Errata for FDA Briefing Package
Arthritis Advisory Committee
November 16, 2010

Division Memorandum

- Page 4, 2nd paragraph: Replace "The variable region was used to produce an expression vector construct to produce full length IgG1λ antibody in Chinese Hamster Ovary (CHO) cell line using standard methodologies." with "The variable region was used to produce an expression vector construct to produce full length IgG1λ antibody in NS0 mouse myeloma cell line using standard methodologies."
- Page 8, 1st paragraph: Clarification of the following statement "These findings guided the design and conduct of the two phase 3 studies (C1056 and C1057) where patients were required to be autoantibody positive, baseline prednisone use was limited to 7.5 mg and above, and comprehensive control of background treatment was implemented to enrich the patient population to help demonstrate efficacy of belimumab."

  Corticosteroid use was specified in the protocols as follows:
  - For subjects on SLE combination therapy, their stable steroid dose was required to be fixed within the range of 0 to 40 mg/day (prednisone or equivalent).
  - For subjects whose only SLE treatment was steroids, their stable steroid dose was required to be fixed within the range of 7.5 to 40 mg/day.
  - For subjects on alternating day doses of steroids, the average of 2 daily doses was used to calculate the average daily steroid dose.
- Page 12, 1st paragraph: Replace "These included a stomach carcinoid (placebo group, day 202), a breast cancer (belimumab 1 mg/kg, day 102), a cervical cancer (belimumab 1 mg/kg, day 439), an ovarian cancer (belimumab 1 mg/kg, day 21, patient died), and a thyroid cancer (belimumab 1 mg/kg, day 378). There were 4 non-melanoma skin cancers, 2 basal cell carcinomas, and 2 squamous cell carcinomas (1 in the placebo group, 3 in the belimumab 1 mg/kg group)." with "These included a stomach carcinoid (placebo group, day 202), a breast cancer (belimumab 1 mg/kg, day 102), a cervical cancer (belimumab 1 mg/kg, day 439), an ovarian cancer (belimumab 1 mg/kg, day 21, patient died), and a thyroid neoplasm (belimumab 1 mg/kg, day 378). There were 4 non-melanoma skin cancers, 2 basal cell carcinomas, and 2 squamous cell carcinomas (1 in the placebo group, 3 in the belimumab 10 mg/kg group)."

Clinical Briefing Document

- Page 6, 3rd paragraph: Replace "Belimumab is expressed in a Chinese Hamster Ovary cell line and manufactured using typical bioreactor and purification methods for therapeutic monoclonal antibodies." with "Belimumab is expressed in an NS0 mouse myeloma cell line and manufactured using typical bioreactor and purification methods for therapeutic monoclonal antibodies."

- Page 7, 1st paragraph: Replace "There were fetal and infant deaths from the control (3 fetus and 2 infants), low (6 fetus and 4 infants), and high dose group (1 fetus and 4 infants) animals, respectively." with "There were fetal and infant deaths from the control (3 fetus and 0 infants), low (6 fetus and 2 infants), and high dose group (3 fetus and 1 infant) animals, respectively."
- Page 23, Corrected Table 12 – last row contains corrections

Table 12: Medication Failure Sensitivity Analyses of the Primary Efficacy Endpoint (Adjusted, Week 52) for Trials 1056 and 1057

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

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

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

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

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

- Table 39 Neoplasms in the Belimumab SLE Trials (data cut-off December 31, 2009) – yellow highlights show corrections

	Placebo	Belimumab 1mg/kg	Belimumab 4 mg/kg	Belimumab 10mg/kg	Total Belimumab
Total Subjects with ≥ 1 Malignancy/Neoplasm	**3**	**5**	**1**	**24**	**30**
Sold Tumors :					
Breast Cancer	1	1	0	2	3
Colon Cancer	0	0	0	2	2
Malignant Melanoma	0	0	0	1	1

Carcinoid Tumor of the Stomach	1	0	0	0	0
Cervical Carcinoma (Stage 0)	0	1	0	0	1
Rectal Cancer	0	0	0	1	1
Renal Cell Carcinoma	0	0	0	1	1
Ovarian Cancer	0	1	0	0	1
Malignant Lung Neoplasm with Mets (Bone/Marrow)	0	0	0	1	1
Hematologic/Lymphatic:					
B-cell Lymphoma	0	0	1	0	1
Nodal Marginal Zone B-cell Lymphoma	0	0	0	1*	1*
Multiple Myeloma	0	0	0	1	1
Non-Melanoma Skin Cancer:					
Basal Cell Carcinoma	1	0	0	3	3
Squamous Cell Carcinoma	0	0	0	4	4
Solid Tumors of Unspecified Classification:					
Hepatic and Lung Neoplasm	0	0	0	1	1
Lung and Thyroid Neoplasm	0	0	0	1	1
Lung Neoplasm	0	0	0	1	1
Thyroid Neoplasm	0	1	0	3	4
Soft Tissue Neoplasm	0	0	0	1	1
Breast Neoplasm	0	1	0	0	0

Reviewer's table based on Sponsor's Table 6-1; Appendix 6 of Summary of Clinical Safety Appendices
* Per 120-day safety update, follow up evaluation revealed this event to be non-malignant lymphadenopathy

- For Table 41, page 51 (Serious Adverse Events in Studies LBSL02, 1056 and 1057) and Table 42, page 53 (SAE Preferred Terms Reported by >5 Subjects in LBSL02, 1056 and 1057), it should be noted that events were not generally included if the incidence was higher in the placebo group than in the belimumab treatment groups.
- In Table 41
    - On page 51, the percentage of cardiac disorders for the belimumab 4 mg/kg group should read 1.8%, not 10%
    - On page 51, an event of Abortion Spontaneous should be listed for the belimumab 1 mg/kg group
    - On page 52, the percentage for the vasculitis and arteriosclerosis events in the belimumab 4 mg/kg group should read 0.9%, not 0.1%.
- In Table 47, page 62
    - For the BLA original analysis in the row entitled, "all hypersensitivity reactions occurring on infusion days (HGS definition)", events in the belimumab 1 mg/kg group should read 9, not 3, with a percentage of 1.3%, not 0.4%. Also, a second event should be noted for the belimumab 4 mg/kg group in the same row.