CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125370

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	March 9, 2011
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	125370/0
Applicant Name	Human Genome Sciences
Proprietary / Established (USAN) Names	Benlysta Belimumab
Dosage Forms / Strength	120 mg lyophilized/5 ml vial, 400 mg lyophilized/20 ml vial
Proposed Indication(s)	(b) (4) adult patients with active, autoantibody-positive systemic lupus erythematosus who are receiving standard therapy.
Action:	*Approval*

3/9/11

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding belimumab and the reader should refer to the reviews in the action package for a more detailed discussion. Belimumab is a human IgG1λ monoclonal antibody (mAb) that was developed for the treatment of systemic lupus erythematosus (SLE). Belimumab binds to soluble circulating ligand B lymphocyte stimulator (BLyS), also known as B-cell Activating Factor belonging to the TNF Family (BAFF). Once bound, belimumab prevents soluble BLyS/BAFF from binding to one of three known receptors on B-cells which ultimately affects B-cell selection and survival. The proposed dosage regimen is 10 mg/kg at two week intervals for the first three doses and at four week intervals thereafter as an intravenous infusion over one hour.

SLE is a chronic systemic autoimmune disorder that affects the skin, joints, kidneys and other organs and occurs predominantly in women. The course of the disease is unpredictable and can range in severity from mild to causing death. There is not a cure for SLE and the limited therapies that are currently in use are aimed at controlling symptoms and reducing end-organ damage. Treatment of SLE involves preventing flares and when they occur reducing their severity and duration. With the exception of aspirin, corticosteroids and hydroxychloroquine, the most commonly used treatments have not been FDA-approved specifically for SLE. These treatments include antimalarial agents, corticosteroids and other immunosuppressive drugs such as cyclophosphamide, mycophenolic acid, azathioprine, and the anti-CD20 monoclonal antibody rituximab. Hydroxychloroquine is the last medication approved by the FDA in the 1950s.

Dr. Yim in her background has a very nice summary describing SLE and how one could theoretically suppose that B-cell depleting therapy should be effective. As she points out however, this has not proven to be the case and indeed Phase 2 results for belimumab were not

successful, but did provide valuable insight into selecting populations of SLE patients that may be responsive. This provided the basis for the sponsor's two pivotal Phase 3 trials.

Although there are several caveats to the efficacy evaluation that I will describe below, the sponsor has demonstrated in two pivotal trials that belimumab was effective in treating a subpopulation of subjects with SLE already receiving standard therapy. Having said that generalization of the effectiveness demonstrated in the two pivotal trials to the broader SLE population is not appropriate. While belimumab may not be the panacea of treatment of SLE that one would hope for, it has demonstrated efficacy in a population of autoantibody positive subjects for the treatment of mainly musculoskeletal and mucocutaneous symptoms.

Efficacy

This has been covered in great detail in Drs. Neuner, Yim, Davi and Chowdhury's reviews and I will present only a high-level overview. At present, there is not a standard outcome measure that has been successfully used in evaluating therapeutic efficacy in SLE. The primary endpoint used in the belimumab trials is new, and has not been validated as to what degree of change is clinically meaningful to demonstrate efficacy in a randomized trial. However, as is often the case, we must make our best judgment on what may constitute an important change and what endpoints have the best face validity, or development for these life-threatening diseases would be totally halted. The team has determined that the endpoint used by the sponsor is appropriate and I agree.

The primary endpoint used for evaluation is a composite that is unique to this application, so we have limited experience in its utility. The SLE Responder Index (SRI) was the primary endpoint used for evaluation and is comprised of 3 components—the SELENA-SLEDAI, the BILAG, and the Physician's Global Assessment. While the composite of these components has not been used for clinical trial determinations by the agency, the individual components are commonly used in SLE clinical studies. The following, taken mostly from Dr. Yim's review (Page 9-10), describes these three components.

> The SLEDAI is a list of 24 items, each with a definition of activity; 16 are clinical items:
>
> seizures, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, and fever
>
> Eight are based on laboratory results:
>
> urinary casts, hematuria, proteinuria, pyuria, low complements, increased DNA binding, thrombocytopenia, and leukopenia).
>
> Scoring is according to whether organ manifestations were present or absent in the last 10 days prior to the assessment visit. Organ involvement is weighted by severity of outcome consequence if that organ is involved; for example arthritis and renal

activity are each multiplied by 4, whereas central nervous system activity is multiplied by 8. The weighted organ manifestations are then summed into a final score, which ranges from 0 to 105 (although in reality in the present era of medical care most patients rarely exceed scores of 20). A SLEDAI of 6 or more has been shown in practice to be consistent with active disease requiring therapy.[1] A clinically meaningful difference used in practice has been reported to be improvement of 6 points or worsening of 8 points.[2] The SLEDAI was modified in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial; this modification, known as the SELENA-SLEDAI, added clarity to some of the definitions of activity in the individual items but did not change the basic scoring system. The SELENA-SLEDAI was the index used in the belimumab pivotal trials.

The Physician's Global Assessment is simply a subjective rating by a single assessor on a visual analog scale ranging from 0 to 10, with 0 being no disease activity and 10 being the most severe disease activity.

The BILAG is an organ-specific 86 question assessment based on the principle of the healthcare provider's intent to treat, which requires the assessor to score organ manifestations as improved (=1), same (=2), worse (=3), or new (=4) over the last month. Within each organ system, multiple manifestations and laboratory tests (as applicable) are combined into a single score for that organ, which is done by a specific computer software program. The resulting scores for each organ can be A through E, where A is very active disease, requiring treatment with immunosuppressive therapy and/or prednisolone (or equivalent) dose of greater than 20 mg/day, B is moderate activity which would require a lower level of immunosuppressive therapy, C is mild stable disease, D is resolved activity, and E indicates the organ was never involved. Eight headings are included: general, mucocutaneous, neuropsychiatric, musculoskeletal cardiorespiratory, vasculitis, renal, and hematologic.

The primary efficacy endpoint, referred to as the SRI response, was a dichotomous composite endpoint, with response defined by achievement of all of the following criteria at week 52.

- $\geq$ 4 point reduction from baseline in SELENA SLEDAI score, and
- No worsening (increase of <0.30 points from baseline) in physician's global assessment (PGA), and
- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment

The concept behind this endpoint was that there would be a measure of reduction in disease activity (SELENA-SLEDAI) and two measures to ensure that improvement in disease activity are not offset by deterioration in overall condition (PGA) or worsening in any specific organ system (BILAG).

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

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

As mentioned above, results from a large Phase 2 trial were not promising. In this study (LBSL02), the primary endpoint was percent change in SELENA-SLEDAI disease activity score at Week 24 and Time to First Mild/Moderate or Severe SLE Flare (as defined by the SELENA-SLEDAI SLE Flare index) over 52 weeks. The results demonstrated that belimumab was not effective for any of the primary or secondary endpoints. However, post-hoc analyses led the sponsor to believe that belimumab may have been effective in the subgroup of patients who were autoantibody positive.

To test this hypothesis, the sponsor designed two large Phase 3 trials, 1056 (mainly North American sites) and 1057 (primarily Asian and Latin American sites). These studies had identical protocols and primary endpoints (SRI at Week 52) with Study 1056 evaluating a longer controlled period of 76 weeks to assess for possible delayed treatment effect. Both Study 1056 and Study 1057 enrolled patients with active, seropositive SLE on stable immunosuppressive medications. Active SLE was defined as a SELENA-SLEDAI disease activity score >6 at screening, and seropositivity was defined as an ANA of at least 1:80 titer and/or an anti-dsDNA of at least 30 IU/mL on at least 2 separate occasions.

It is important to note that subjects were excluded if they had severe active lupus nephritis, CNS lupus, a history of treatment with targeted B-cell therapy, abatacept within 1 year, intravenous cyclophosphamide within 6 months, anti-TNF therapy, IV immunoglobulin (IVIG), prednisone at doses greater than 100 mg/day, plasmapheresis within 3 months, or live vaccine within 1 month of study entry. Therefore, the efficacy and safety of belimumab is unknown in these clinical scenarios.
The results of Trials 1056 and 1057 are demonstrated in the table below from Dr. Yim's (page 14).

Table 1: Proportion of Patients with an SRI Response at Week 52

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

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)

[2]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline PGA

[3]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline BILAG domain involvement (at least 1A/2B vs at most 1B)

As demonstrated above, the differences between the belimumab and placebo treatment groups are statistically significant for each trial, but are fairly small in magnitude. The results for Trial 1057 are also somewhat more robust than those of Trial 1056. The population studied in Trial 1056 was mainly North American subjects and may therefore be a more accurate representation of the efficacy one can expect from domestic use. It is curious that across the agency we now have several large multi-national trials where the results more often than not are more robust from foreign countries. One would not think that this should be due to genetic differences (at least for European sites) as the United States is fairly genetically diverse and should not differ greatly from European sites, but perhaps it does demonstrate regional differences in health care that we are not yet able to identify or capture.

In any regard, although the results are not as impressive as we have seen for some other biologic agents (e.g. TNF therapy for rheumatoid arthritis), I do think that belimumab was effective in the population studied. It should not be forgotten that the evaluation for efficacy in this drug, while complicated, also did not allow a lot of 'room for play' in some of the subcomponents. As an example, the placebo percentages for 'No Worsening in PGA' and 'No New 1A/2B BILAG Domain' were already in excess of 60%, not allowing a lot of room for improvement. Also, as Dr. Yim points out, the difference in proportion of responders between belimumab and placebo widens as the difference required for success in the SLENA-SLEDAI threshold is increased, again indicating that some subjects received a greater magnitude of response. Also, for both Phase 3 trials the sponsor performed percent change in SELENA-SLEDAI disease activity score (the primary endpoint for trial LBSL02-which failed) which

demonstrate statistical significant changes for both studies at the 10 mg/kg dose at Week 52. I consider this a fairly persuasive sensitivity analysis that demonstrates the sponsor's enrichment strategy had merit (results in addendum from E-mail exchange with Dr. Davi) and that if the same primary endpoint would have been used as in Trial LBSL02 (which failed) the outcome would have been the same.

As this will be the first SLE drug approved in decades and therefore may receive a great deal of attention, it should be stressed that the efficacy was somewhat limited, and confined only to an enriched subgroup of the total SLE population. Dr. Davi notes that "medication failures" are not balanced across treatment groups and are always higher for the placebo group (e.g. 17%, 9% and 10% for placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab in Trial 1056). It could be viewed that imputing medication failures as efficacy failures may have a proportionally greater bias for the treatment effect in favor of belimumab since this was a dichotomous scale. It could also be viewed that this provides further evidence that belimumab did have an effect above and beyond placebo as there were less medication failures with active drug requiring rescue therapy. Most of the many secondary analyses trended in the right direction (e.g. severe flares), and while not statistically significant, prednisone use decreased in a higher proportion of subjects taking belimumab compared to placebo. This is an important consideration as corticosteroid use has many adverse side-effects as well and decreased use would be welcomed by clinicians and patients. It is concerning that subgroup analysis revealed that African American subjects, at best had a neutral response and at worse seemed to do more poorly with belimumab therapy. There was limited enrollment, which should give us some caution in not over-interpreting this result, but this will need further evaluation and labeling highlighting this result until further data are available. I note that Dr. Chowdhury questions the durability of response, as Trial C1056 lost statistical significance at Week 76. While this is true, treatment difference in SRI response at Week 76 was very similar to the result at Week 52 with the possible exception that the dropout rate in the 10 mg/kg Belimumab group increases more than it does in the other treatment groups. This increase dropout rate would affect power to determine statistical differences, and the extension was not designed for this specific evaluation. This may or may not be a concern and evaluating for continued clinical response is something that can be monitored for in clinical practice.

As this disease is heterogeneous, it should be expected that, as with any disease, there are probably subgroups that may be responsive, and other subgroups that are not. However, given the limitations on the study population in Trials 1056 and 1057, generalization of the effectiveness demonstrated in the two pivotal trials to the broader SLE population is not appropriate. On the other hand, it is appropriate to identify a subgroup that may be responsive, and use that group (enrich) in the trial. While belimumab may not be the panacea of treatment of SLE that one would hope for, I believe it has demonstrated efficacy in a population of autoantibody positive subjects for the treatment of mainly musculoskeletal and mucocutaneous symptoms.

Safety

Death:

There was a slight imbalance in death across the trials that were not favoring belimumab. This demonstrated in Table 2 below from Dr. Yim's review (Page 22).

Table 2: Exposure-Adjusted Incidence of Death in the IV SLE Controlled Studies

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

Adapted Sponsor's Table 4-2; P. 25 of Appendix 4 of the Summary of Clinical Safety

There were few events, so it is difficult to draw firm conclusions. There did not seem to be one predominant cause which may indicate a drug specific effects, although there was a trend based on infection, which may be expected from a drug with B-cell modulation.

Serious Adverse Events:

As with most immune modulating agents, events of concern are malignancy and infection. It is also interesting to note that there was an imbalance in psychiatric and depression adverse events not favoring belimumab.

For malignancy, there did not appear to be an imbalance between the placebo group and the belimumab 10 mg/kg group. For infections, there were 2 opportunistic infections in subjects receiving belimumab of disseminated CMV and Acinetobacter bacteremia. There were 4 infection related deaths with a numerical imbalance that favored placebo treatment over belimumab treatment.

The psychiatric adverse events are nicely summarized in Dr. Chowdhury's review (Page 13). For suicides, there were two completed suicides across the double-blind placebo controlled studies, both in patients treated with belimumab. There was an additional completed suicide in a belimumab treated patient during a safety extension. There were four cases of suicide attempts or suicidal ideation, all in patients treated with belimumab. Psychiatric and nervous system adverse reactions classified as serious adverse events were numerically more common in patients treated with belimumab than with placebo. Depression was the most frequent serious adverse event under the psychiatric disorder category with 0.1% (1 patient), 0.4% (3 patients), and 0.4% (3 patients), occurring in patients in the placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg groups, respectively. Psychiatric events not classified as serious adverse events, specifically depression/depressed mood, were more frequent in patients treated with belimumab than with placebo. The frequencies of depression/depressed mood were 30 (4.4%), 43 (6.4%), 12 (10.8%), and 36 (5.3%) in placebo, belimumab 1 mg/kg, belimumab 4 mg/kg, and belimumab 10 mg/kg groups, respectively.

While there are no known biological mechanisms for suicides and psychiatric events with belimumab at this time (and it is a large molecule that should not pass the blood-brain-barrier), and patients with SLE have a greater risk of suicide[3,4], there was a numerical imbalance that favored placebo over belimumab in these double-blind placebo-controlled studies. If true, perhaps this could represent some type of down-stream event that we do not yet understand. To further evaluate this finding, the sponsor conducted a formal C-CASA methodology. The new formal analyses did not reveal any new findings or new patterns. The Agency psychiatrists opined that the finding was not convincing, but a definitive conclusion could not be made from the limited data as the numbers of events were not very large, and there were no dose-response or temporal clustering. While this is true, it still remains that there was an imbalance and randomization should have assured that patients at risk for these reaction, if not drug related, were equivalent across groups and more events should have occurred in the placebo group. While there are few events, and sometimes spurious findings occur with few events, this is something that needs further evaluation, which is planned for in the required safety study.

Regarding the required safety study, the sponsor will enroll 5,000 subjects in a 5-year study [redacted] (b) (4)

While there is always a tension between attributable risk, severity of safety issue and desire to define precisely the amount of risk, we must also be practical in determining a feasible study size. It is also important to remember that we will not only be obtaining an upper bound of the 95% confidence interval, but we will also be determining a point estimate that will add to the body of safety knowledge. As such, and remembering that 'the perfect should not be the enemy of the good', we have determined that this is probably the largest safety study that the sponsor could perform.

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[3] Bachen EA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorder in women with systemic lupus erythmatosus. Arthritis and Rheum 2009: 61:822-829.

[4] Harris EC, Barraclough BM. Suicide as an outcome for medical disorders. Medicine 1994; 73:281-296.

The safety summary for this application had the concerns noted above. Belimumab appears to be clearly associated with an increase in infections and serious infections, which is not unexpected. This and the other concerns noted above do not preclude approval when balanced against the efficacy of belimumab in the face of the severity of the disease being treated and paucity of effective therapies. While there are therapies that are used off-label for SLE that are felt to be effective, they too all have serious concerns. Safety concerns that we have noted should be prominently expressed in the label, as for the most part they can be monitored for by clinicians and patients as long as they are aware.

Advisory Committee Meeting

An Arthritis Advisory Committee (AAC) meeting was held on November 16, 2010 to discuss this application. The Committee overall voted that there was substantial evidence of efficacy (10-yes, 5-no), and safety (14-yes, 1-no). The committee also voted 13-yes and 2-no that belimumab should be approved. They voiced many of the same concerns regarding the efficacy and safety results as expressed in my review above and recommended that labeling carefully address these issues.

Conclusions and Recommendations

The sponsor has demonstrated that the proposed dose of belimumab does have efficacy. There are also several safety concerns as noted above. SLE can be a devastating disease, and all treatments at present have safety concerns, some equal to or perhaps even worse than belimumab. When considering any drug for approval, the combination of severity of disease, available treatments and unique safety and efficacy of the drug in question with this background must be considered. Belimumab will most likely be a welcomed addition to the armamentarium of drugs for those taking care of SLE, but must be used in the context of its limitations.

The sponsor will be required to institute a Medication Guide. They will also be required to conduct a large controlled safety trial to evaluate further the safety issues such as mortality, infection, malignancy, suicides and psychiatric events. Further, they will be required to have a pregnancy registry.

There are still unanswered efficacy questions regarding belimumab. As such, the sponsor will be asked to perform Post-marketing Commitment Studies (PMC) to include further efficacy trials in subjects with lupus nephritis and African American patients.

With the above considerations, I believe that belimumab should be approved if appropriate labeling can be agreed upon.

Addendum:

Study 1056

Human Genome Sciences
BLISS76, HGS1006–C1056

TE7.12 SELENA SLEDAI % change from baseline by visit[3] (LOCF, AP Section: 8.3.1.6)

Visit		Placebo N=275	1 mg/kg N=271	10 mg/kg N=273
Week 48				
	n	274	269	271
	Mean ± SE	−26.92 ± 2.67	−33.83 ± 2.39	−34.75 ± 2.81
	Median (Min, Max)	−28.57 (−100.0, 225.00)	−33.33 (−100.0, 140.00)	−40.00 (−100.0, 200.00)
	LS Mean ± SE[2]	−29.62 ± 4.41	−36.36 ± 4.52	−37.54 ± 4.33
	Treatment differences (95% CI)[2] vs. placebo		−6.74 (−13.99, 0.51)	−7.92 (−15.16, −0.69)
	P–value[2]		0.0683	0.0319
Week 52				
	n	274	269	271
	Mean ± SE	−25.97 ± 2.72	−33.87 ± 2.44	−35.94 ± 2.80
	Median (Min, Max)	−28.99 (−100.0, 225.00)	−33.33 (−100.0, 140.00)	−42.86 (−100.0, 200.00)
	LS Mean ± SE[2]	−29.53 ± 4.46	−37.29 ± 4.56	−39.55 ± 4.37
	Treatment differences (95% CI)[2] vs. placebo		−7.76 (−15.08, −0.43)	−10.02 (−17.33, −2.71)
	P–value[2]		0.0379	0.0073

[1]P–value: 0.6754 from ANOVA for comparison of baseline absolute values across 3 groups without adjusting for any covariates
[2]All statistics, including the difference in LSM (least square means), were from ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for the baseline SELENA SLEDAI score (<=9 vs. >=10), baseline proteinuria level (<2 g/24 hour vs. >=2 g/24 hour equivalent) and race (African descent or indigenous–American descent vs.other)
[3]Five subjects have baseline SELENA SLEDAI score of 0 and therefore are excluded from % change calculation.

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Study 1057

Human Genome Sciences
BLISS52, HGS1006–C1057

TE7.12 SELENA SLEDAI % change from baseline by visit (LOCF, AP Section: 8.3.1.6)

Visit		Placebo N=287	1 mg/kg N=288	10 mg/kg N=290
Week 48				
	n	287	288	290
	Mean ± SE	−34.53 ± 2.44	−37.52 ± 2.72	−46.07 ± 2.33
	Median (Min, Max)	−40.00 (−100.0, 100.00)	−50.00 (−100.0, 200.00)	−57.14 (−100.0, 110.00)
	LS Mean ± SE[2]	−29.52 ± 3.45	−33.57 ± 3.36	−40.94 ± 3.46
	Treatment differences (95% CI)[2] vs. placebo		−4.06 (−10.91, 2.80)	−11.42 (−18.25, −4.60)
	P–value[2]		0.2456	0.0011
Week 52				
	n	287	288	290
	Mean ± SE	−34.76 ± 2.50	−38.73 ± 2.44	−45.60 ± 2.45
	Median (Min, Max)	−40.00 (−100.0, 150.00)	−50.00 (−100.0, 150.00)	−50.00 (−100.0, 200.00)
	LS Mean ± SE[2]	−29.58 ± 3.38	−34.79 ± 3.29	−40.29 ± 3.40
	Treatment differences (95% CI)[2] vs. placebo		−5.22 (−11.94, 1.51)	−10.71 (−17.40, −4.01)
	P–value[2]		0.1281	0.0018

[1]P–value: 0.4114 from ANOVA for comparison of baseline absolute values across 3 groups without adjusting for any covariates
[2]All statistics, including the difference in LSM (least square means), were from ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for the baseline SELENA SLEDAI score (<=9 vs. >=10), baseline proteinuria level (<2 g/24 hour vs. >=2 g/24 hour equivalent) and race (African descent or indigenous–American descent vs.other)

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