Clinical Experience in Latin America with Blisibimod Amongst Subjects with Active, Moderate-to-Severe Systemic Lupus Erythematosus: Data From the Phase 2b PEARL-SC Study

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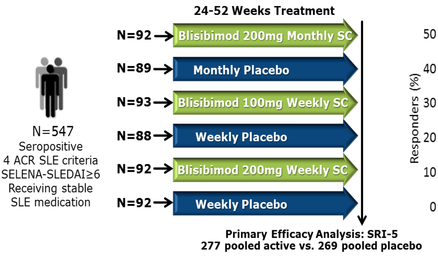
Introduction

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). 71% of the subjects enrolled in the study were in Latin America.



Key Inclusion Criteria

- Fulfill at least 4 of the ACR criteria for SLE.
- Receiving stable standard-of-care SLE medication.
- 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 last 18mo

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, and ≥8
- 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 and renal biomarkers
- Safety and tolerability

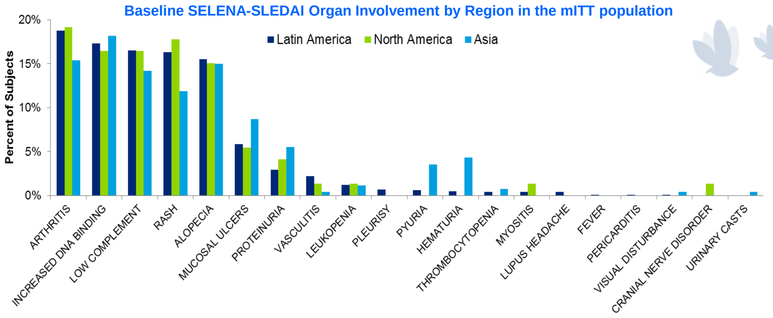
Subjects were invited to participate in an open-label extension study after completion of this trial

Study Population

- A total of 388/547 (70.9%) subjects were enrolled from Argentina (n=51), Brazil (n=102), Chile (n=16), Colombia (n=102), Mexico (n=62) and Peru (n=55).
- The commonest SELENA–SLEDAI organ descriptors amongst Latin American subjects were: arthritis 18.7%; rash 16.3%; increased dsDNA binding 17.3%; low complement 16.5%; alopecia 15.5%; mucosal ulceration 5.9% and proteinuria 2.9%.

Results

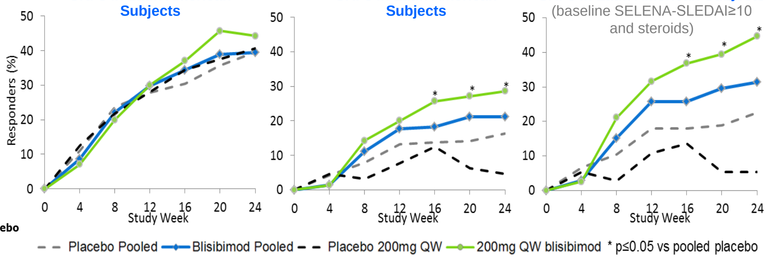
Baseline SELENA-SLEDAI Organ Involvement by Region in the mITT population



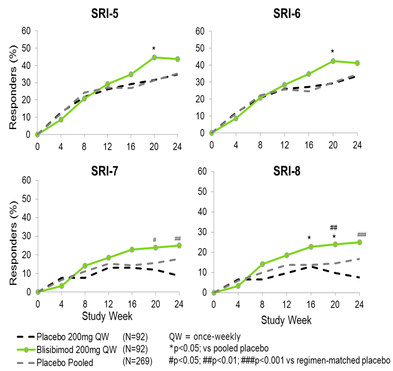
SRI-5 in Latin American Subjects

SRI-8 in Latin American Subjects

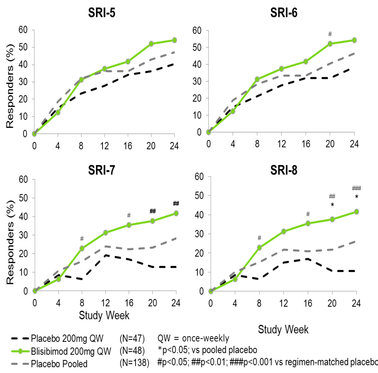
SRI-8 in Latin American Subjects (baseline SELENA-SLEDAI≥10 and steroids)



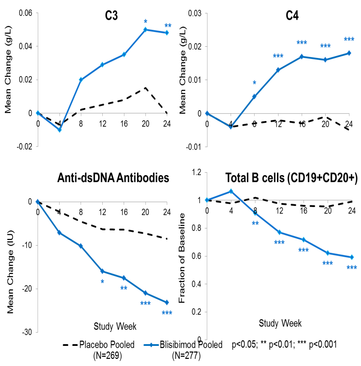
Increases in SRI Response with more Stringent SELENA-SLEDAI Criteria in mITT Population



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

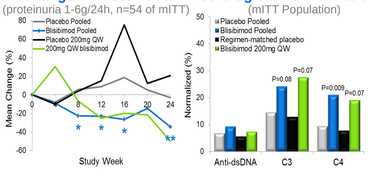


Change in SLE Biomarkers in the mITT Population

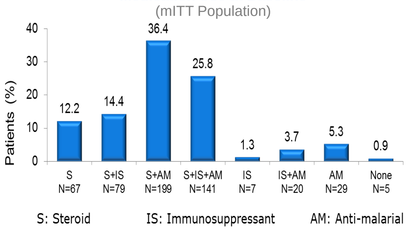


Change in Proteinuria (proteinuria 1-6g/24h, n=54 of mITT)

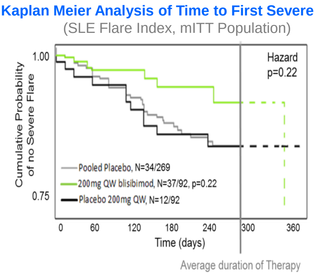
Serological Normalization (mITT Population)



Medication Use at Baseline (mITT Population)



Kaplan Meier Analysis of Time to First Severe Flare (SLE Flare Index, mITT Population)



Demographics

Demographics	
Age	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

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
Prednisone >7.5 mg/day, %	60.1
Immunosuppressive use, %	45.0
Anti-malarial use, %	70.9

Summary of Safety, mITT Population

	Placebo %, N=266	Pooled Blisibimod %, N=280	200 mg QW %, 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

- The findings in the Latin American population corroborate the findings in the modified intent-to-treat population for the study. Significantly more subjects on 200mg QW blisibimod met the SRI-8 efficacy variable compared with placebo amongst:
  - All Latin American subjects enrolled
  - Latin American subjects with baseline SELENA-SLDEAI≥10, and receiving steroid.
- Across all geographies, a significant reduction in proteinuria was observed in subjects with baseline proteinuria (1-6g/24hour) receiving blisibimod.
- A tendency toward lower risk of severe flares was observed with 200mg QW blisibimod in the mITT population.
- Significant decreases in B cells, and improvements in anti-dsDNA, C3 and C4 directly and indirectly corroborate blisibimod's effect on B cell physiology in the mITT population.
- These data support further evaluation of 200mg QW blisibimod using the SRI-8 endpoint in patients with seropositive SLE, and also in patients with B-cell mediated renal diseases.
- The Phase 3 program with blisibimod in SLE, and a Phase 2 study in IgA Nephropathy will commence in H1 2013.

References

- Furie RA, et al. Blisibimod, an Inhibitor of B Cell Activating Factor, in Patients with Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheum*. 2012 64 (12):4169.
- 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 systemic lupus erythematosus (SLE). *Arthritis Rheum* 2008, 58:S565.

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