (ECL)-based assay in studies.

Serum belimumab concentrations were measured using either an enzyme-linked immunosorbent assay (ELISA) in studies LBSL01, LBSL02, and LBRA01 or an electrochemiluminescence (ECL)-based assay in studies C1058, C1056, and C1057. ECL assay has greater dynamic range and allows higher through-put.

Table 9. The analytical methods used in each study.

Assay	ELISA	ECL	ECL (modified assay)[1]
Clinical Study (Development Phase)	LBSL01 (Ph 1) LBRA01 (Ph 2) LBSL02 (Ph 2)	C1056 (Ph 3) C1057 (Ph 3) C1058 (Ph 1 SC)	C1057 (Ph 3) C1058 (Ph 1 SC)
Platform	ELISA	ECL-based	
Matrix	Human serum	Human serum	
Capture reagent	Biotinylated BLyS bound to streptavidin-coated ELISA plate	Biotinylated BLyS bound to streptavidin-coate (b) (4) plate	
Detection reagent	Anti-human IgG Fc-HRP	Polyclonal rabbit anti-belimumab followed by SULFO-TAG polyclonal goat anti-rabbit IgG	

Source: Page 12 out of 15 in section 2.7.1 Summary of Biopharmaceutic Studies.

2.6.3 What was the assay performance for belimumab concentration measurement?

The PK assay was appropriately qualified and is suitable for the quantitative determination of belimumab in human serum.

The assay performance was displayed in the Tables 10 and 11 for ELISA and ECL assay, respectively.

Table 10. Summary of qualification parameters for ELISA PK assay.

Parameter	Report Section	Qualification Result
LLOD	8.2.1	0.137 ng/mL
LLOQ	8.2.2	0.277 ng/mL
HLOQ	8.2.2	20 ng/mL
Linearity	8.2.3	(R^2 of 0.995 over the linear range)
Range of standard curve (in 0.2% serum)	8.2.4	0.277 - 20 ng/mL
Maximum serum concentration	8.3.1	0.2%
LLOQ in undiluted serum	8.3.2	138.5 ng/mL
Background variation	8.3.3	3/108 samples LLOQ > 138.5 ng/mL
Precision:[a]		
Repeatability	8.4.1	3.44 - 11.75%
Intermediate, day-to-day	8.4.1	10.33 - 13.32%
Intermediate, analyst-to-analyst	8.4.1	0.00 - 13.50%
Total precision	8.4.1	10.33 - 18.88%
Accuracy	8.4.2	87.02% to 107.45%.
Linearity (spiked serum)	8.4.3	R^2 value of 0.997 over the linear range

[a]Range observed

Source: page 48 out of 51 in the Assay qualification report HG19399.SLE.0.023.

The ELISA PK assay was appropriately qualified and is suitable for the quantitative determination of belimumab in human serum.

Table 11. Summary of qualification parameters for ECL PK assay.

Parameter	Section of the Report	Validation Results
Parameters of the standard curve		
%Recovery of mean back calculated concentration of calibrators	5.1.1	Standard calibrators 1-8 have acceptable %recovery : 95.8 to 102.6%
%RE of mean back calculated concentration of calibrators	5.1.1	Standard calibrators 1-8 have acceptable relative error : -4.2 to 2.6%
%TE of mean back calculated concentration of calibrators	5.1.1	Standard calibrators 1-8 have acceptable total error : 1.4 to 8.8%
Anchor points	5.1.1	Standard calibrator 9 is considered an anchor point
LLOQ (on the plate)	5.1.1	0.250 ng/mL
ULOQ (on the plate)	5.1.1	120 ng/mL
Range	5.1.1	0.250 to 120 ng/mL
R^2	5.1.1	>0.980 for all plates
Parameters of sample analysis		
LLOQ in undiluted matrix	5.2.1	0.100 µg/mL (1:400 dilution)
HLOQ in undiluted matrix	5.2.1	960 µg/mL (1:8,000 dilution)
Precision	5.2.1	5.5% to 10.9% for the 1: 400 dilution 5.6% to 21.1% for the 1: 8,000 dilution
Accuracy	5.2.1	-9.6% to 17.8% for the 1:400 dilution -5.7% to 11.2% for the 1:8,000 dilution
CV acceptance criteria for samples	-	20%
Stability	5.3	Belimumab is stable at 6 days at -20°C, 7 days at 4°C, 1 Day at 22°C, and can undergo 3, 5 and 7 freeze/thaw cycles
Long term stability at -80°C	5.3	Belimumab spikes had acceptable recovery after >3 years at -80°C
Specificity	5.5	All Spikes <LLOQ
Backgroundl variation	5.6	Normal Donors 21/21samples <LLOQ SLE patients 45/46 samples <LLOQ

Source: Page 53 out of 120 in report TR 06-10-002.

The ECL PK assay was appropriately validated and is suitable for the quantitative determination of belimumab in human serum.

2.6.4 What bioanalytical methods were used to assess the formation of anti-belimumab antibodies?

The immunogenicity detection method used on samples from the Phase 1 study, LBSL01, comprised of 2 screening assays designed to detect anti-belimumab antibodies and assess

whether these antibodies bound the fragment crystallizable region (Fc) or fragment antigen-binding region (Fab) of belimumab. The Phase 1 assay has the following deficiencies: Anti-kappa HRP reagent in the IgG assay could not detect ADA with lambda chains; Sensitivity of the assays was dependent on pre-dose sera signal; The assay sensitivity decreased as the sera background increases; Belimumab concentration greater than 5 μg/ml could interfere with each screening assay; the assay did not take account for ADA already bound to belimumab in serum.

For the Phase 2 study, serum samples are initially screened for antibodies that bind the antibody antigen binding (Fab) fragment of belimumab (belimumab-Fab) in a direct-binding format. The confirmative assay used the same method performed in the presence of excess belimumab with the exception that controls and serum samples are added to belimumab-Fab coated plates in the presence and absence of 100 μg/mL of belimumab. However, the matrix affects unknown and the effect on BLyS levels was unknown. In the Phase 3 study, the assay used an ECL-based (b) (4) bridging assay. For detailed description in the assay performance review, please see the CMC review.

Table 12. Belimumab immunogenicity screening and confirmatory assays.

Clinical Study in which Assay Used (Phase)	LBSL01 (Ph 1)	LBRA01 (Ph 2) LBSL02 (Ph 2)	C1056; C1057 (Ph 3) LBSL99; LBRA99 (Ph 2 continuation studies) C1058 (Ph 1-SC)
Assay name	**IgG Screening Assay[1]**	**Screening Assay (Assay A)**	
Capture reagent	Belimumab ($IgG_1\lambda$)	Belimumab Fab fragment ($IgG_1\lambda$ Fab)	Belimumab Fab-Biotin Captured (after reaction with serum sample and detection reagent) on streptavidin coated plate
Detection reagent	Anti-human κ –HRP	Protein A/G-HRP	Belimumab Fab-SULFO-TAG
Criterion for Positive Result	If mean A_{450} postdose ≥ 2 x mean A_{450} predose	sample signal > assay cut point[2]	sample signal ≥ assay cut point[3]
LOD	5 µg/mL	0.5 µg/mL	0.1 µg/mL
Drug interference[4] (belimumab →LOD)	Up to 5 µg/mL no effect	1.0 µg/mL→ 4.0 µg/mL	40 µg/mL → 2 µg/mL
Assay name	**Fab Screening Assay[1]**	**Confirmatory Assay (Assay B)**	
Capture reagent	Belimumab Fab fragment (IgG_1/λ Fab)	Belimumab Fab fragment (IgG_1/λ Fab)	Belimumab- Biotin Captured (after reaction with serum sample and detection reagent) on streptavidin coated plate
Competitor	None	Belimumab	Belimumab, TACI:Fc
Detection reagent	Anti-human (IgG+IgM+IgA) –HRP	Protein A/G-HRP	Belimumab-SULFO-TAG
Criteria for Positive Result	If mean A_{450} postdose ≥ 2 x mean A_{450} predose	signal in the presence of belimumab < signal in the absence of belimumab ($p \leq 0.05$, z-test)	Percent reduction in the log-transformed signal in the presence of belimumab ≥ 8.09%; and Ratio of the log-transformed signals in the presence of TACI:Fc and belimumab > 1.035
LOD	5 µg/mL	NA	0.1 µg/mL
Drug interference[4] (belimumab →LOD)	Up to 5 µg/mL no effect	NA	10 µg/mL → 1 µg/mL[5]
Reference for IgG, Fab, Screening or Confirmatory Assays	TR-PD-06-03-006 (Qualification)	TR-06-04-039 (RA samples, Qualification) TR-06-03-022 (SLE samples, Qualification)	TR-06-07-018 (Qualification) TR-06-07-028 (Validation)

Source: Page 39 in Section 2.7.2 Summary of Clinical Pharmacology Studies.

2.6.5 What was the performance of the neutralizing assay for belimumab?

The neutralizing assay for belimumab in Phase 3 studies was robust and fully validated.

Phase 1 study used fluorometric immunoassay methods to evaluate the presence of neutralizing anti-belimumab antibody in a serum sample. The Phase 1 neutralization assay was sensitive to both belimumab (≥ 15 ng/ml) and BLyS, and the stability was not assessed. For the Phase 2 neutralization assay, the inhibitory activity of the anti-belimumab decreased as the percent serum

in the assay increases and drug interference occurred at ≥ 20 ng/ml. For the Phase 3 studies, a neutralization of binding assay using the (b) (4) ECL platform was developed to determine whether ADA are able to neutralize belimumab binding to BLyS. See the tables below for the assay performance. For detailed description in the assay performance review, please see the CMC review.

Table 13: Belimumab neutralization assays.

Clinical Study in which Assay Used (Phase)	LBSL01 (Ph 1)	LBRA01 (Ph 2) LBSL02 (Ph 2)	C1056; C1057 (Ph 3) LBSL99; LBRA99 (Ph 2 continuation studies) C1058 (Ph 1-SC)
Capture reagent	Belimumab (IgG_1/λ)	Belimumab (IgG_1/λ)	BLyS receptor 3:Fc (BR3:Fc)biotin bound to streptavidin-coated plate
Detection reagent	Europium-labeled BLyS (Eu-BLyS)	Eu-BLyS	BLyS-SULFO-TAG
Criterion for Positive Result	If mean postdose ≤ mean predose (p< 0.01 unpaired 1-tailed t-test)	mean postdose < mean predose (p≤ 0.01 unpaired 1-tailed t-test) or mean postdose >20% lower than mean predose	If mean postdose ≥29% greater than predose (or Negative Control)
LOD	1.5 µg/mL	0.75 µg/mL	0.4 µg/mL
Drug interference (belimumab →LOD)[1]	Up to 15 ng/mL no effect	Up to 20 ng/mL no effect	0.25 µg/mL → 2µ/mL
Reference for Neutralization Assay	HG19399.SLE.0.022 (Qualification)	HG19399.SLE.0.034 (Qualification)	TR-06-07-027 (Qualification), TR-06-08-012 (Validation)

[1] Concentration of belimumab in serum above which serum belimumab interferes with assay ability to reliably detect anti-belimumab antibodies.

Source: page 40 in section 2.7.2 Summary of clinical pharmacology studies.

3 LABELING STATEMENTS

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in <u>underline blue font</u>.

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX 1. INDIVIDUAL STUDY REVIEW

LBSL01

Study Title: A Phase 1, Multi-Center, Double-Blind, Single and Double Dose-Escalation Study to Evaluate the Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of LymphoStat-B® (Monoclonal Anti-BLyS Antibody) in Subjects with Systemic Lupus Erythematosus

Objectives:

Primary: To evaluate the safety, tolerability, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenously (IV) administered belimumab in subjects with systemic lupus erythematosus (SLE).

Secondary: To evaluate the effect of belimumab on clinical disease activity, total serum IgG (and IgM, IgA, and IgE), and concentrations of peripheral mature B lymphocytes and plasmacytoid cells, as well as biological markers of SLE disease activity, including autoantibodies.

Study Design: This was a Phase 1, multi-center, randomized, double-blind, placebo-controlled, dose escalation study of belimumab in subjects with SLE. Dose levels of 1, 4, 10, and 20 mg/kg belimumab were administered IV as a single dose (Cohorts 1-4) or double dose (2 doses, 21 days apart; Cohorts 5-8). The study included a screening period (Days -28 to -1), a treatment period (Day 0 for single dose cohorts; Days 0 and 21 for double dose cohorts), and a follow-up period (last dose of study agent through Day 84 and Day 105 for single and double dose cohorts, respectively). Safety, efficacy, PK, and PD assessments were made throughout the study.

		Planned			Treated & Completed		
	Dose Level	Active	Placebo	Total	Active	Placebo	Total
Single Dose							
Cohort 1	1 mg/kg	7-8	1-2	8-10	8	2	10
Cohort 2	4 mg/kg	7-8	1-2	8-10	7	2	9
Cohort 3	10 mg/kg	7-8	1-2	8-10	7	2	9
Cohort 4	20 mg/kg	7-8	1-2	8-10	7	1	8
Double Dose							
Cohort 5	1 mg/kg	7-8	1-2	8-10	7	2	9
Cohort 6	4 mg/kg	7-8	1-2	8-10	7	2	9
Cohort 7	10 mg/kg	7-8	1-2	8-10	7	2	9
Cohort 8	20 mg/kg	7-8	1-2	8-10	7	0	7
All Cohorts		56-64	8-16	64-80	57	13	70

Study Population: A total of 64-80 subjects were planned for this study; 70 were treated and all completed the study.

Data Analysis: In total, 70 subjects with SLE were enrolled into 8 cohorts. Thirteen subjects received placebo, and 57 subjects received belimumab. Demographics were generally balanced among treatment groups. For single dose cohorts, 86% of subjects were female, 34% were white and 59% black, with an age range of 22 to 80 years, and weight range of 41 to 114 kg. For double dose cohorts, all subjects were female, 54% were white and 46% black, with an age range of 22 to 61 years, and weight range of 55 to 125 kg. Serum belimumab concentrations were detected in all subjects following belimumab dosing and all 57 subjects who received belimumab treatment were considered evaluable for PK from this study.

Blood samples were collected at scheduled times to determine the serum belimumab concentrations for PK assessment. In subjects receiving a single dose of belimumab, blood was collected prior to dosing, at 5 minutes, 1, 3, 6 and 24 hours following administration and on Days 2, 4, 7, 14, 21, 28, 42, 56 and 84. For subjects receiving 2 doses of belimumab, blood was collected prior to the 1st infusion, at 5 minutes, 1, 3, 6 and 24 hours, and on Days 2, 4, 7, 14 and 21. Following the 2nd infusion on Day 21, blood was collected at 5 minutes, 1, 3, 6 and 24 hours, and on Days 23, 25, 28, 35, 42, 49, 63, 77 and 105. Serum belimumab concentrations were determined using an ELISA assay, with a lower limit of quantitation (LLOQ) of 138.5 ng/mL. PK parameters were assessed by compartmental analysis. Descriptive statistics were used to summarize the PK parameters and serum belimumab concentration-time results. Linearity was assessed using 2-way analysis of variance (ANOVA).

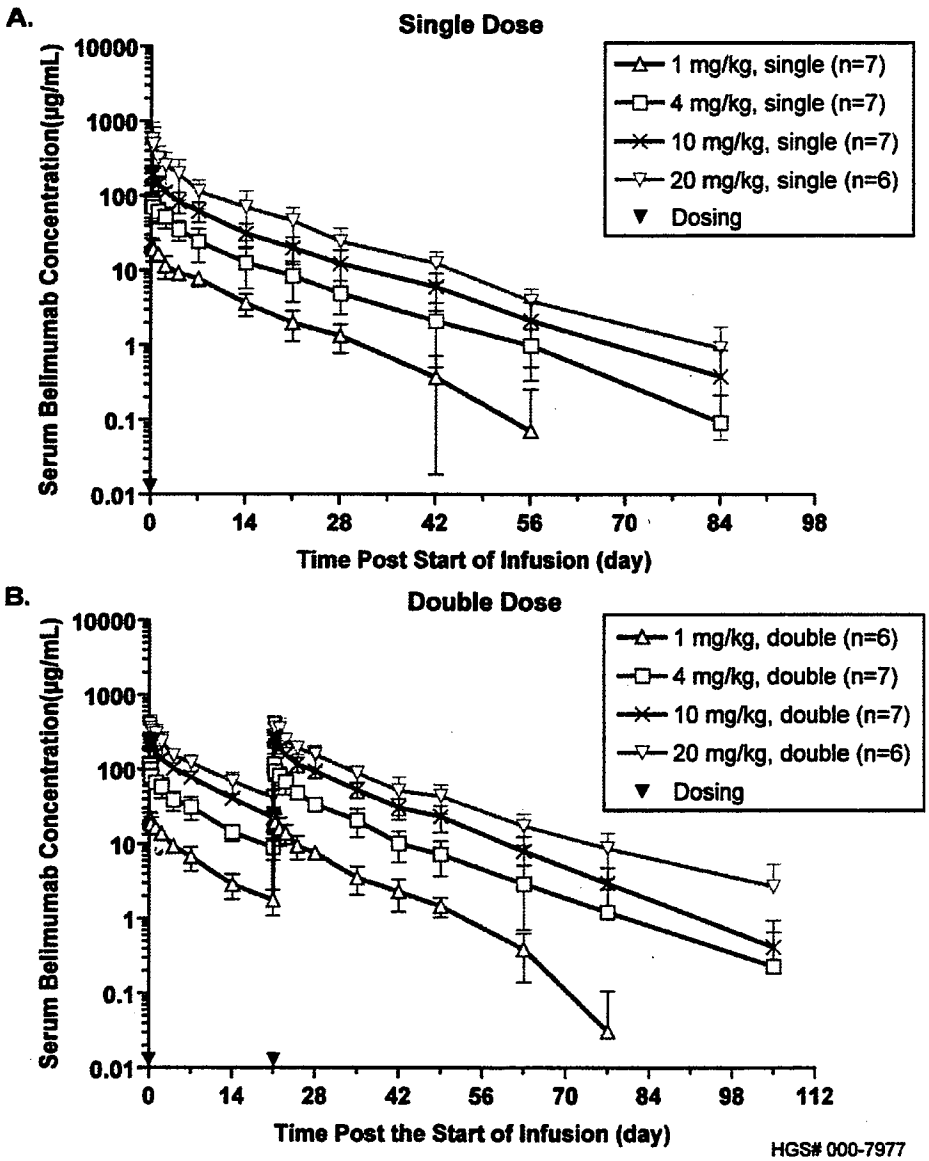
Results: Following single IV administration, serum belimumab concentrations declined in a bi-exponential manner, with a mean distribution half-life ($t1/2,\alpha$) of 1.0 to 1.8 days and a mean terminal elimination half-life ($t1/2,\beta$) of 8.5 to 11.3 days. The mean volume of distribution for the central compartment (V1) ranged from 45 to 53 mL/kg, approximating the plasma volume (43 mL/kg). The mean steady-state volume of distribution (Vss) ranged from 73 to 112 mL/kg, about twice the mean V1 and one-fourth to one-half of the extracellular fluid volume (~260 mL/kg, Davies and Morris, 1993), suggesting that belimumab localizes primarily in the plasma compartment and the interstitial fluid spaces of more permeable tissues. The CL of belimumab after a single IV dose ranged from 6.9 to 7.3 mL/day/kg across the single cohorts, which is much less than the glomerular filtration rate (2571 mL/day/kg), indicating that renal clearance is not a major component of belimumab clearance. The mean residence time (MRT) ranged from 11.1 to14.0 days across the single dose cohorts.

Following IV administration of 2 doses of belimumab given 21 days apart, the mean $t1/2,\alpha$ ranged from 1.0 to 2.2 days, while the mean $t1/2,\beta$ ranged from 9.6 to 14.1 days. The mean V1 (40 to 57 mL/kg), Vss (69 to 102 mL/kg), CL (5.6 to 7.0 mL/day/kg), and MRT (11.0 to 16.1 days) were similar to the corresponding values in single dose cohorts. Drug accumulation for the maximum serum drug concentration (Cmax) averaged 9% when 2 doses of 4, 10 or 20 mg/kg were administered 21 days apart, which was as expected based on the $t1/2,\beta$ for those cohorts. Mean serum belimumab concentration-time profiles are presented in Figure 1.

There were no statistically significant differences in PK parameters between single and double dose cohorts. Overall, belimumab PK were dose-proportional across the 1 to 20 mg/kg dose range in this study.

Two subjects had positive anti-belimumab antibody responses, and the observed serum concentrations were 2- to 3.5-fold lower than the predicted values at the time points when positive anti-belimumab antibodies were detected, suggesting an altered PK profile for these 2 subjects.

Figure 1. Serum belimumab concentrations (mean ± SD) following single or double (Days 0 and 21) IV doses given as 2-hour infusion (LBSL01).



Upper panel – single dose, lower panel – 2 doses (Days 0 and 21). One subject in the single dose 20 mg/kg group did not receive a full dose due to an urticarial reaction and 1 subject in the 1 mg/kg double dose cohort was misdosed on the 2nd dose. Two subjects (1 in the 1 mg/kg single dose cohort and 1 in the 20 mg/kg, double dose cohort 8) tested positive for anti-belimumab antibodies. Serum concentration data from these 4 subjects were not included in the plot (Report LBSL01.PK, Figures 1 and 2).

Table 3: Mean (±SD) PK parameters following a single IV dose of belimumab at 1, 4, 10 and 20 mg/kg given at a 2-hour infusion.

	Cohort 1 1 mg/kg (n = 7)[a]	Cohort 2 4 mg/kg (n = 7)	Cohort 3 10 mg/kg (n = 7)	Cohort 4 20 mg/kg (n = 6)[b]
C_{max} (µg/mL)	22.3 ± 4.2	81.2 ± 24.6	192.4 ± 34.9	523.9 ± 293.7
C_{max}/Dose (kg/mL)	0.0223 ± 0.0042	0.0203 ± 0.0061	0.0192 ± 0.0035	0.0262 ±0.0147
$AUC_{0-\infty}$ (day•µg/mL)	156 ± 46	629 ± 258	1510 ± 315	3384 ± 1424
$AUC_{0-\infty}$/Dose (day•kg/mL)	0.1561 ± 0.0456	0.1572 ± 0.0646	0.1510 ± 0.0315	0.1692 ± 0.0712
$t_{1/2,\alpha}$ (day)	0.96 ±0.61	1.49 ± 0.76	1.84 ± 0.89	1.27 ± 0.43
$t_{1/2,\beta}$ (day)	8.46 ± 2.21	9.88 ± 2.18	10.63 ± 2.89	11.34 ± 3.02
V_1 (mL/kg)	44.90 ± 7.12	52.69 ± 18.59	52.91 ± 10.20	53.17 ± 40.89
V_{ss} (mL/kg)	73.29 ± 13.64	82.33 ± 22.31	86.30 ± 16.77	111.67 ± 95.72
CL (mL/day/kg)	7.15 ± 3.18	7.20 ± 2.48	6.90 ± 1.57	7.33 ± 4.38
MRT (day)	11.13 ± 3.08	12.18 ± 3.22	13.03 ± 3.59	14.01 ± 4.17

Dose response with respect to changes in anti-dsDNA for subjects with baseline values ≥ 10 IU/mL was analyzed using a repeated measures approach to model percent change from baseline across time points as a function of belimumab dose, number of injections, and baseline value. A statistically significant relationship was observed for a greater percent decrease in anti-dsDNA with increasing dose of belimumab (slope = -1.2403, p = 0.0406)

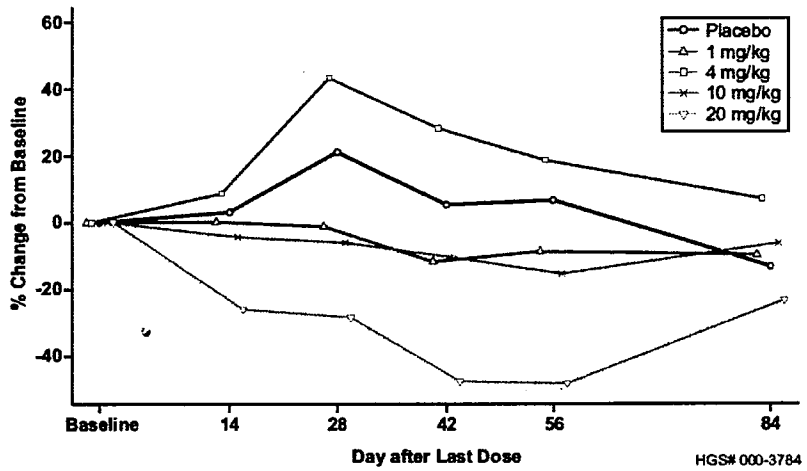


Figure 8 Mean percent change in anti-dsDNA levels for subjects with baseline values ≥ 10 IU/mL (n = 31) by dose level

The median CD20+ percentage of lymphocytes at baseline was similar in the placebo (10.8-13.5%) and belimumab (12.5-15.0%) treatment groups. In general, the mean percent decrease in CD20+ cell count was greater for belimumab treatment groups relative to placebo.

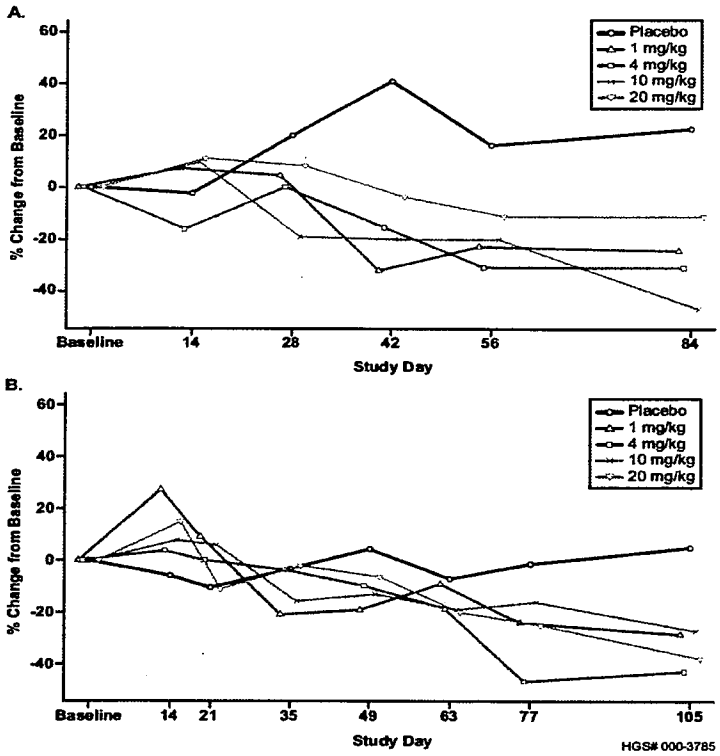


Figure 9 **Median percent change in CD20$^+$ cells - single dose (A) and double dose (B) cohorts**

No statistically significant differences in SLE Flare Index results were observed over the course of the study. The majority of subjects did not have a flare as shown in the following figures for the single and double dose cohorts, respectively.

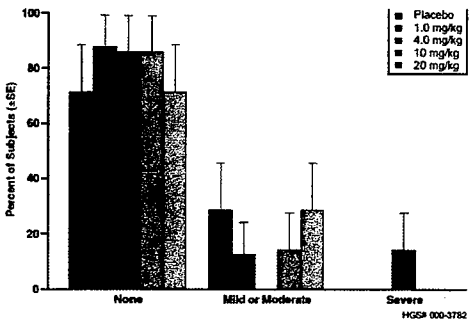


Figure 6 **Worst SLE Flare Index result - single dose cohorts**

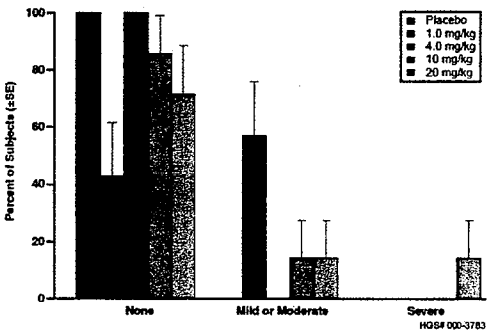
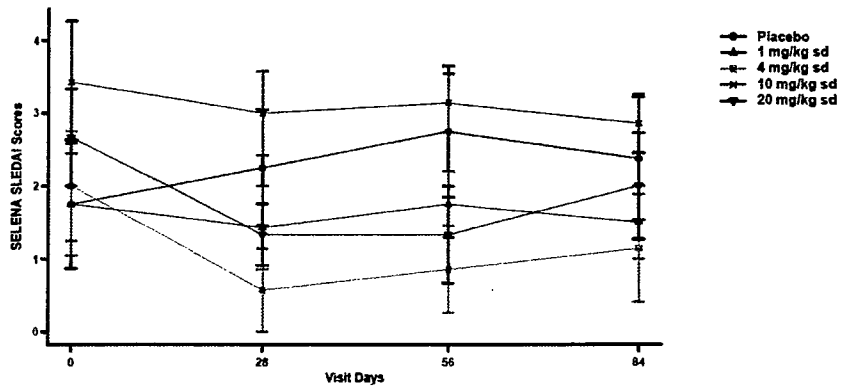


Figure 7 **Worst SLE Flare Index result - double dose cohorts**



F11A Mean +/- SE scores for SELENA SLEDAI - single dose cohorts

Conclusions:

- Following IV administration, serum belimumab concentrations declined in a bi-exponential manner, with a mean t1/2,α of 1.0 to 2.2 days and mean t1/2,β of 8.5 to 14.1 days.
- After IV administration, belimumab was distributed to tissues with the mean Vss ranging from 69 to 112 mL/kg, which is about twice the mean V1 ranging from 40 to 57 mL/kg.
- Renal clearance is not a major component of belimumab clearance.
- There were no significant differences in PK parameters between single and double dose cohorts. Belimumab PK are linear across the 1 to 20 mg/kg dose range in this study.
- Belimumab did not show any evidence of clinical activity as measured by the SELENA SLEDAI, the SLE Flare Index, the SF-36 Health Survey, and the Physician Global Assessment (PGA).
- The biological activity of belimumab was evidenced by a significant reduction in CD20+ cells. Further evidence of biological activity included reductions in CD138+ (plasmacytoid) cells at some time points and a dose-related decrease in anti-dsDNA and IgG levels.
- Biological and clinical effects of belimumab were not anticipated in this study, since only 1 or 2 doses were administered to each subject and subjects generally entered the study with low disease activity.

C1058

Study Title: a Phase 1, randomized, parallel-group, open-label, single-dose study of belimumab in healthy subjects. Belimumab was administered SC as a single injection or IV as a 1-hour infusion at a dose of 100 mg for the evaluation of absolute SC bioavailability.

Objectives: • To evaluate the absolute bioavailability of belimumab administered SC in healthy subjects.

• To evaluate the safety of SC administration of belimumab compared with IV administration in healthy subjects.

Study Design: This was a randomized, parallel-group, open-label, single-dose study of belimumab in healthy subjects. The study was designed to evaluate the absolute bioavailability and safety of a single dose of belimumab administered SC to healthy subjects. Subjects were randomized to receive 100 mg of belimumab by either IV infusion or SC injection.

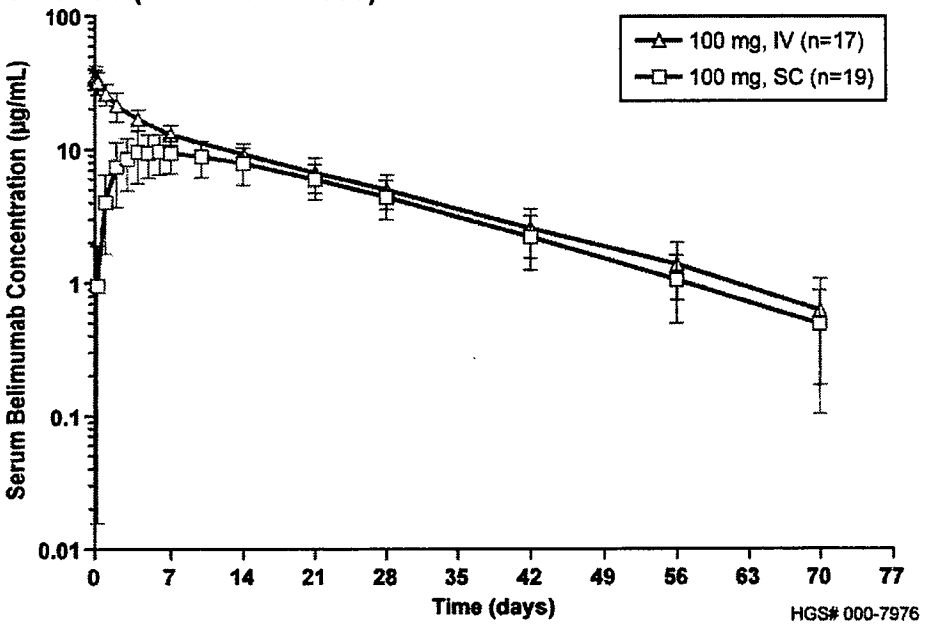
Study Population: In total, 36 healthy subjects were treated in this study, 17 in the IV group and 19 in the SC group. Demographics were generally balanced between the 2 treatment groups: 53% of subjects were female, 81% were white and 2.8% black, with an age range of 18 to 63 years, and weight range of 54 to 113 kg. The SC injections were given in the abdomen of 10 subjects and thigh of 9 subjects. All 36 subjects were considered evaluable for PK.

Data Analysis: Blood samples were collected at scheduled times to determine the serum belimumab concentrations for PK assessment. In subjects receiving a single SC injection, blood was collected prior to dosing, at 6 and 24 hours following injection and on Days 2, 3, 4, 5, 6, 7, 10, 14, 21, 28, 42, 56, and 70. For subjects receiving a single IV infusion, blood was collected prior to dosing, at 5 minutes, 1, 3, 6, and 24 hours following infusion and on Days 2, 4, 7, 14, 21, 28, 42, 56, and 70. Serum concentrations were determined using an ECL-based assay, with a LLOQ of 100 ng/mL. PK parameters were assessed by non-compartmental analysis. Descriptive statistics were used to summarize the PK parameters and serum belimumab concentration-time results.

Results: Following IV administration, the serum belimumab concentration displayed biphasic kinetics. The mean Cmax and AUC0-∞ values were 36.7 μg/mL and 413 day•μg/mL, respectively. The initial volume of distribution was about 36 mL/kg, estimated using dose and Cmax, which was close to plasma volume. The mean Vss was 63 mL/kg, about 1.7-fold of the estimated initial volume of distribution, and about one forth of the extracellular fluid volume (~260 mL/kg, Davies and Morris, 1993). The mean volume of distribution in the terminal phase (Vz) was 62 mL/kg. Overall, the results for volume of distribution were slightly smaller than those in the Phase 1 study of SLE subjects. The mean CL was 3.3 mL/day/kg, which was about 2-fold lower than that in the Phase 1 study of SLE subjects. The mean terminal elimination half-life of belimumab was 13.5 days, and the mean value of MRT was 19.7 days. Following SC administration, the Cmax was reached at a median time of 5.0 days postdose. The mean Cmax and AUC0-∞ values were 10.7 μg/mL and 286 day•μg/mL, respectively. The mean apparent volume of distribution (Vz/F) was 90 mL/kg and apparent clearance (CL/F) was 5.1 mL/day/kg. The mean terminal elimination half-life was 12.6 days, which is comparable to that for IV administration. The mean absorption time (MRTSC-MRTIV) following SC administration was 3.4 days. The bioavailability (F) of SC administration and its 95% confidence interval (CI) were calculated using both average bioequivalence method and approach described in the literature. The F (95% CI) was 67.2% (56.5% to 78.0%), calculated using a formula in the literature and 65.8% (55.6 % to 77.9%), using the average bioequivalence method. Mean serum belimumab concentrations-time profiles are presented in Figure below. The

presence of anti-belimumab antibodies, observed in 2 subjects, had no obvious effect on the serum belimumab concentration-time profile for either subject.

Figure 1. Serum belimumab concentration (mean ± SD) following single IV or SC dose (HGS1006-C1058).



Conclusions: The results of this study indicate that a single dose of belimumab administered SC is bioavailable in healthy subjects and is generally well tolerated:

- An absolute bioavailability of 67% was calculated for SC belimumab.
- Compared with the IV group, higher percentages of subjects in the SC group experienced AEs and study agent-related AEs. However, most of the AEs were mild. There was no difference between treatment groups in the number of subjects with moderate AEs. No severe or serious AEs were reported in either group.
- Laboratory abnormalities were minimal and generally transient.
- One subject in the IV group had a transient positive anti-belimumab antibody response, and 1 subject in the SC group had a persistent positive response. Test results for neutralizing antibodies were negative. No safety findings were associated with the anti-belimumab antibody responses.
- Increases in CD20+/27+ memory B cell counts, decreases in CD20+ and CD20+/27- naïve B cell counts, and reductions in IgG, IgA, and IgM relative to baseline were observed in both treatment groups.

LBSL02 & C1056 & C1057

There were sparse PK sampling in these three studies. The PK were evaluated using the population approach, please see pharmacometrics review for details.

APPENDIX 2: DRAFT LABELING PROPOSED BY SPONSOR

(b) (4)

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX 3: PHARMACOMETRICS REVIEW

Office of Clinical Pharmacology
Pharmacometrics review

BLA	125370	*Submission Dates*	0000 (06/09/2009)
Brand Name		BENLYSTA® (proposed)	
Generic Name		Belimumab	
Reviewer		Ping Ji, Ph.D.	
Team Leader		Yun Xu, Ph.D.	
Pharmacometrics Reviewer		Ping Ji, Ph.D.	
Pharmacometrics Team Leader		Yaning Wang, Ph.D.	
OCP Division		Division of Clinical Pharmacology-II	
OND Division		Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)	
Sponsor		Human Genome Sciences, Inc	
Relevant IND(s)		BB-IND 9970	
Submission Type; Code		351(a)	P
Formulation; Strength(s)		Single-use vials of belimumab lyophilized powder with 120 mg/5-mL vial and 400 mg/20-mL vial	
Indication		(b) (4) in adult patients with active, autoantibody positive, systemic lupus erythematosus who are receiving standard therapy.	
Proposed Dosing Regimen		Recommended dosage regimen is 10 mg/kg at 2 week intervals for the first 3 doses and at 4 week intervals thereafter as an intravenous infusion over one hour.	

1 Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Are the PK parameters reported in the label supported by the population PK analysis submitted by the sponsor?

Yes, the PK variables for the 10 mg/kg reported in the label are supported by the population PK analysis submitted by the sponsor.

The PK variables for the 10 mg/kg reported in the label are supported by the population PK analysis submitted by the sponsor and reproduced by the reviewer (Table 1).

Table 1. Population Pharmacokinetic Parameters in Patients with SLE after Intravenous Infusion of belimumab 10 mg/kg.[a]

Pharmacokinetic Parameter	Population Estimates (n = 563)
Peak concentration (C_{max}, μg/mL)	313
Area under the curve ($AUC_{0-\infty}$, day•μg/mL)	3,083
Distribution half-life ($t_{½}$, days)	1.75
Terminal half-life ($t_{½}$, days)	19.4
Systemic clearance (CL, mL/day)	215
Volume of distribution (Vss, L)	5.29

[a]Intravenous infusions were administered at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

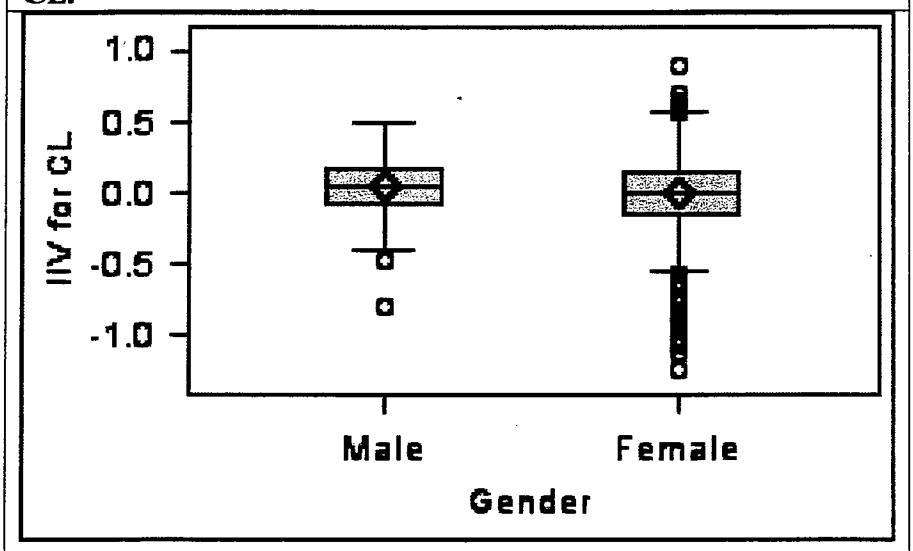
1.1.2 What are the effects of intrinsic factors on the PK of belimumab?

Sex, age and race were not significant covariates for the belimumab PK. As weight increased, the systemic clearance also increased.

The effect of sex, age, weight, and race on the PK of belimumab was assessed using the population PK approach from four studies in SLE patients (Studies LBSL01, LBSL02, C1056, C1057).

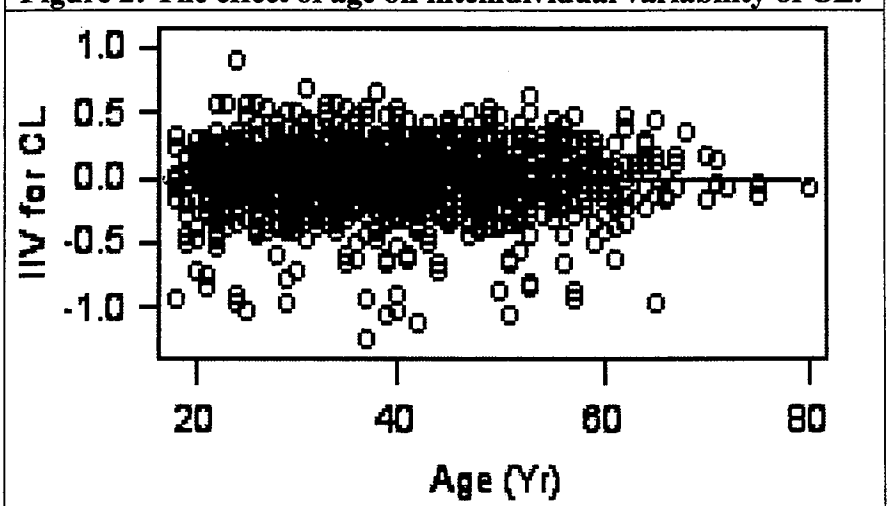
Sex Gender did not significantly influence belimumab pharmacokinetics in the largely (94%) female study population. However, the number of males is small.

Figure 1: The effect of gender on interindividual variability of CL.



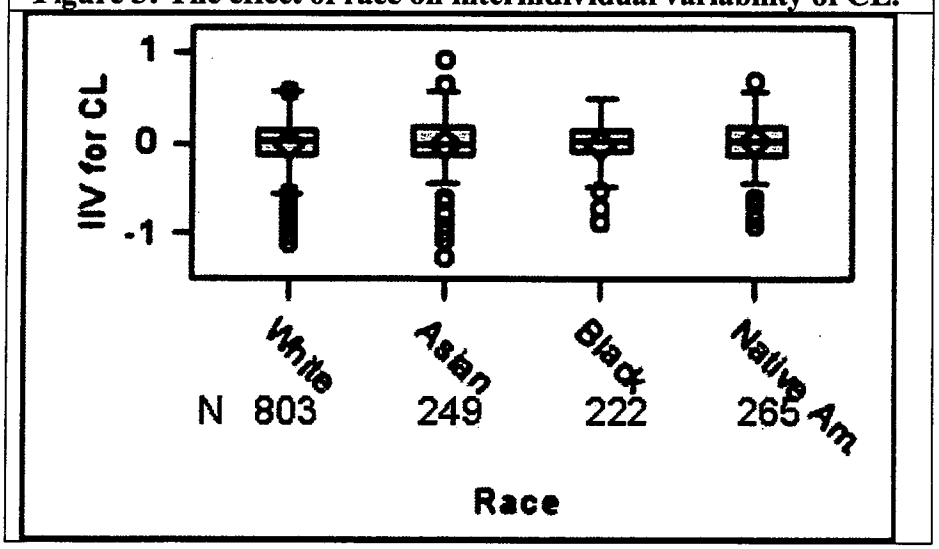
Age Age did not significantly influence belimumab pharmacokinetics in the study population, where the majority of subjects (70%) were between 18 and 45 years of age. Belimumab has not been studied in the pediatric patients. Limited pharmacokinetic data are available in elderly patients.

Figure 2: The effect of age on inteindividual variability of CL.



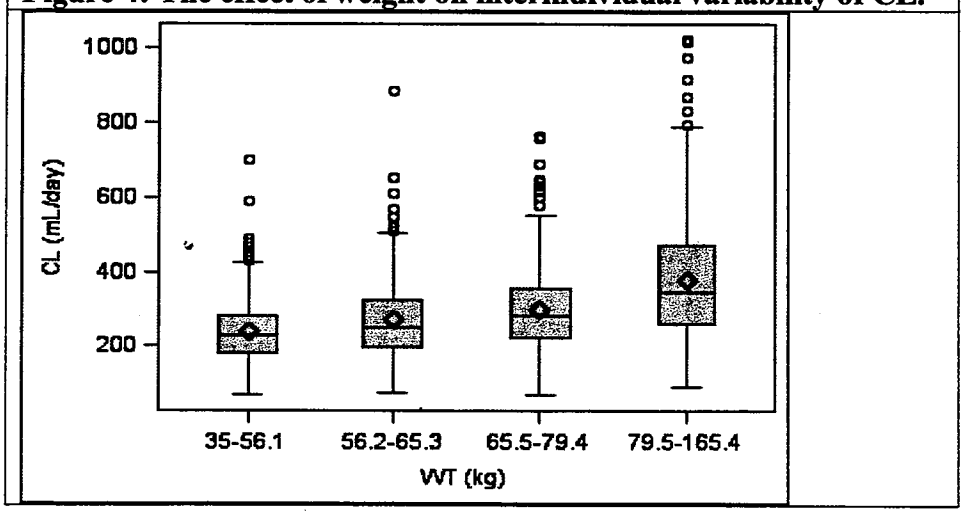
Race Race did not significantly influence belimumab pharmacokinetics. The racial distribution was approximately 53% white/Caucasian, 16% Asian, 16% Alaska native/American Indian, and 14% black/African American.

Figure 3: The effect of race on interindividual variability of CL.



Weight As body weight increased, the systemic clearance of belimumab also increased.

Figure 4: The effect of weight on interindividual variability of CL.

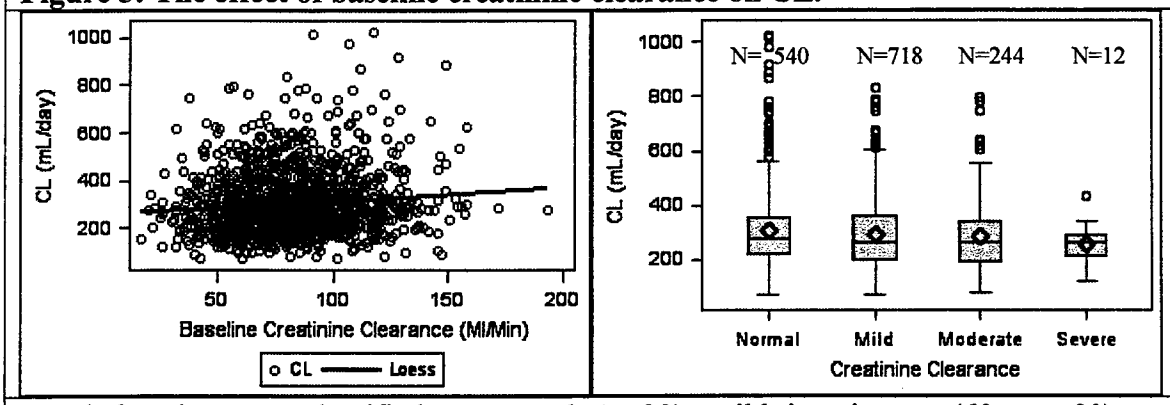


Renal impairment

No formal study was conducted to assess the effect of renal impairment on the belimumab PK. The population PK analysis showed that baseline creatinine clearance was a covariate of CL.

However, the median value of CL in normal, mild, moderate, and sever renal impairment patients were similar and were 277, 259, 260, and 264 mL/day, respectively.

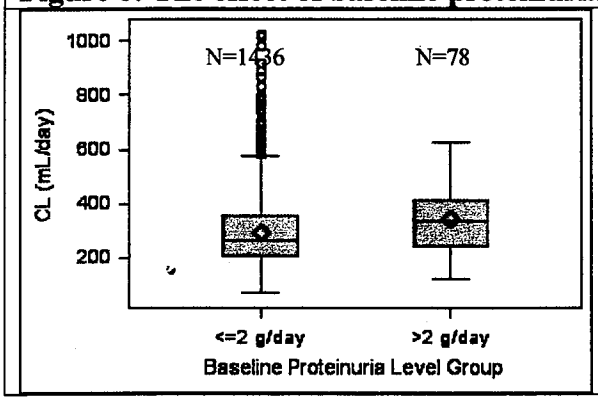
Figure 5: The effect of baseline creatinine clearance on CL.



Renal function was classified as normal (≥ 90), mild impairment (60 to <90), moderate impairment (30 to <60), and severe impairment (< 30).

Baseline protenuria level was also a population covariate of CL. The CL was slightly higher (16%) in patients with baseline proteinuria level greater than 2 g/day as compared to less then or equal to 2 g/day. However, the difference in CL is not likely to be clinically significant and no dose adjustment is needed.

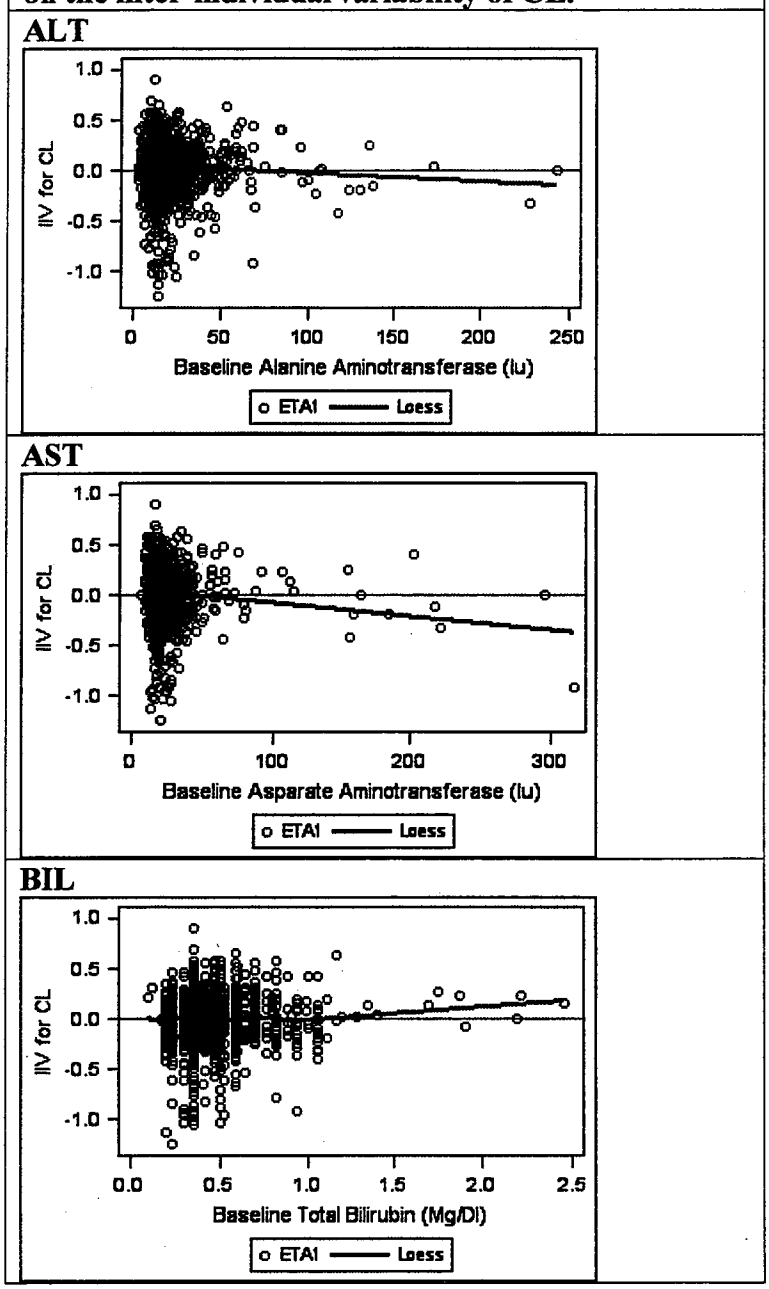
Figure 6: The effect of baseline proteinuria level on CL.



Hepatic Impairment

No formal study was conducted to assess the effect of hepatic impairment on the belimumab PK. Belimumab has not been studied in patients with severe hepatic impairment. The population PK analysis showed that the interindividual variability of CL cannot be explained by the baseline value of alanine aminotransferase (ALT), aspirate aminotransferase (AST), and total bilirubin level (BIL).

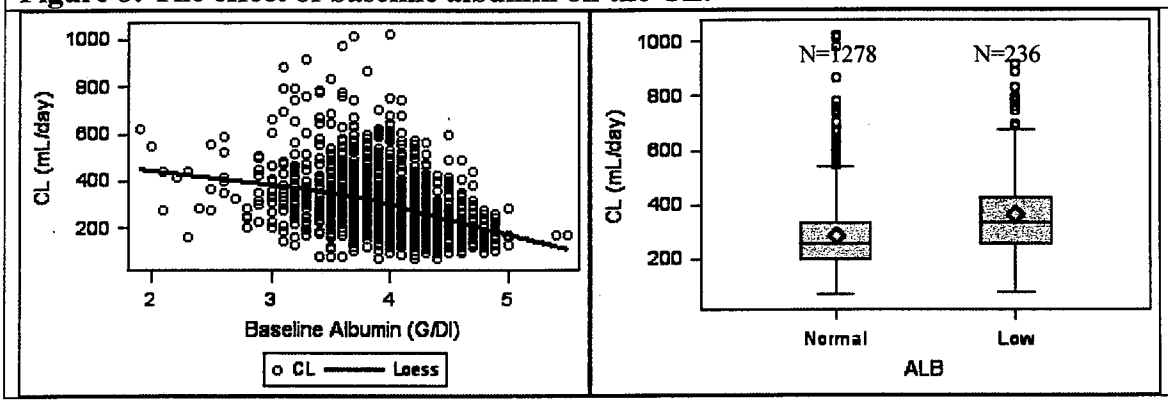
Figure 7: The effect of baseline AST, ALT and BIL on the inter-individual variability of CL.



A moderate increase in clearance (30%) was observed for patients with low levels albumin compared to normal patients. The median albumin level in the low group was 3.3 g/dL which is close to normal level of (3.5 g/dL and above). The median value of albumin in the normal

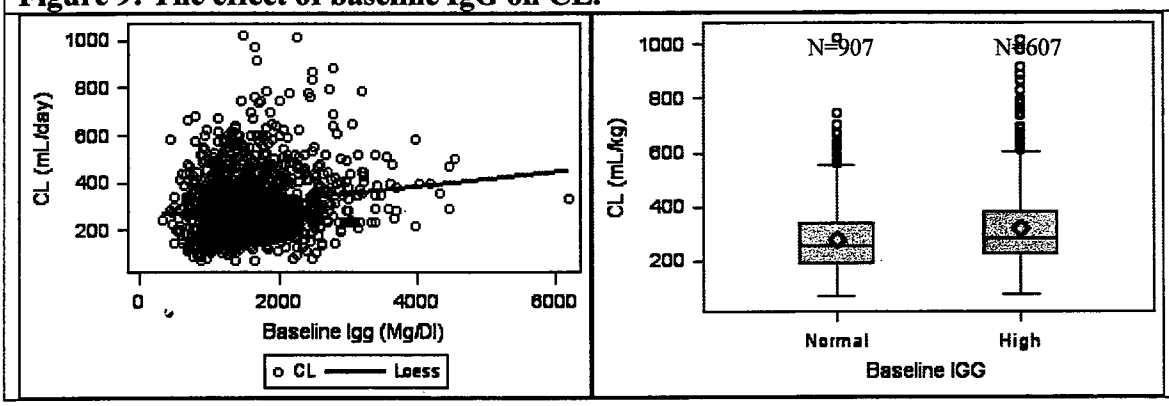
groups was 4.1 g/dL. Median values of clearance in the low and normal groups are 258 and 335 mL/day, respectively.

Figure 8: The effect of baseline albumin on the CL.



A slightly increase in clearance (10%) was observed for patients with high levels IgG compared to normal patients. The median IgG level in the high group was 2010 mg/dL, and the median IgG level in the normal group was 1230 mg/dL (the cutoff value was 1816 mg/dL). The median value of albumin in the normal groups was 4.1 g/dL. Median values of clearance in the normal and high groups are 256 and 281 mL/day, respectively.

Figure 9: The effect of baseline IgG on CL.



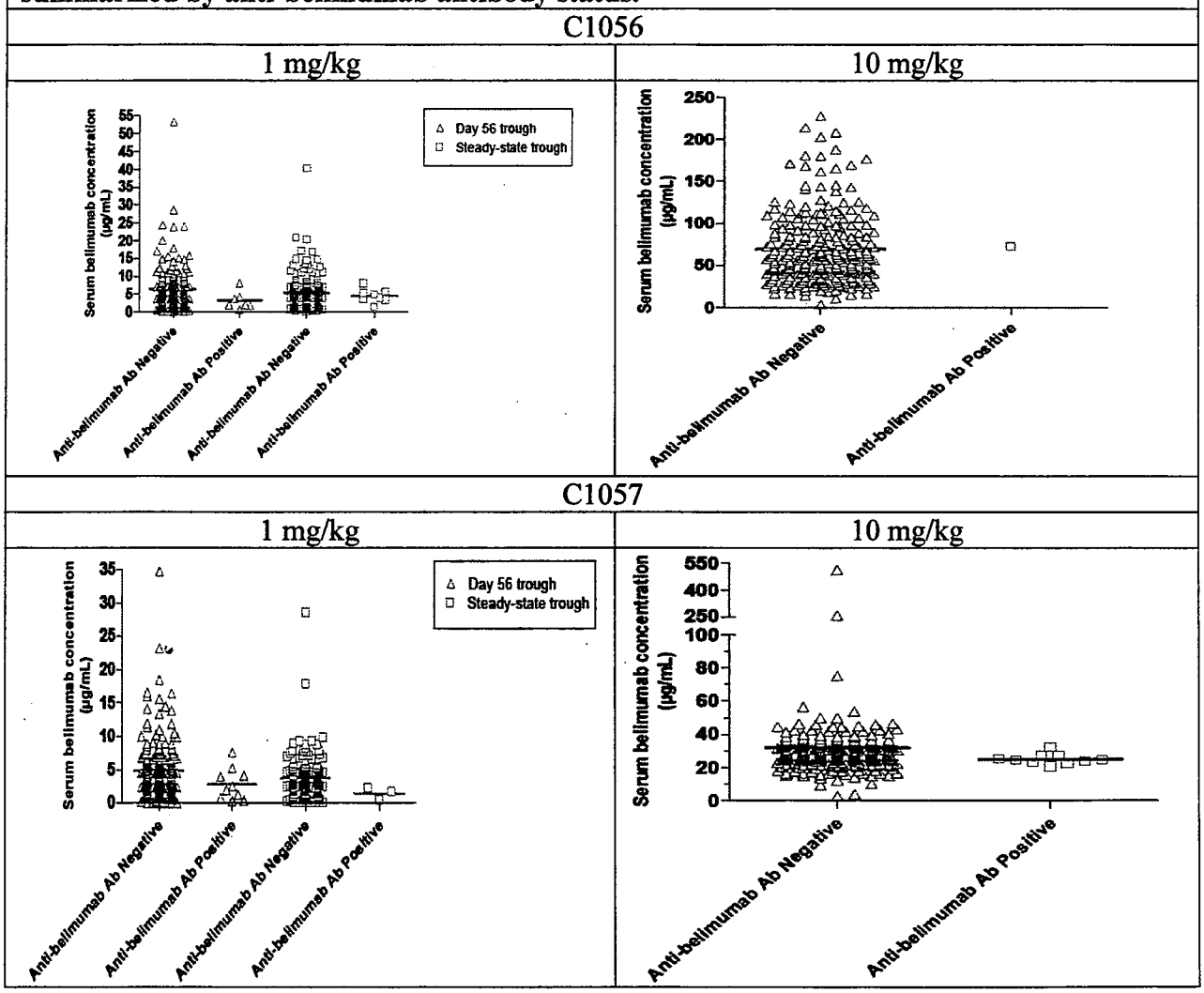
1.1.3 What are the effects of immunogenicity on the PK, efficacy, and safety of belimumab?

Limited immunogenicity data showed that Immunogenicity did not appear to significantly affect the PK, safety and efficacy of belimumab.

PK In the Phase 3 SLE studies, samples for immunogenicity assessment were drawn on Day 0, and Weeks 8, 24, 52/Exit and Week 76/Exit (in Study C1056), as well as 8-week follow-up (for subjects discontinuing treatment and not entering the extension period of the study). For subjects who had a positive anti-belimumab antibody response at the 8-week follow-up, a serum sample

was obtained, if possible, at least 6 months after the last dose of study agent or upon completion and/or unblinding of the study, whichever was later. In the two Phase 3 studies C1056 and C1057, 13.1% of SLE patients in 1 mg/kg and 0.9% of SLE patients in 10 mg/kg showed positive immunogenicity response. The trough belimumab concentration for antibody positive patients was within the range of those for antibody negative patients. The population analysis did not show a statistically significant effect of anti-belimumab antibodies on clearance. The immunogenicity assay in the Phase 1 and 2 studies was not robust (please see the immunogenicity assay review for details). Therefore, the immunogenicity results from these studies are not discussed here.

Figure 10: Trough serum belimumab concentrations following IV infusions of belimumab summarized by anti-belimumab antibody status.



Safety The immunogenicity status for subjects in Phase 3 studies (where immunogenicity was most reliably measured) who experienced infusion and hypersensitivity reactions is listed in

Table 6. Of 76, 88, and 84 Phase 3 subjects in the placebo, 1 mg/kg and 10 mg/kg groups, respectively, that experienced an infusion or hypersensitivity reaction, 4 subjects (1 in the placebo group, 2 in the 1 mg/kg group, and 1 in the 10 mg/kg group) also had persistent positive immune responses to belimumab. Eight subjects in the 1 mg/kg group that had an infusion or hypersensitivity reaction had transient immune responses to belimumab, and the remaining subjects who experienced an infusion or hypersensitivity reaction did not have detectable anti-belimumab antibodies.

Table 2. Immunogenicity summary in Phase 3 studies among subjects with infusion reactions and hypersensitivity reactions.

TA145 Immunogenicity Summary in Phase 3 Studies among subjects with infusion reactions and hypersensitivity reactions

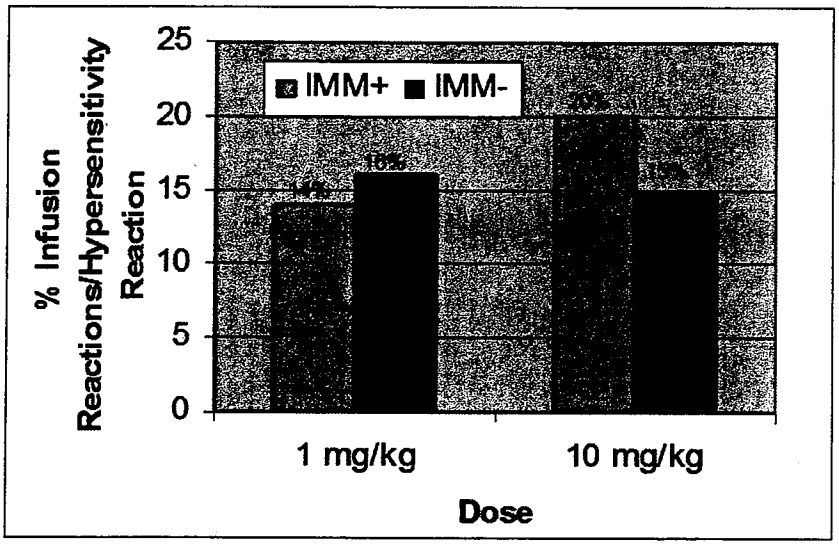
	Placebo N=562	1 mg/kg N=559	10 mg/kg N=563
n	76	88	84
Persistent Positive[1]	1 (1.3%)	2 (2.3%)	1 (1.2%)
NA/Negative —> positive	1 (1.3%)	2 (2.3%)	1 (1.2%)
Median max Assay B signal[3] (range)	619.0 (619, 619)	1071.5 (952, 1191)	1056.0 (1056, 1056)
Max Assay B signal > 1000 ECL	0/ 1 (0.0%)	1/ 2 (50.0%)	1/ 1 (100%)
Max Assay B signal > 10,000 ECL	0/ 1 (0.0%)	0/ 2 (0.0%)	0/ 1 (0.0%)
Neutralizing any time post baseline [4]	1/ 1 (100%)	0/ 1 (0.0%)	0/ 1 (0.0%)
Transient Positive[2]		8 (9.1%)	
NA/Negative —> positive		7 (8.0%)	
Positive —> negative		1 (1.1%)	
Median max Assay B signal[3] (range)		1337.5 (586, 9386)	
Max Assay B signal > 1000 ECL		4/ 8 (50.0%)	
Max Assay B signal > 10,000 ECL		0/ 8 (0.0%)	
Neutralizing any time post baseline [4]		1/ 3 (33.3%)	
Negative	75 (98.7%)	78 (88.6%)	83 (98.8%)

[1]Persistent positive refers to positive immunogenic response at 2 or more assessments or at the final assessment.
[2]Transient positive refers to positive immunogenic response at only 1 assessment and negative at final.
[3]Maximum Assay B signal (without inhibitor) observed per subject among confirmed positive assay B samples.
[4]Neutralizing any time post-baseline among subjects with neutralization assay results available.

Source: Page 4118 of 4999 in the Section 2.7.4 Summary of Clinical Safety Appendices.

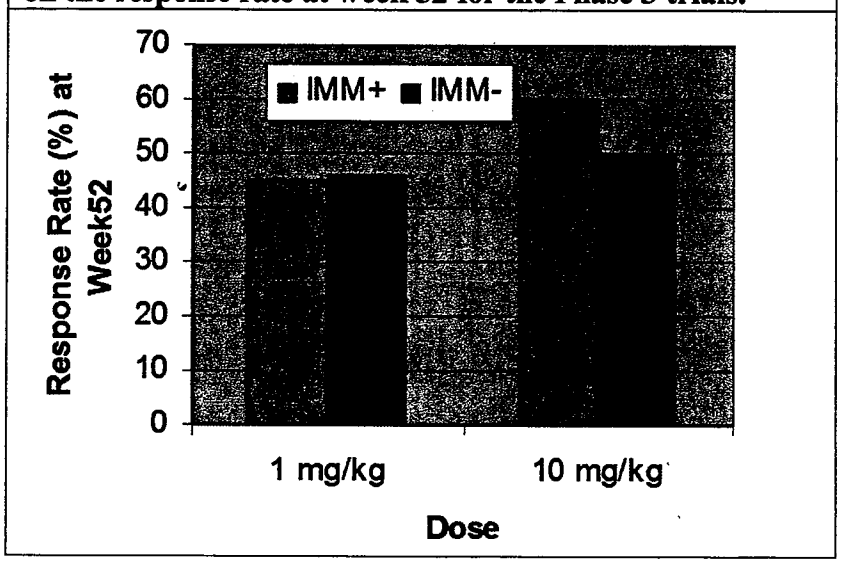
As summarized in Figure 11, for antibody positive patients in 1 mg/kg, the percent infusion reactions/hypersensitivity reaction was 14%; whereas for antibody negative patients in 1 mg/kg, the percent infusion reactions/hypersensitivity reaction was 16%. Similarly, for antibody positive patients in 10 mg/kg, the percent infusion reactions/hypersensitivity reaction was 20%; whereas for antibody negative patients in 10 mg/kg, the percent infusion reactions/hypersensitivity reaction was 15%. Therefore, the percent infusion reactions/hypersensitivity reaction was comparable between antibody positive patients and antibody negative patients.

Figure 11: The effect of anti-belimumab antibody status on the incidence of infusion reactions/hypersensitivity reaction for the Phase 3 trials.



Efficacy The presence of anti-belimumab antibody did not appear to affect effectiveness of belimumab (Figure 12). In the two Phase 3 studies, for anti-belimumab antibody positive patients, the percent responders at week 52 based on primary endpoint analysis was 60% (3/5) at 10 mg/kg and 45% (33/73) at 1 mg/kg. For anti-belimumab antibody negative patients, the percent responders at week 52 based on primary endpoint analysis was 50% (282/558) at 10 mg/kg, and 46% (225/486) at 1 mg/kg.

Figure 12: The effect of anti-belimumab antibody status on the response rate at week 52 for the Phase 3 trials.



It is of note that as the incidence of immunogenicity is uncommon and the immunogenicity assay was sensitive to biologic concentrations, no definitive conclusion can be made on the effect of immunogenicity on PK, safety, and efficacy.

1.2 Recommendations

None.

1.3 Labeling Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in <u>underline blue font</u>.

(b) (4)

(b) (4)

2 Pertinent regulatory background

The submission dated on 09 June 2010 is the original submission for belimumab. The sponsor is seeking the marketing approval for the indication in the adult patients with active, autoantibody positive systemic lupus erythematosus (SLE) who are receiving standard therapy. Belimumab clinical program includes five clinical studies including 1 Phase 1 study, 2 Phase 2 studies (one in SLE patient and one in in RA patients), and 2 Phase 3 studies. The proposed dosing regimen is 10 mg/kg at 2 week intervals for the first 3 doses and at 4 week intervals thereafter as an intravenous infusion over one hour.

3 Results of Sponsor's Analysis

3.1 Population Pharmacokinetic Analysis

The key findings from sponsor's population PK analysis (*study report: HGS1006-POPPK*) in SLE patients are summarized below:

- Belimumab follows linear 2-compartment pharmacokinetics with a terminal half-life of 19.4 days and steady-state volume of distribution of 5.29 L in the targeted Phase 3 population with 10 mg/kg dosing.
- The population estimates for the structural PK parameters in the targeted Phase 3 population for the 10 mg/kg dose group are as follows (weight normalized parameters based on median body weight of 66.3 kg in study population):
  - Total systemic clearance CL is 215 mL/day (3.24 mL/day/kg).
  - Central volume of distribution V1 is 2560 mL (38.6 mL/kg).
  - Inter-compartmental clearance Q is 459 mL/day (6.92 mL/day/kg).
  - Peripheral volume of distribution V2 is 2730 mL (41.2 mL/kg).
- Belimumab exposure is approximately dose-proportional.
- The presence of anti-belimumab antibodies was relatively uncommon and therefore no definitive conclusions can be drawn regarding the effects of immunogenicity on belimumab PK.
- No dose adjustments are required based on age, gender, race, disease activity, co-medications, baseline characteristics or other tested factors. The predicted effects of these characteristics were either not statistically significant or not clinically relevant. Systemic clearance of belimumab increased with body weight. The effect of weight was adjusted by the body-weight based dosing regimen.

Table 2 shows the parameter estimates for the belimumab final model.

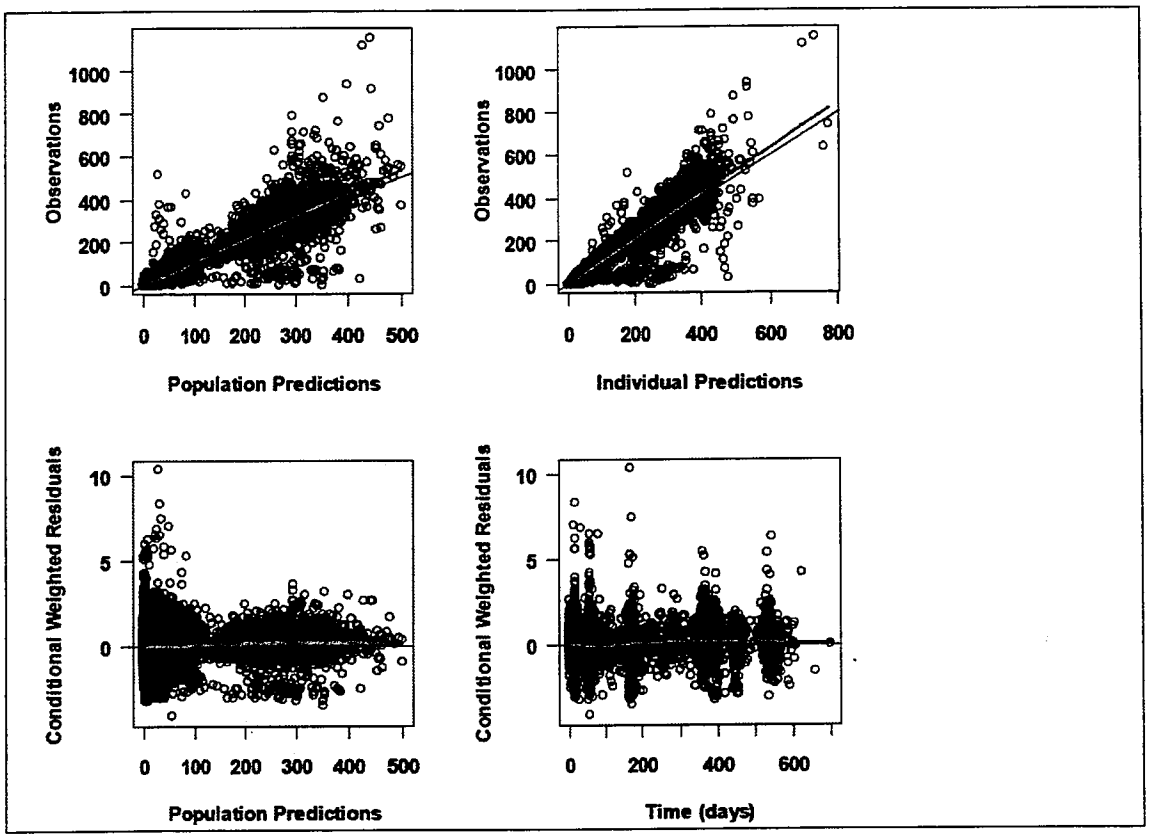
Table 4: Belimumab PK parameters.

Parameters	Implementation	Estimate	%CV
Fixed effects			
CL (mL/day)	THETA(1)	215	1.95
Effect of BWT on CL	x (BWT/66.3)$^{THETA(5)}$	0.506	11.1
Effect of BCCL on CL	x (BCCL/79.9)$^{THETA(8)}$	0.217	11.3
Effect of SPUS on CL	x (1+ THETA(9))	0.143	35.2
Effect of ACEI on CL	x (1+ THETA(11))	0.0851	21.4
Effect of STDY=LBSL01 on CL	x (1+ THETA(12))	0.949	6.90
Effect of STDY= LBSL02 on CL	x (1+ THETA(13))	0.717	4.10
Effect of STER on CL	x (1+ THETA(17))	0.0603	22.7
Effect of BALB on CL	x (BALB/4.0)$^{THETA(19)}$	-0.829	9.49
Effect of BIGG on CL	x (BIGG/1480)$^{THETA(20)}$	0.322	6.96
V1 (mL)	THETA(2)	2560	0.961
Effect of BWT on V1	x (BWT/66.3)$^{THETA(6)}$	1.14	7.38
Effect of BBMI on V1	x (BBMI/25.1)$^{THETA(7)}$	-0.616	15.7
Effect of BHGB on V1	x (BHGB/12.4)$^{THETA(10)}$	-0.291	23.3
Effect of STDY=LBSL01 on V1	x (1+ THETA(14))	0.366	12.7
Effect of STDY= LBSL02 on V1	x (1+ THETA(15))	0.269	6.69
Effect of BWBC on V1	x (BWBC/5.6)$^{THETA(18)}$	-0.0810	20.0
Q (mL/day)	THETA(3)	459	10.8
V2 (mL)	THETA(4)	2730	4.03
Effect of RDOS on V2	x (RDOS/10) $^{THETA(16)}$	0.379	8.34
Inter-individual variability			
ω^2_{CL}	OMEGA(1,1)	0.0699	6.27
ω^2_{V1}	OMEGA(2,2)	0.0398	28.4
$\omega^2_{CL/V1}$	OMEGA(2,1)	0.0261	17.3
ω^2_{V2}	OMEGA(3,3)	0.0969	35.2
Residual variability			
$\sigma^2_{proportional}$	SIGMA(1)	0.0887	4.01
$\sigma^2_{additive}$	SIGMA(2)	0.0139	32.8

Abbreviations: %CV, standard error as percentage of estimate; V1, volume of distribution for the central compartment; CL, clearance; V2, volume of distribution for the peripheral compartment; Q, intercompartmental clearance; BWT, baseline body weight; BCCL, baseline calculated creatinine clearance; SPUS, baseline proteinuria level group; BALB, baseline albumin level; BIGG, baseline IgG level ACEI, baseline ACE inhibitor use; STDY, study code; STER, steroid use; BDNA, baseline anti-dsDNA; BBMI, baseline BMI; BHGB, baseline hemoglobin; BWBC, baseline white blood cell count; RDOS, dose group.

The standard goodness-of-fit plots for the final model run369 is shown in the Figure 13.

Figure 13: Standard goodness-of-fit plots for final model (run369; black line, identity to zero line; redline, loess fit).



Reviewer's Comments: The reviewer agrees with the sponsor's conclusions. The reviewer confirmed the sponsor's analyses by independently running the NONMEM codes and reproducing the plots prepared by the sponsor.

4 Reviewer's Analysis

4.1 Introduction

Reviewer repeated sponsor's population analysis and reassessed the covariate effect. As the immunogenicity results form the Phase 1 sutdy and the Phase 2 study were not reliable, reviewer reassessed the effect of immunogenicity on the PK, safety, and efficacy of belimumab based on the Phase 3 data only.

4.2 Objectives

The reviewer's analysis objectives are:

1. Repeat sponsor's population PK analysis and reassess the covariate effect.
2. Evaluate the immunogenicity effect on PK, safety, and efficacy based on the Phase 3 data.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 5.

Table 5. Analysis Data Sets		
Study Number	**Name**	**Link to EDR**
C1057	Dem.xpt	\\Cbsap58\m\eCTD_Submissions\STN125370\0000\m5\datasets\c1057\analysis\dem.xpt"
C1056	Dem.xpt	\\Cbsap58\m\eCTD_Submissions\STN125370\0000\m5\datasets\c1056\analysis\dem.xpt"
Lbsl01	Dem.xpt	\\Cbsap58\m\eCTD_Submissions\STN125370\0000\m5\datasets\lbsl01\analysis\dem.xpt"
Lbsl02	Dem.xpt	\\Cbsap58\m\eCTD_Submissions\STN125370\0000\m5\datasets\lbsl02\analysis\dem.xpt"

4.3.2 Software

SAS and NONMEM were used for the reviewer's analyses.

4.4 Results

Reviewer confirmed sponsor's analysis by rerunning the model and assessing the covariate effects (Figures 1 to 9). The effect of anti-belimumab antibody status on belimumab clearance was also reassessed using the Phase 3 data.

In the two Phase 3 studies C1056 and C1057, 13.1% of SLE patients in 1 mg/kg and 0.9% of SLE patients in 10 mg/kg showed positive immunogenicity response. The trough belimumab concentration for antibody positive patients was within the range of those for antibody negative patients (Figure 10). The presence of anti-belimumab positive antibody did not appear to affect the safety and efficacy of belimumab (Figures 11 and 12). The immunogenicity assay in the Phase 1 and 2 studies was not robust (please see the immunogenicity assay review for details). Therefore, the immunogenicity results from these studies are not discussed here.

APPENDIX 4: GENOMICS GROUP REVIEW

NDA/BLA Number	125370
Submission Date	June 9, 2010
Applicant Name	Human Genome Sciences
Drug Name	Belimumab
Proposed Indication	(b) (4) in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE)
Primary Reviewer	Shashi Amur, Ph.D.
Secondary Reviewer	Michael Pacanowski, Pharm.D., M.P.H

1 Background

The current submission is a BLA for belimumab (BENLYSTA), a fully human IgG1λ monoclonal antibody that binds to and inhibits the activity of soluble human B-lymphocyte stimulator (BLyS). The proposed indication is (b) (4) adults with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

Two key issues exist for this review from the perspective of the Genomics Group:

1. The proposed label states that belimumab "significantly reduced circulating CD19+, CD20+, naïve, and activated B cells, plasma cells, and the SLE B-cell subset…IgG and anti-dsDNA, and [increased] complement (C3 and C4)", and includes a shift table for key biomarkers.
2. In the two pivotal Phase 3 trials, belimumab did not appear to be effective in reducing SLE disease activity in African-American/African heritage (black) subjects, and potentially was associated with adverse outcomes.

The purpose of this review is to evaluate 1) the appropriateness of labeling language related to pharmacodynamic and disease activity biomarker changes based on their relationship with clinical outcomes, and 2) the effect of belimumab on the pharmacodynamic and disease activity biomarker as support for the apparent lack efficacy of in black subjects.

2 Submission Contents Related to Genomics/Biomarkers

The clinical development program for belimumab consisted of one Phase 1 trial (LBSL01 [n=70]), one Phase 2 trial (LBSL02 [n=449]) and two Phase 3 trials (C1056 [n=819] and C1057 [n=865]).

C1056 and C1057 evaluated included subjects with autoantibody-positive (antinuclear antibody [ANA] ≥1:80 and/or anti-dsDNA antibody ≥30 IU/mL), active SLE (SELENA-SLEDAI ≥6). Subjects were randomly assigned at a 1:1:1 ratio to receive 1 mg/kg belimumab, 10 mg/kg belimumab or placebo, stratified based on SELENA SLEDAI score (6-9 vs ≥10), proteinuria

level (<2 g/24 hour vs ≥2 g/24 hour) and race (African descent or indigenous-American descent [AIA] vs other). Subjects received belimumab as a 1-hour infusion Days 0, 14, and 28, then every 28 days for 48 weeks in C1057 or 72 weeks in C1056. The primary efficacy endpoint was the SLE responder index (SRI) response rate at Week 52. The SRI is a composite endpoint defined as >4 point reduction SELENA-SLEDAI *and* no new BILAG A or 2 BILAG B symptoms *and* no increase of <0.3 points in physician's global assessment. Secondary endpoints included the components of the primary endpoint, prednisone (equivalent) reduction ≥25% from baseline to ≤7.5 mg/day (in subjects whose prednisone equivalent dose was >7.5 mg/day), and change in SF-36 physical component summary (PCS) at Week 2.

In the Phase 3 trials, the applicant evaluated numerous biomarkers SLE disease activity and belimumab pharmacodynamics as follows: immunoglobulins (IgG, IgA, IgM), autoantibodies (anti-Sm, anti-dsDNA, ANA, anti-ribosomal P, anticardiolipins), C-reactive protein, complement (C3 and C4), BlyS, lymophocytes, peripheral mature B lymphocytes (CD19+, CD20+), naïve (CD20+/CD27-), activated (CD20+/CD69+), short-lived plasma B cells (CD20-/CD27bright), plasma B cells (CD20-/CD138+), SLE B cell subset (CD19+/CD27bright/CD38bright), memory B cell (CD20+/CD27+), CD3+/CD4+ T-cells and CD3+/CD8+ T cells. Samples were generally drawn at baseline and every 4-8 weeks throughout the trial periods for most biomarkers. B and T cell subsets were assessed only in C1056 and samples were obtained at baseline and at Weeks 8, 24, 52 and 76.

3 Key Questions and Summary of Findings

3.1 Do the biomarker data help predict or support clinical responses to belimumab the Phase 3 trials?

- ***Belimumab significantly alters SLE disease activity biomarkers (e.g., anti-dsDNA, complement) and other pharmacodynamic biomarkers (BlyS, B- and T-lymphocytes).***
- ***Differential efficacy was noted based on baseline levels of C3 and C4, suggesting greater benefit of belimumab in subjects with higher levels of serologic activity.***
- ***Changes in C3, C4, and naïve B-cells, were significantly correlated with response to belimumab.***
- ***These biomarkers, in isolation, did not adequately predict response in placebo- or belimumab-treated subjects.***

3.1.1 Biomarker changes following belimumab treatment

3.1.1.1 Sponsor's analysis

Treatment with belimumab led to greater reductions in IgG and anti-dsDNA and increases in complement (C3 and C4) than placebo, and more belimumab-treated subjects had normalization of these biomarkers than placebo. These changes were observed as early as week 8 and were sustained through Week 52. Table 1 illustrates the shifts from abnormal to normal biomarker

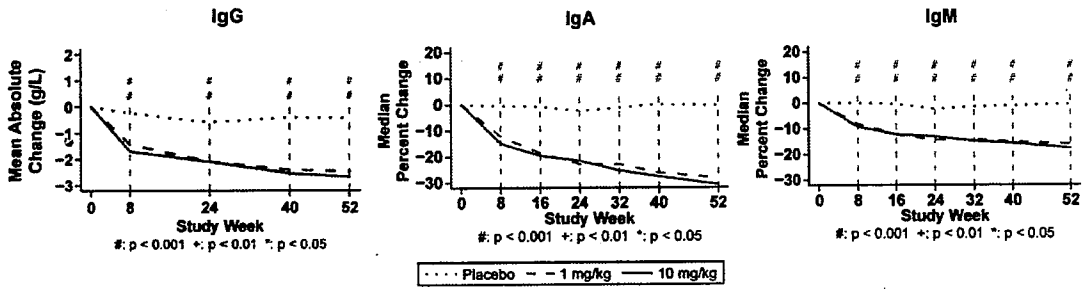
levels in the pooled C1056 and C1057 population. This table is included in the sponsor's proposed labeling under *Clinical Pharmacology: Pharmacodynamics*.

(b) (4)

[redacted]

Immunoglobulins: Hypergammaglobulinemia (IgG) was present at baseline in 44% of the Phase 3 trial subjects. Belimumab reduced immunoglobulin (IgA, IgG, IgM) concentrations as early as Week 8, as shown in the following figure. At Week 52 in C1056, the median percent reduction for IgG was approximately 14% in both the 1 mg/kg and 10 mg/kg belimumab groups. The median percent decreases observed in IgM levels were 28% and 31% in the 1 mg/kg and 10 mg/kg groups, respectively. Similar results were observed in C1057. IgG or IgM did not change in the placebo group in the C1056 trial, while a 3.6% and 3.2% reduction was observed for IgG and IgM levels, respectively, in C1057. Significant reductions in IgA were also observed with median percent reductions from 16-18% with belimumab compared to 0.7-2.7% with placebo. No dose-response was apparent.

Figure 1: Change in immunoglobulin levels with belimumab treatment



Autoantibodies: Belimumab decreased anti-dsDNA as early as Week 8 and the effect persisted through week 52. However, no dose response was observed. The median percentage reduction in anti-dsDNA levels at Week 52 in the pooled dataset was 18-19% for belimumab, while no change was observed in the placebo group. A higher proportion of belimumab-treated subjects showed a conversion from seropositive to seronegative status for ANA, anti-Smith (anti-Sm) and anti-ribosomal-P antibodies, as shown in the following table.

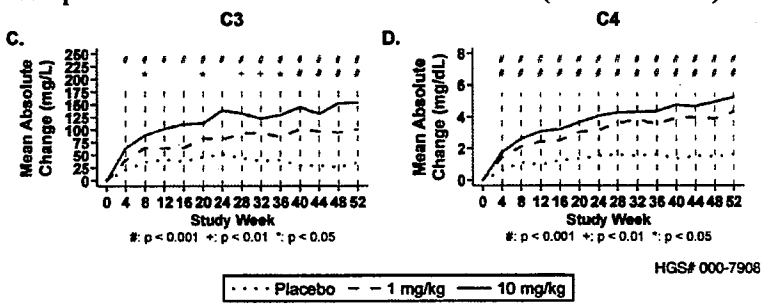
Table 2: Autoantibody shifts from baseline to Week 52 (C1056+C1057)

	C1056			C1057			Both Studies		
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	Placebo N = 562	1 mg/kg N = 559	10 mg/kg N = 563
Anti-dsDNA[1]									
Pos to Neg	10/121 (8.3%)	23/135 (17.0%)	19/131 (14.5%)	9/159 (5.7%)	24/179 (13.4%)	31/182 (17.0%)	19/280 (6.8%)	47/314 (15.0%)	50/313 (16.0%)
Neg to Pos	7/77 (9.1%)	3/75 (4.0%)	1/74 (1.4%)	7/66 (10.6%)	6/59 (10.2%)	3/60 (5.0%)	14/143 (9.8%)	9/134 (6.7%)	4/134 (3.0%)
ANA[2]									
Pos to Neg	7/179 (3.9%)	11/196 (5.6%)	8/179 (4.5%)	5/208 (2.4%)	10/225 (4.4%)	11/228 (4.8%)	12/387 (3.1%)	21/421 (5.0%)	19/407 (4.7%)
Neg to Pos	12/18 (66.7%)	6/12 (50.0%)	16/25 (64.5%)	8/15 (53.3%)	7/13 (53.8%)	5/14 (35.7%)	20/33 (60.6%)	13/25 (52.0%)	21/39 (53.8%)
Anti-Sm[3]									
Pos to Neg	9/50 (18.0%)	9/47 (19.1%)	13/47 (27.7%)	13/70 (18.6%)	23/78 (29.5%)	29/84 (34.5%)	22/120 (18.3%)	32/125 (25.6%)	42/131 (32.1%)
Neg to Pos	0/1	0/1	0/3	0/2 (0%)	0/1 (0%)	0/2 (0%)	0/3 (0%)	0/2 (0%)	0/5 (0%)
aCL[4,5,6]									
Pos to Neg	30/82 (36.6%)	23/69 (33.3%)	22/57 (38.6%)	26/65 (40.0%)	45/81 (55.6%)	44/91 (48.4%)	56/147 (38.1%)	68/150 (45.3%)	66/148 (44.6%)
Neg to Pos	-	-	0/3	0/1	0/2	0/3	0/1	0/2	0/6
aCL IgG[4]									
Pos to Neg	21/43 (48.8%)	21/38 (55.3%)	18/30 (60.0%)	13/42 (31.0%)	42/58 (72.4%)	30/56 (53.6%)	34/85 (40.0%)	63/96 (65.6%)	48/86 (55.8%)
Neg to Pos	1/3 (33.3%)	0/8	0/7	0/4	0/9	1/14 (7.1%)	1/7 (14.3%)	0/17 (0%)	1/21 (4.8%)
aCL IgM[5]									
Pos to Neg	2/6 (33.3%)	4/10 (40.0%)	5/9 (55.6%)	3/9 (33.3%)	7/19 (36.8%)	13/24 (54.2%)	5/15 (33.3%)	11/29 (37.9%)	18/33 (54.5%)
Neg to Pos	1/40 (2.5%)	0/36	0/28	0/37	1/48 (2.1%)	0/46	1/77 (1.3%)	1/84 (1.2%)	0/74
aCL IgA[6]									
Pos to Neg	14/50 (28.0%)	7/40 (17.5%)	15/42 (35.7%)	17/37 (45.9%)	22/43 (51.2%)	26/48 (54.2%)	31/87 (35.6%)	29/83 (34.9%)	41/90 (45.6%)
Anti-ribosomal P[7]									
Pos to Neg	7/17 (41.2%)	3/8 (37.5%)	5/9 (55.6%)	9/57 (15.8%)	22/61 (36.1%)	26/51 (51.0%)	16/74 (21.6%)	25/69 (36.2%)	31/60 (51.7%)

1 Anti-dsDNA: Positive (≥ 30 IU/mL); Negative (< 30 IU/mL).
2 ANA: Postive (≥ 80 titer); Negative (< 80 titer).
3 Anti-Sm: Positive (≥ 15 U/mL); Negative (< 15 U/mL).
4 aCL IgG: Positive (≥ 10 GPL U/mL); Negative (< 10 GPL U/mL).
5 aCL IgM: Positive (≥ 10 MPL U/mL); Negative (< 10 MPL U/mL).
6 aCL IgA: Positive (≥ 15 APL U/mL); Negative (< 15 APL U/mL).
7 Anti-ribosomal P: Positive (> 25 EU/mL); Negative (≤ 25 EU/mL).

Complement: Complement levels increased in belimumab-treated subjects. A higher proportion of subjects receiving belimumab with low complement at baseline had normalized complement levels at Week 52. Fewer belimumab-treated subjects with normal complement levels at baseline experienced a decrease in complement levels, compared with subjects receiving placebo. The decrease was observed as early as Week 4 in subjects treated with 10 mg/kg belimumab and was sustained up to Week 76. The time course of C3 and C4 changes are shown in the figure below. A dose response was apparent.

Figure 2: Change in complement levels with belimumab treatment (C1056+C1057)

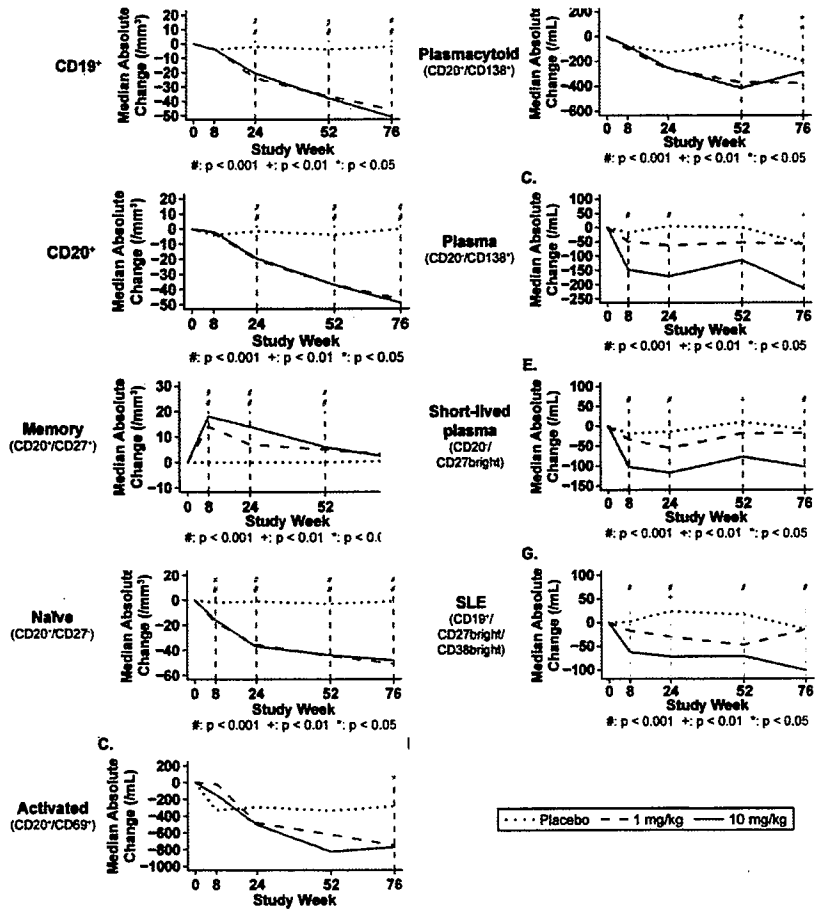


B and T cell subsets: B and T cell subsets were evaluated only in C1056. Belimumab treatment significantly reduced the following B- or T-cell populations after 52 weeks of treatment:

- CD19+ and CD20+ B cells. No dose response was observed.
- Naïve (CD20+/CD27-) B cells and activated B cells (CD20+/CD69+). Significant differences were observed as early as week 8 in the naïve B cells (28-32% with belimumab, 2-9% with placebo) whereas activated B cells continued to decrease to Week 52 (40-49% with belimumab and 16% with placebo). No dose-response was observed.
- Plasmacytoid (CD19+20+138+) cells. Changes were observed by Week 24 for belimumab (43-45%) compared with placebo (20%). No dose-response was observed.
- Short-lived plasma B cells (CD20-/CD27bright), plasma B cells (CD20-/CD138+) and the SLE B cell subset (CD19+/CD27bright/CD38bright). A dose response was observed.

The following cell populations increased:
- Memory B cells (CD20+/CD27+). No dose response was observed.
- Helper T-cells (CD3+/CD4+) and suppressor T-cells (CD3+CD8+). This expansion may be due to the reduction in CD19+ and CD20+ B cell populations.

Figure 3: Change in B- cell subsets with belimumab treatment (C1056)



3.1.1.2 Reviewer's analysis

The sponsor's findings noted above were confirmed (results not shown).

3.1.2 Biomarker relationships with belimumab efficacy

3.1.2.1 Sponsor's analysis

The sponsor prespecified subgroup analyses based on anti-dsDNA, C3 and C4. Additional post-hoc analyses were conducted for ANA, anti-Sm, and BlyS. In general, subjects with a higher degree of serological activity (anti-dsDNA positive, high ANA ≥1:640, low C3, low C4), had a greater response with belimumab 10 mg/kg relative to placebo compared with subjects without these characteristics. This was mainly driven by a different response rate in placebo subjects. Baseline complement appeared to show an interaction with treatment effects. As shown Table 3, individuals with normal complement at baseline had high placebo response rates relative to those with low complement, and did not demonstrate significant treatment effects. Belimumab responses were higher among those with low complement, and a clear dose-response was observed.

Table 3: Treatment effects on primary efficacy endpoint by baseline complement abnormality

	N	Observed Response Rate	AOR[1]	95% CI		Interaction P-value
Complement by treatment interaction						0.0360
C3 and C4 normal						
Placebo	215	47.9%	-	-	-	
1 mg/kg	222	53.1%	1.331	0.892	1.985	
10 mg/kg	201	48.7%	1.030	0.683	1.555	
C3 or C4 low, but not both						
Placebo	143	37.06%	-	-	-	
1 mg/kg	112	44.64%	1.513	0.884	2.587	
10 mg/kg	135	55.56%	2.414	1.447	4.026	
C3 and C4 low						
Placebo	204	30.39%	-	-	-	
1 mg/kg	225	40.00%	1.647	1.079	2.513	
10 mg/kg	227	49.34%	2.469	1.623	3.756	

Source: Table 2.7.3-51 from Summary of Clinical Efficacy

An analysis of subjects with low BLyS levels at baseline identified no treatment by subgroup interactions for any of the response components, although the response rates were variable, inconsistent and, in general, less robust than observed for the subgroup of subjects with BLyS levels above the LOQ (0.5 ng/mL). Only 37 subjects had BLyS levels below the LOQ (< 0.5 ng/mL), making the results uninterpretable, according to the sponsor.

No difference in B cell AUC of percent change from baseline in responders vs non-responders was observed for naïve, activated or memory B cells (results not shown).

Correlative analyses were not presented for other biomarkers (e.g., autoantibodies).

3.1.2.2 Reviewer's analysis

Baseline biomarker concentrations

The relationship between abnormal core SLE disease activity biomarkers and treatment effects at 52 weeks in the pooled C1056 and C1057 trials are shown in the following table. Response rates in the placebo arm tended to be higher in subjects with negative anti-dsDNA, normal/high C3 and normal/high C4, relative to those with positive anti-dsDNA and low complement. C3 and C4 levels appeared to interact significantly with treatment, such that subjects with low C3 and C4 had substantially greater treatment effects relative to placebo. This is consistent with greater efficacy in individuals who have higher disease activity (supported by analysis of SLEDAI subgroups performed by the sponsor; results not shown). The findings were consistent for the BILAG response endpoint (which does not include immunologic markers).

Table 4: Primary efficacy endpoint by baseline biomarker status and treatment (C1056+C1057)

Population	Primary Endpoint Response Rate						Treatment Comparisons			
	Placebo		1 mg/kg		10 mg/kg		1 mg/kg vs. Placebo	10 mg/kg vs. Placebo	P	P-int
	n	%	N	%	n	%	OR (95%CI)	OR (95%CI)		
Overall	218	38.8	258	46.2	285	50.6	1.36 (1.07-1.73)	1.65 (1.30-2.10)	0.0002	
Anti-dsDNA										
Positive	136	35.8	178	45.4	203	51.1	1.52 (1.13-2.04)	1.96 (1.46-2.63)	<0.0001	0.1689
Negative	82	44.8	80	47.9	82	49.4	1.16 (0.75-1.78)	1.19 (0.77-1.84)	0.6905	
IgG										
Low/normal	114	40.9	142	47.4	147	56.3	1.32 (0.92-1.90)	1.88 (1.31-2.70)	0.0029	0.4859
High	104	37.0	116	45.2	138	46.2	1.38 (0.99-1.91)	1.48 (1.07-2.05)	0.0429	
C3										
Normal/high	139	44.3	159	51.1	152	50.5	1.35 (0.98-1.86)	1.31 (0.95-1.81)	0.1343	0.0475
Low	79	31.8	99	39.9	133	50.8	1.47 (1.01-2.15)	2.32 (1.61-3.36)	<0.0001	
C4										
Normal/high	120	46.3	127	51.8	119	50.4	1.26 (0.88-1.81)	1.20 (0.83-1.73)	0.4134	0.0325
Low	98	32.3	131	41.7	166	50.8	1.53 (1.09-2.13)	2.24 (1.61-3.11)	<0.0001	

n is the number of responders based on composite endpoints.
Odds ratios (OR), 95% confidence intervals (95%CI) adjusted for stratification variables (baseline SLEDAI, proteinuria, race), and trial; MITT population
P-values based on Wald test for global effect

Other biomarkers that vary continuously were screened for relationships with the primary efficacy endpoint using logistic regression. As shown in the following table, C3, and C4, were predictive of response to belimumab ($p<0.05$). The R^2 values for the model with only the individual biomarkers (without including other covariates) were approximately 1%. The findings were consistent for the BILAG response endpoint (which does not include immunologic markers).

Table 5: **Relationship between baseline biomarker concentrations and primary response at 52 weeks (C1056+C1057)**

Biomarker	Baseline Median (IQR) in Responders (R) vs. Non-Responders (NR)		OR (95%CI)	P
	R (N=761)	NR (N=923)		
C3 (per 100 mg/L)	960 (560, 1190)	900 (680, 1120)	1.08 (1.05-1.12)	<0.0001
C4 (per 10 mg/dL)	15 (9, 23)	13 (8, 21)	1.28 (1.16-1.41)	<0.0001
Odds ratios (OR), 95% confidence intervals (95%CI) adjusted for stratification variables (baseline SLEDAI, proteinuria, race), and trial; MITT population				

ROC curves were constructed for the above biomarkers using baseline data from the two Phase 3 clinical trials (separately). The table below summarizes the area-under the ROC curve (AUROC) for biomarkers that were predictive in the logistic regression models in the pooled analysis population. The AUROC values suggest that no single biomarker is capable of discriminating responders vs. non-responders with a high degree of sensitivity or specificity.

Table 6: **Predictive value of baseline values for disease activity biomarkers towards treatment response**

Biomarker	AUROC	
	C1056	C1057
C3	0.50	0.52
C4	0.53	0.52

Biomarker changes

Biomarker changes from baseline to 52 weeks in subjects completing 52 weeks of treatment with the study agents were evaluated in the overall trial population (not stratifying by treatment). Changes analyzed include absolute change, percent change, and area under the curve (AUC) for percent change, with and without log-transformation as needed for highly skewed data. The percent changes for biomarkers outlined in the following table were predictive of response (absolute changes and AUC percent changes were consistent). The R^2 values for the model with only the individual biomarkers (without including other covariates) were approximately 3-4%.

Table 7: **Relationship between biomarker changes and primary response at 52 weeks (C1056+C1057)**

Biomarker	Median (IQR) Biomarker Changes (Percent Change) in Responders (R) vs. Non-Responders (NR)		OR (95%CI)*	P
	R	NR		
C3 (N=1432)	60 (-40, 180)	5 (-100, 130)	1.39 (1.13-1.70)*	0.0017
C4 (N=1432)	2 (-1, 4)	3 (0, 7)	1.15 (1.01-1.32)*	0.0394
CD19+20+27- (naïve; N=532)	-15.5 (-30, -1)	-22 (-34, -4)	0.98 (0.97-1.00)	0.0228
Odds ratios (OR), 95% confidence intervals (95%CI) adjusted for stratification variables (baseline SLEDAI, proteinuria, race), trial and treatment; 52-week population *relative risk per 10% change				

AUROC curves for the biomarkers noted in the previous table (as percent change) were calculated to evaluate their performance as predictors of the primary efficacy endpoint, as shown

in the following table. Based on the AUROC curves, none of the biomarkers tested showed sufficient correlation to the efficacy endpoint.

Table 8: **Predictive value of baseline values for disease activity biomarkers towards treatment response**

Biomarker	AUROC	
	C1056	C1057
C3	0.52	0.57
C4	0.51	0.54
CD19+20+27- (naïve)	0.50	Not available

3.2 Do biomarker changes support the observed lack of belimumab efficacy in black subjects?

- ***Blacks demonstrated lower response rates following belimumab treatment as compared to placebo, which appears to be driven in part by higher placebo response rates.***
- ***Imbalances were noted in baseline disease activity, and discontinuation rates prior to 52 weeks were substantially higher in blacks receiving belimumab as compared to placebo and all non-black subjects.***
- ***For biomarkers that demonstrated a relationship with disease response (C3, C4, naïve B cells), changes following treatment with belimumab were similar in blacks and non-blacks.***
- ***Among blacks, the most predictive baseline covariate for response (overall and in the placebo arm) was C4. Trends toward a biomarker*treatment interaction were evident in blacks and non-blacks alike.***
- ***Due to the small sample size, heterogeneity in treatment effects as a function biomarker levels could not be definitively concluded for the black population.***
- ***The lack of efficacy in blacks appears to be driven by different disease characteristics, and belimumab appears to be efficacious in certain subgroups of the black population (specifically those with higher levels of disease activity as reflected by SLEDAI scores or complement levels).***

3.2.1 Efficacy and safety in black subjects

3.2.1.1 Sponsor's analysis

As shown in the following table, the placebo response was higher (44%) in blacks than in the overall and non-black populations (35-39%). The response rates to belimumab treatment were lower in black subjects (31% and 36% with 1 mg/kg and 10 mg/kg, respectively) than in the overall and non-black population (39-47% and 47-60% with 1 mg/kg and 10 mg/kg, respectively).

Table 9: **Primary efficacy endpoint response rates at Week 52 by race (C1056+C1057)**

	Placebo N = 562	1 mg/kg N = 559	10 mg/kg N = 563
Overall	218 (38.8%)	258 (46.2%)	285 (50.6%)
Race			
White -Caucasian	94/270 (34.8%)	125/268 (46.6%)	133/260 (51.2%)
Black - African American or African Heritage	22/50 (44.0%)	15/48 (31.3%)	18/50 (36.0%)
Alaska Native or American Indian	61/125(48.8%)	74/131 (56.5%)	75/126 (59.5%)
Asian	41/116 (35.3%)	44/112 (39.3%)	59/127 (46.5%)

Source: Table 2.7.3-48 from Summary of Clinical Efficacy

Disease activity between the populations generally was similar, while subjects of black race had greater organ damage as measured by SLICC damage index (1.18 vs 0.73) and less proteinuria. Use of concomitant SLE medications was generally comparable between subjects of black and other races, although more black subjects were receiving immunosuppressants (56% vs 48%) and mycophenolate (19% vs 10%).

The following baseline characteristics were identified as significant predictors of Week 52 response, irrespective of whether a subject was treated with belimumab or placebo (listed in order of significance): baseline SELENA SLEDAI, complement (normal/high C3 and C4, low C3 or C4, low C3 and C4), immunosuppressive use, region (US/Canada, Western Europe, Eastern Europe, Americas excluding US/Canada, and Asia), SLICC/ACR Damage Index score, and anti-dsDNA.

Belimumab appeared to be efficacious in blacks in the Phase 2 trial, LBSL02, as measured by a $\geq$ 4 point reduction in SLE SLEDAI scores. In this study, the placebo response was 22 % in blacks and the response rates to belimumab treatment were 46% and 29% with 1 mg/kg and 10 mg/kg, respectively. Based on the Phase 2 trial, the sponsor has suggested that belimumab has efficacy in the black subgroup, and the poorer response observed in the Phase 3 trials is a chance finding in a small subgroup. The sponsor has suggested that the lower disease activity, as measured by SELENA SLEDAI, BILAG A scores and proteinuria, in the black subjects might explain the discrepant results.

3.2.1.2 Reviewer's analysis

Consistent with the sponsor's findings, blacks appeared to have poorer outcomes on belimumab as compared to placebo. Blacks tended to have higher placebo response rates, and lower belimumab response rates as compared to non-blacks. Thus, a trend toward ineffectiveness of treatment with belimumab compared to placebo was apparent in blacks. Belimumab also appeared to be ineffective in the black population completing 52 weeks of treatment (results not shown).

Table 10: Primary efficacy endpoint response rates at Week 52 by race (C1056+C1057)

Population	Primary Endpoint Response Rate						Treatment Comparisons			
	Placebo		1 mg/kg		10 mg/kg		1 mg/kg vs. Placebo	10 mg/kg vs. Placebo	P	P-int
	n	%	n	%	n	%	OR (95%CI)	OR (95%CI)		

Overall	218	38.8	258	46.2	285	50.6	1.36 (1.07-1.73)	1.65 (1.30-2.10)	0.0002	
Black	22	44.0	15	31.2	18	36.0	0.60 (0.26-1.39)	0.75 (0.33-1.70)	0.4870	0.0648
Non-Black	196	38.3	24	47.6	267	52.1	1.46 (1.13-1.88)	1.79 (1.39-2.30)	<0.0001	

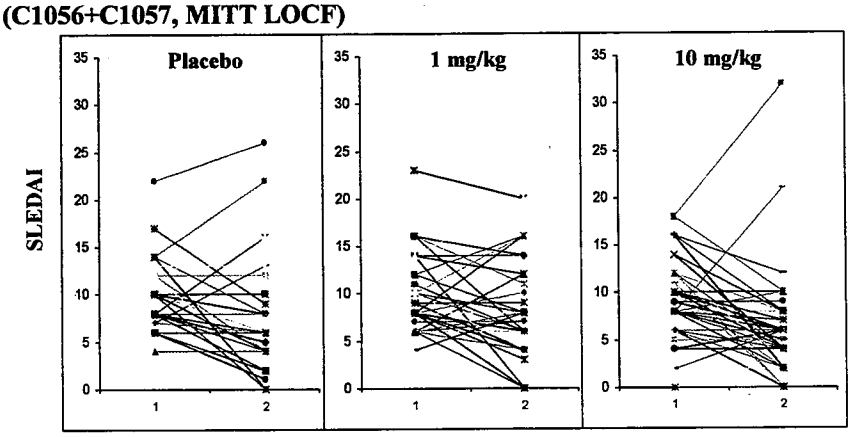
n is the number of responders based on composite endpoint
Odds ratios (OR), 95% confidence intervals (95%CI) adjusted for stratification variables (baseline SLEDAI, proteinuria, race), and trial; MITT population
P-values based on Wald test for global effect

The following baseline characteristics differed between black and non-black subjects: proteinuria (black 0.36 g/24h, non- black 0.50 g/24h), BMI (black 28 kg/m^2, non-black 25 kg/m^2), low IgG (black 35%, non- black 58%), low C4 (black 45%, non- black 57%), mycophenolate use (black 19%, non-black 10%), which is consistent with the sponsor's analysis.

Baseline factors consistently predictive of response to belimumab (using 3 different model selection techniques with baseline proteinuria, SLEDAI, race, and trial as forced covariates) included country, anti-dsDNA, C3 and C4, immunosuppressive use, and BILAG 1A/1B. All of these factors remained predictive of response in non-blacks. However, in blacks, only baseline C4 was predictive of response. The model R^2 values are approximately 14-15% in the overall population and the race subgroups.

To examine whether belimumab was having an adverse effect on disease activity in blacks, individual changes between baseline and week 52 in SLEDAI scores were evaluated (using LOCF). In the placebo, 1 mg/kg, and 10 mg/kg groups, 7 (14%), 10 (21%), and 5 (10%) black subjects had worsening disease activity, respectively. Rates of no change were similar. Black subjects completing 52 weeks had lower rates of worsening (data not shown). In contrast, in the placebo, 1 mg/kg, and 10 mg/kg groups, 63 (12%), 48 (9%), and 39 (7%) non-black subjects had worsening disease activity, respectively.

Figure 4: **Individual changes in SLEDAI score in blacks from baseline (1) to Week 52 (2) (C1056+C1057, MITT LOCF)**



The incidence of AE categories of interest in the pooled black population are summarized in the table below. AE rates were generally lower or comparable to placebo among non-blacks. Blacks tended to have higher discontinuation rates on belimumab than non-blacks. Treatment-

emergent AEs were more common among AEs in non-blacks. Consistent dose-response relationships were not observed for study regimen interventions, serious AEs, or severe/life-threatening AEs in blacks.

Table 11: Adverse event rates at 52 weeks by race and treatment arm (C1056+C1057)

	Incidence per 100 Person-Years					
	Black (n=148)			Non-Black (n=1536)		
	P	1 mg/kg	10mg/kg	P	1 mg/kg	10mg/kg
N	50	48	50	273	268	270
Person-years	46	43	43	452	474	469
Discontinuations before 52 weeks*	22	31	36	12	8	9
Treatment-emergent AE	28	30	38	60	56	58
Severe/ life-threatening AE	4.3	7.0	0	8.8	7.4	7.7
Serious AE	8.7	7.0	2.3	8.8	8.8	9.8
Related AE (probable/definite)	0	4.7	2.3	8.0	7.6	8.5
Interruption/discontinuation/modification	2.2	7.0	4.7	7.7	7.4	7.2

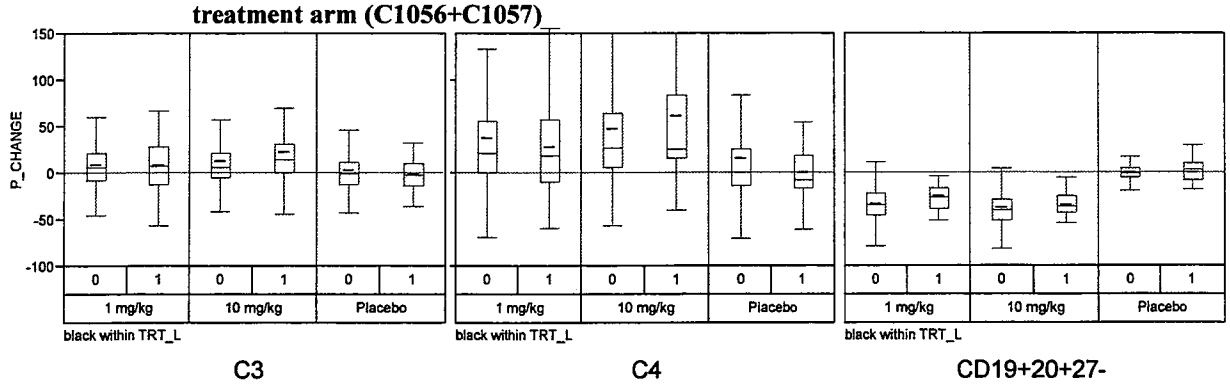
MITT
*reported as percentage

3.2.2 Biomarker models to support efficacy in blacks

To the extent that belimumab exerts its clinical benefit through modulation of immune mediators that BLyS regulates, the presence or absence biomarker changes would support the pharmacological activity and efficacy, or lack thereof, of belimumab in blacks. To be supportive, the biomarker should 1) correlate with changes in disease activity, specifically, the incidence of the primary efficacy endpoint in all subjects regardless of treatment, and 2) change to a greater extent following treatment with belimumab than placebo.

As noted in previous sections, baseline anti-dsDNA, C3, and C4 were significantly related to response in the overall population, as were changes in C3, C4, and CD19+20+27- (naïve) following treatment. Generally, these biomarkers accounted for a small proportion of the overall variability in response as reflected by the model fit statistics and correlation coefficients (in linear regression with SLEDAI [not shown]). Belimumab significantly reduced C3, C4 and CD19+20+27- (naïve). While the biomarkers are not robust surrogates for clinical endpoints, they indicate that belimumab is biologically active and effectively reduces serologic disease activity in blacks to a similar extent as whites (consistent with the figure under section 3.2.1.2).

Figure 5: Changes from baseline to week 52 in biomarker concentrations in blacks vs. non-blacks by treatment arm (C1056+C1057)



On the x-axis, 0 refers to non-blacks, 1 refers to blacks

Blacks tended to have higher placebo responses, which may have diminished the differentiation of belimumab. As such, placebo response for the primary efficacy endpoint was modeled in non-blacks and blacks. In non-blacks, country, baseline PGA, baseline SLEDAI, anti-dsDNA, complement, and immunosuppressive use were predictive of placebo response. In blacks, country and C4 were predictive of placebo response. The following table shows the relative odds of response in the placebo and treatment groups by race and baseline C4 status, since this factor was consistently predictive of response, and differed in blacks vs. non-blacks at baseline. Among both black and non-black subjects, those with normal/high C4 at baseline tended to demonstrate no treatment effects relative to placebo, whereas those with low C4 demonstrated a positive response to belimumab. The analysis in the black population was underpowered (17 events total), limiting the ability to detect significant treatment effects in this subgroup.

Table 12: Response rates and treatment effects by race and baseline C4 status (C1056+C1057)

Population	Primary Endpoint Rate – Week 52						Treatment Comparisons			
	Placebo		1 mg/kg		10 mg/kg		1 mg/kg vs. Placebo	10 mg/kg vs. Placebo	P	P-int
	n	%	n	%	n	%	OR (95%CI)	OR (95%CI)		
Overall	218	38.8	258	46.2	285	50.6	1.36 (1.07-1.73)	1.65 (1.30-2.10)	0.0002	
Non-Black										
C4 Normal/high	102	44.7	116	52.5	110	52.4	1.36 (0.93-1.99)	1.37 (0.93-2.02)	0.1898	0.1125
C4 Low	94	33.1	127	43.8	157	51.8	1.60 (1.13-2.26)	2.29 (1.63-3.22)	<0.0001	
Black										
C4 Normal/high	18	58.1	11	45.8	9	34.6	0.69 (0.22-2.13)	0.41 (0.13-1.30)	0.3173	0.1037
C4 Low	4	21.1	4	16.7	9	37.5	0.67 (0.13-3.27)	1.89 (0.46-7.79)	0.3013	

n is the number of responders based on composite endpoints.
Odds ratios (OR), 95% confidence intervals (95%CI) adjusted for stratification variables (baseline SLEDAI, proteinuria, race), and trial; MITT population
P-values based on Wald test for global effect

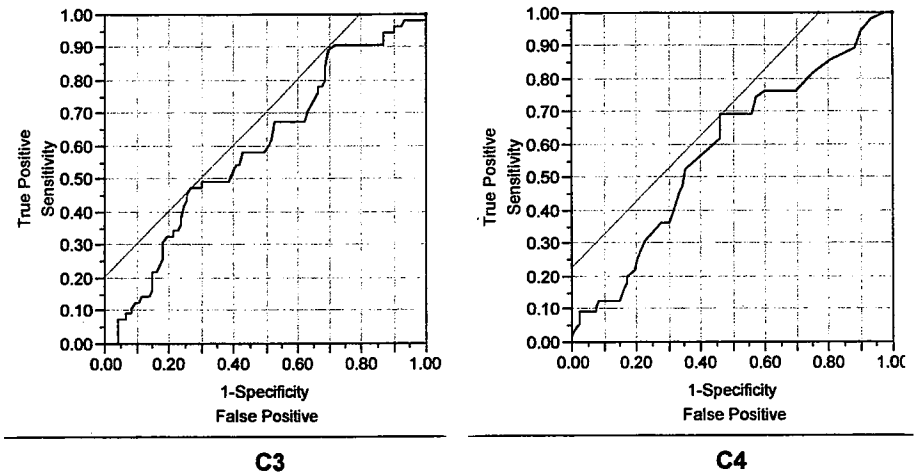
AUROC curves for the biomarkers (as baseline) were calculated to evaluate their predictive performance for the primary efficacy endpoint, as shown in the Table 13. Based on the AUROC curves, C3 and C4 were more predictive of response in blacks than the overall population.

Percent change in C3 and C4 levels did not show correlation to the efficacy endpoint in either trial.

Table 13: Baseline biomarker AUROC for primary efficacy endpoint in blacks

Biomarker	AUROC		
	C1056	C1057	Pooled
C3	0.61	0.56	0.59
C4	0.57	0.68	0.58

Figure 6: Baseline biomarker ROC curves for primary efficacy endpoint in blacks (C1056+C1057)



4 Summary and Conclusions

4.1 Biomarker relationships with efficacy

- Belimumab significantly alters SLE disease activity biomarkers (e.g., anti-dsDNA, complement) and other pharmacodynamic biomarkers (BlyS, B- and T-lymphocytes).
- Differential efficacy was noted based on baseline levels of C3 and C4, suggesting greater benefit of belimumab in subjects with higher levels of serologic activity.
- Changes in C3, C4, and naïve B-cells, were significantly correlated with response to belimumab.
- These biomarkers, in isolation, did not adequately predict response in placebo- or belimumab-treated subjects.

4.2 Lack of efficacy in blacks

- Blacks demonstrated lower response rates following belimumab treatment as compared to placebo, which appears to be driven in part by higher placebo response rates.
- Imbalances were noted in baseline disease activity, and discontinuation rates prior to 52 weeks were substantially higher in blacks receiving belimumab as compared to placebo

and all non-black subjects.

- For biomarkers that demonstrated a relationship with disease response (C3, C4, naïve B cells), changes following treatment with belimumab were similar in blacks and non-blacks.
- Among blacks, the most predictive baseline covariate for response (overall and in the placebo arm) was C4. Trends toward a biomarker by treatment interaction were evident in blacks and non-blacks alike.
- Due to the small sample size, heterogeneity in treatment effects as a function biomarker levels could not be definitively concluded for the black population.
- The lack of efficacy in blacks appears to be driven by different disease characteristics, and belimumab appears to be efficacious in certain subgroups of the black population (specifically those with higher levels of disease activity as reflected by SLEDAI scores or complement levels).

5 Recommendations

The Genomic Group has reviewed the biomarker studies submitted by the applicant in the original BLA for belimumab. The application is acceptable from the perspective of the Genomics Group.

5.1 Label recommendations

(b) (4)

(b) (4) This supports the pharmacologic activity and clinical efficacy of belimumab relative to placebo. Labeling should reflect the findings of the black subgroup in the Phase 3 trials. Specific label recommendations are provided in section 3 of the Office of Clinical Pharmacology review.

5.2 Comments to Clinical Team

Based on the apparent lack of demonstrated efficacy in black subjects enrolled in trials C1056 and C1057, the sponsor proposes in the AC meeting background package that future studies will be designed to enroll greater numbers of black patients so that clinical outcomes in black patients can be better elucidated. We agree and recommend that the proposed trial be designed to assess treatment effects in black subjects with varying levels of disease activity.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125370	**Brand Name**	TBD
OCP Division (I, II, III, IV, V)	II	**Generic Name**	Belimumab
Medical Division	DPARP	**Drug Class**	
OCP Reviewer	Ping Ji	**Indication(s)**	(b) (4) in adult patients with active, autoantibody-positive SLE
OCP Team Leader	Yun Xu	**Dosage Form**	Single-use vial of lyophilized powder
Pharmacometrics Reviewer	Ping Ji	**Dosing Regimen**	Recommended dosage regimen is 10 mg/kg at 2 week intervals for the first 3 doses and at 4 week intervals thereafter as an intravenous infusion over one hour.
Date of Submission	July 9, 2010	**Route of Administration**	IV
Estimated Due Date of OCP Review	Oct 9, 2010	**Sponsor**	Human Genome Science
Medical Division Due Date	Oct 9, 2010	**Priority Classification**	P
PDUFA Due Date	Dec 9, 2010		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	x			
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	x	1		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	x	2		
Phase 3:	x	2		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -		1		
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	x	1		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		8		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	x			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_y_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

8/2/2010

Reviewing Clinical Pharmacologist — Date

Yun Xu — 8/2/2010

Team Leader(Actg.) — Date