# Blisibimod, an Inhibitor of B cell Activating Factor, in Patients with Moderate-to-Severe Systemic Lupus Erythematosus

Richard A Furie, MD[1]; Morton A Scheinberg, MD[2]; Gustavo Leon, MD[3]; Edgar B Ramiterre, MD[4]; Matthew Thomas, MD[5]; Alvina Chu, MD[6]; Renee S Martin, PhD[6]; Michelle A Petri, MD[7]; for the PEARL-SC Study.
[1]North Shore–Long Island Jewish Health System, Lake Success, New York, USA, [2]Rheumatology Hospital Abreu Sodre Pesquisa Clínica, São Paulo, Brazil, [3]Rheumatology Gynecology & Reproduction Institute, Lima, PERU, [4]Brokenshire Memorial Hospital, Davao City, Philippines, [5]Health and Research Centre, Trivandrum, Kerala India, [6]Anthera Pharmaceuticals, Hayward, California USA, [7]Hopkins University School of Medicine, Baltimore, Maryland, USA

## 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 $IgG_1$ Fc domain. As with other Fc-containing molecules, it has a long serum half life of ~ 10 days (Stohl 2008).

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.

## Methods and Materials


**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

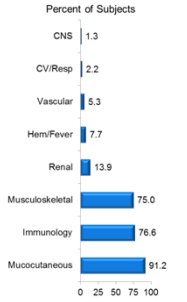
Subjects were invited to participate in an open-label extension study after completion of this trial

## Results

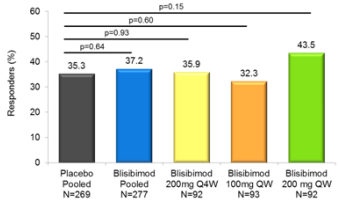
### Summary of Demographics

| | |
|---|---|
| **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

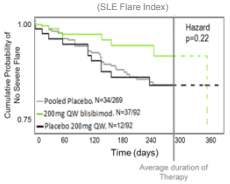



### SRI-5 Response at Week 24 in the mITT population



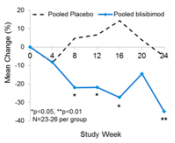

### Kaplan Meier Analysis of Time to First Severe Flare

(SLE Flare Index)

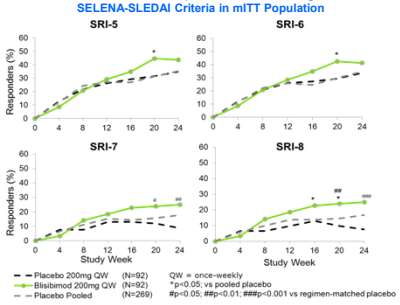



### Decrease in Proteinuria

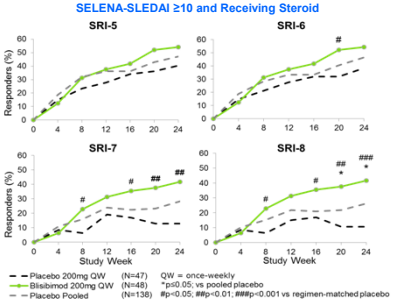
Subgroup: baseline proteinuria=1-6 g/24h




### 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




### SRI Responses in mITT Population

| Endpoint | Placebo Pooled N=269 | Placebo 200mg Q4W N=89 | Placebo 100mg QW N=88 | Placebo 200mg QW N=92 | Blisibimod Pooled N=277 | Blisibimod 200mg Q4W N=92 | Blisibimod 100mg QW N=93 | Blisibimod 200mg QW N=92 | ΔSRI 200mg QW |
|---|---|---|---|---|---|---|---|---|---|
| SRI-5 | 95 35.3% | 31 34.8% | 32 36.4% | 32 34.8% | 103 37.2% *p=0.635 | 33 35.9% *p=0.925 #p=0.884 | 30 32.3% *p=0.603 #p=0.561 | 40 43.5% *p=0.154 #p=0.227 | 8.7% |
| SRI-6 | 93 34.6% | 30 33.7% | 32 36.4% | 31 33.7% | 97 35.0% *p=0.901 | 29 31.5% *p=0.588 #p=0.754 | 30 32.3% *p=0.695 #p=0.561 | 38 41.3% *p=0.237 #p=0.288 | 7.6% |
| SRI-7 | 48 17.8% | 16 18.0% | 24 27.3% | 8 8.7% | 55 19.9% *p=0.521 | 15 16.3% *p=0.711 #p=0.765 | 17 18.3% *p=0.887 #p=0.149 | 23 25.0% *p=0.119 #p=0.003 | 16.3% |
| SRI-8 | 45 16.7% | 16 18.0% | 22 25.0% | 7 7.6% | 55 19.9% *p=0.321 | 15 16.3% *p=0.905 #p=0.765 | 17 18.3% *p=0.692 #p=0.272 | 23 25.0% *p=0.089 #p<0.001 | 17.4% |

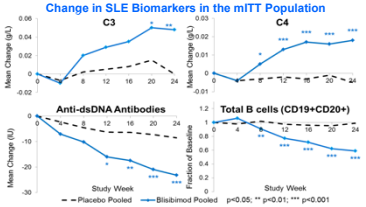
ΔSRI calculated for 200mgQW blisibimod - 200mgQW placebo; #vs regimen-matched placebo, *vs pooled placebo

### SRI Responses in Subjects withSELENA-SLEDAI≥10, Receiving

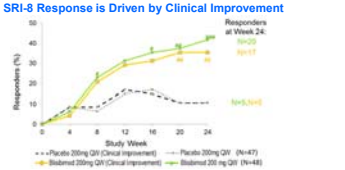
| Endpoint | Placebo Pooled N=138 | Placebo 200mg Q4W N=44 | Placebo 100mg QW N=47 | Placebo 200mg QW N=47 | Blisibimod Pooled N=140 | Blisibimod 200mg Q4W N=42 | Blisibimod 100mg QW N=50 | Blisibimod 200mg QW N=48 | ΔSRI 200mg QW |
|---|---|---|---|---|---|---|---|---|---|
| SRI-5 | 65 47.1% | 21 47.7% | 25 53.2% | 19 40.4% | 64 45.7% *p=0.682 | 21 50.0% *p=0.819 #p=0.833 | 17 34.0% *p=0.084 #p=0.057 | 26 54.2% *p=0.482 #p=0.18 | 13.8% |
| SRI-6 | 64 46.4% | 21 47.7% | 25 53.2% | 18 38.3% | 63 45.0% *p=0.682 | 20 47.6% *p=0.971 #p=0.992 | 17 34.0% *p=0.100 #p=0.057 | 26 54.2% *p=0.428 #p=0.121 | 15.9% |
| SRI-7 | 39 28.3% | 13 29.5% | 20 42.6% | 6 12.8% | 45 32.1% *p=0.517 | 12 28.6% *p=0.983 #p=0.921 | 13 26.0% *p=0.773 #p=0.085 | 20 41.7% *p=0.105 #p=0.002 | 28.9% |
| SRI-8 | 36 26.1% | 13 29.5% | 18 38.3% | 5 10.6% | 45 32.1% *p=0.291 | 12 28.6% *p=0.795 #p=0.921 | 13 26.0% *p=0.996 #p=0.194 | 20 41.7% *p=0.054 #p<0.001 | 31.1% |

ΔSRI calculated for 200mgQW blisibimod - 200mgQW placebo; #vs regimen-matched placebo, *vs pooled placebo

### Change in SLE Biomarkers in the mITT Population




### SRI-8 Response is Driven by Clinical Improvement




Clinical Improvement meets SRI-8 criteria without counting low complement, increased DNA binding, thrombocytopenia, leukopenia

### Summary of Adverse Events

| | 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)

## Conclusions

- Blisibimod was safe and well-tolerated at all dose levels with no meaningful imbalances in serious adverse events or infections compared with placebo.
- While the primary endpoint was not achieved, analyses identified patient populations and endpoints with superior responses to regimen-matched placebo:
  - Subjects treated with 200mg QW achieving SRI-7 and SRI-8 response criteria.
  - Subjects with baseline SELENA-SLEDAI≥10 and receiving steroids treated with 200mg QW and meeting SRI-7 and SRI-8 response criteria.
- Early onset of response was observed across all SRI analyses in the mITT population and in subjects with SELENA-SLEDAI≥10 who were receiving steroid therapy.
- Significant improvements in proteinuria, C3, C4 and anti-dsDNA were observed in subjects treated with blisibimod.
- The data support further evaluation of 200mg QW blisibimod using more stringent thresholds of the SRI in patients with severe seropositive SLE.
- Phase 3 clinical studies with blisibimod are anticipated to commence in Q1 2013.

## References

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.

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.

Presented at the American College of Rheumatology Annual Meeting, November 10-14 2012, Washington DC, USA