THE SUBCUTANEOUS BAFF INHIBITOR, BLISIBIMOD, SIGNIFICANTLY REDUCES PROTEINURIA IN SUBJECTS WITH MODERATE-TO-SEVERE SYSTEMIC LUPUS ERYTHMATOSUS

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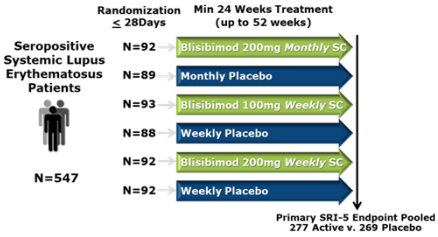
Introduction

Blisibimod is a potent and selective inhibitor of soluble and membrane-bound forms of BAFF (K_D = 1 pM, Hsu 2012). It is a peptibody dimer, comprised of 4 high-affinity binding domains fused to a fully-human IgG1 Fc domain. As with other Fc-containing molecules, it has a long serum half life of ~ 10 days (Stohl 2008).

Methods and Materials

The PEARL-SC study evaluated the efficacy and safety of subcutaneously-administered blisibimod on top of standard-of-care medication in patients with moderate-to-severe, seropositive SLE (SELENA-SLEDAI ≥ 6).



Key Inclusion Criteria

- Fulfill at least 4 of the criteria for SLE defined by the ACR.
- Receiving stable SLE treatment.
- Seropositive for ANA or anti-dsDNA antibodies.

Key Exclusion Criteria

- Severe vasculitis, CNS lupus, lupus nephritis.
- Anemia, neutropenia, or thrombocytopenia.
- Malignancy within past 5 years
- Exposure to B cell depleting therapy in the past 18 months.

The primary efficacy endpoint compared responder rates in the pooled active and pooled placebo groups using the SLE Responder Index (SRI-5) at week 24, defined as:

- ≥5 point improvement in the SELENA-SLEDAI AND
- No new BILAG 1A or 2B organ domain flares AND
- No worsening in Physician's Global Assessment (PGA) (< 0.3 increase)
- No new or increased doses of steroids or immunosuppressives beyond protocol-mandated limits.

Secondary end point analyses included:

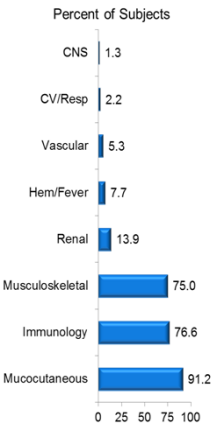
- SRI response using more stringent forms of the SRI requiring improvements in SELENA-SLEDAI score of ≥6, ≥7, ≥8 and ≥9
- SRI response in subgroups of subjects with more severe disease, SELENA-SLEDAI ≥10 and receiving corticosteroids
- Time to, and incidence of SLE flare
- Changes in SLE biomarkers
- Safety and tolerability

Subjects were invited to participate in an open-label extension study after completion of this trial

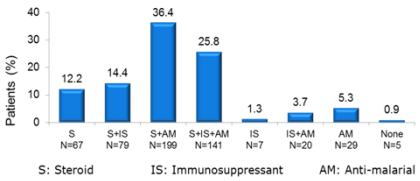
Summary of Demographics

Demographics	
Age (years)	37.5
Weight (kg)	65.6
Gender, %	
Female	94.0
Male	6.0
Race, %	
White	25.0
Asian	19.7
Black or African	8.4
Other	46.8
Region, %	
Asia/Pacific	19.0
Latin America	71.1
North America	9.9
SLE Duration (years)	6.1
Baseline Disease Characteristics	
SELENA-SLEDAI (mean, SD)	10.1 (3.6)
BILAG 1A or 2B, %	50.3
PGA (mean score, SD)	1.4 (0.4)
Proteinuria > 2g/24h, %	4.4
ANA >1:80, %	78.8
Anti-dsDNA ≥30 IU, %	68.4
Low C3 (< 900 mg/L), %	42.4
Low C4 (<16 mg/dL), %	50.2
Prednisone dose (mg/day)	12.0
Steroid >7.5 mg prednisone/day, %	60.1
Immunosuppressive use, %	45.0
Anti-malarial use, %	70.9

Baseline Disease Characteristics

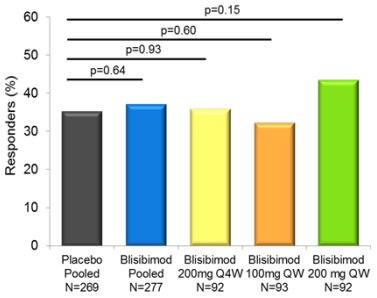


Medication Use at Baseline



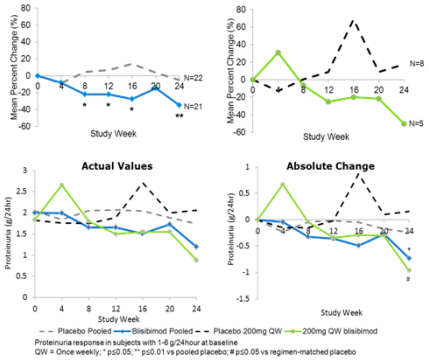
Results

SRI-5 Response at Week 24 in the mITT population

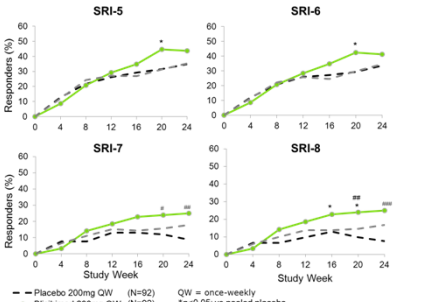


Effect of Blisibimod on Proteinuria

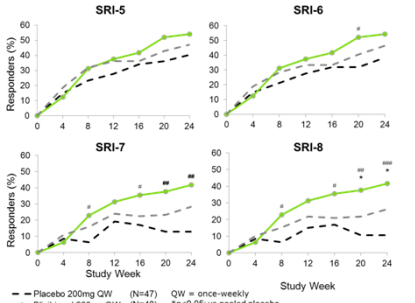
Subgroup: Baseline proteinuria = 1-6g/24hour (n=23-26 per group)



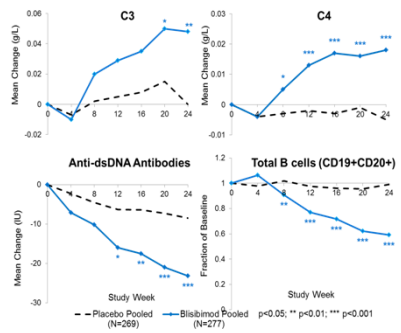
Increases in SRI Response with more Stringent SELENA-SLEDAI Criteria in mITT Population



Increases in SRI Response in Subjects with Baseline SELENA-SLEDAI ≥10 and Receiving Steroid

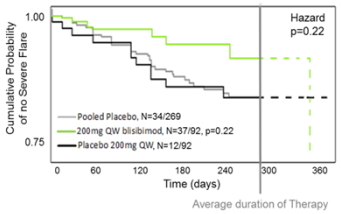


Change in SLE Biomarkers in the mITT Population



Kaplan Meier Analysis of Time to First Severe Flare

(SLE Flare Index, mITT Population)



Summary of Safety, mITT Population

	Pooled Placebo N=266	Pooled Blisibimod N=280	200mg QW Blisibimod N=92
Overview (% incidence)			
AE	85.0	82.5	83.7
Serious AE	15.8	11.1	7.6
AEs related to study drug	37.2	40.0	48.9
AEs leading to withdrawal	7.9	5.7	6.5
AEs leading to death	1.1	1.4	1.1
Severe Infection AEs	1.1	1.4	2.2
Severe Injection site reactions	0	0	0
Serious Adverse Events, n(%)			
Herpes zoster	2 (0.8)	2 (0.7)	0
Pneumonia	4 (1.5)	3 (1.1)	2 (2.2)
Urinary tract infections	2 (0.8)	2 (0.7)	0
SLE	3 (1.1)	2 (0.7)	0
Deep vein thrombosis	2 (0.8)	3 (1.1)	1 (1.1)

- 2 malignancies were reported (1 blisibimod, 1 placebo)
- 6 subjects withdrew due to pregnancy (3 blisibimod, 3 placebo)

Discussion

Blisibimod is safe and well-tolerated in patients with SLE, and significantly improved SRI responder rates and other SLE disease manifestations.

- Significant improvements in proteinuria, and a trend toward normalization of the urine protein:creatinine ratio was observed:
  - In subjects with baseline urinary protein excretion equivalent to 1-6 g/24hrs, treatment with blisibimod resulted in significantly greater reductions in proteinuria compared to placebo from Week 8 through Week 24. At week 24, blisibimod treatment resulted in a mean reduction in proteinuria of 0.73g/24 hours (-35.0%) compared to 0.24g/24 hours (-5.1%) in those treated with placebo (p=0.045).
  - The reduction in proteinuria in the blisibimod 200mg QW dose group was 50.1% (0.96g/24 hours) compared with +17.7% (0.16g/24 hours) in the regimen matched placebo group
- The study identified a patient population with significant disease burden that is predicted to respond better to subcutaneous blisibmod (200mg QW).
- The application of a more stringent endpoint is likely to demonstrate meaningful clinical improvement.
- Significant decreases in B cells, and improvements in anti-dsDNA, C3 and C4 directly and indirectly corroborate blisibimod's effect on B cell physiology.

Conclusions

- These data support further evaluation of 200mg QW blisibimod using more stringent thresholds of the SRI in patients with seropositive SLE including mucocutaneous or musculoskeletal disease.
- Further evaluation of the effect of blisibimod in B cell-associated renal disease such as IgA Nephropathy or Lupus Nephritis is warranted.
- Phase 3 trials with blisibimod in SLE and a Phase 2 study in IgA Nephropathy will commence in Q1 2013.

References

- Hsu H et al. A novel modality of BAFF-specific inhibitor AMG623 peptibody reduces B-cell number and improves outcomes in murine models of autoimmune disease. Clin Exp Rheumatol. 2012;30(2) 197.
- Stohl W et al. Phase 1a Single- and Phase 1b Multiple-Dose Studies of AMG 623 (an Anti-BAFF Peptibody) in SLE. ACR; October, 2008.

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