Effects Of Chronic Treatment With Blisibimod, An Inhibitor Of B Cell Activating Factor, On Renal and Inflammation Biomarkers In Patients With Systemic Lupus Erythematosus: Observations From the Placebo-Controlled PEARL-SC and Open-Label Extension Studies

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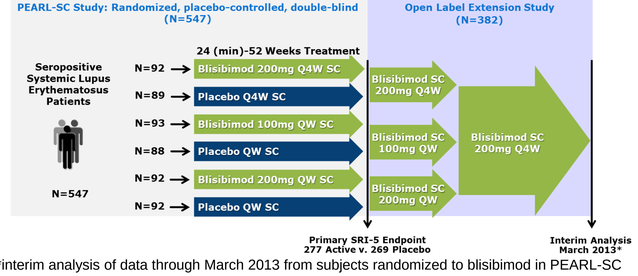
Introduction

Blisibimod is a potent and selective inhibitor of soluble and membrane-bound forms of BAFF (K_D = 1 pM, Hsu *et al.* 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 *et al*. 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 (Furie *et al.* 2012).

Study and Subjects



*interim analysis of data through March 2013 from subjects randomized to blisibimod in PEARL-SC

Key Inclusion Criteria to the PEARL-SC study

- Fulfill at least 4 of the criteria for SLE defined by the ACR.
- SELENA-SLEDAI≥6.
- Receiving stable SLE treatment.
- Seropositive for ANA or anti-dsDNA antibodies.

Key Exclusion Criteria to the PEARL-SC study

- 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.

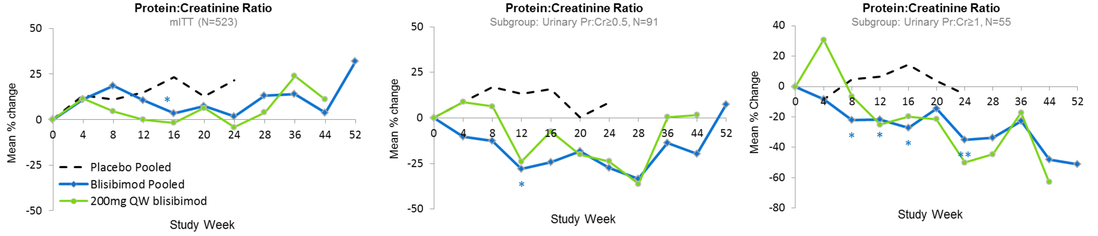
PEARL-SC Demographics and Baseline Disease Characteristics

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	
SELENA-SLEDAI (mean, SD)	10.1 (3.6)
BILAG 1A or 2B, %	50.3
PGA (mean score, SD)	1.4 (0.4)
Proteinuria > 1g/24h, %	9.9
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

Results

Durability of Blisibimod Effect on Protein:Creatinine Ratio in mITT Population and Amongst Patients with Elevated Urinary Protein at Baseline

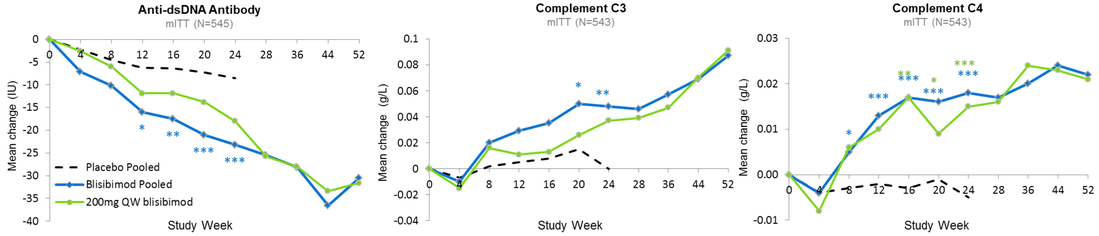


N	4	8	12	16	20	24	28	36	44	52
Blisibimod Pooled	266	255	251	246	243	237	224	214	198	136
Blisibimod 200QW	86	86	84	80	79	79	77	69	66	41
Placebo Pooled	257	246	241	238	232	227				

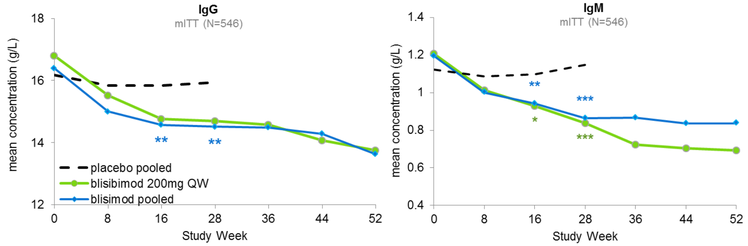
	4	8	12	16	20	24	28	36	44	52
Blisibimod Pooled	39	39	37	37	38	36	37	32	28	17
Blisibimod 200QW	8	10	10	10	10	10	10	9	6	4
Placebo Pooled	47	46	45	43	42	38				

	4	8	12	16	20	24	28	36	44	52
Blisibimod Pooled	23	24	22	22	23	21	22	17	14	7
Blisibimod 200QW	2	4	4	4	4	4	4	3	1	0
Placebo Pooled	28	26	26	25	26	23				

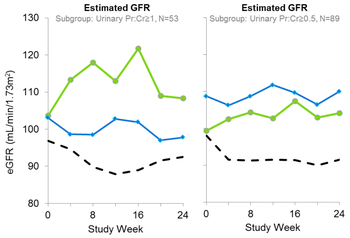
Durability of Blisibimod Effect on anti-dsDNA Autoantibodies and Complement C3 and C4 in Patients with SLE



Durability of Blisibimod Effect on Serum Immunoglobulins IgG and IgM in Patients with SLE



Effects on eGFR



*p≤0.05; ** p≤0.01; *** p≤0.001

Adverse Events in the PEARL and Open-Label Extension Studies

	PEARL-SC		Open-Label
	Placebo N=266	Blisibimod N=280	Blisibimod N=380
Overview (% incidence)			
AEs	85	82.5	60.5
Serious AEs	15.8	11.1	4.7
AEs Related to Study Drug	37.2	40	40
AEs Leading to Withdrawal	7.9	5.7	5.7
AEs Leading to Death	1.1	1.4	0
Severe Infection AEs	1.1	1.4	1.3
Severe Injection Site Reactions	0	0	0
Serious Adverse Events Occurring in >1 Subject, n(%)			
Herpes zoster	2 (0.8)	2 (0.7)	0
Pneumonia	4 (1.5)	3 (1.1)	1 (0.3)
Urinary tract infections	2 (0.8)	2 (0.7)	1 (0.3)
SLE	3 (1.1)	2 (0.7)	0
Deep vein thrombosis	2 (0.8)	3 (1.1)	0
Cellulitis	0	0	3 (0.8)

- 2 malignancies were reported in the PEARL study (1 blisibimod, 1 placebo), none in the Open-Label study

Conclusions

- At the time of this interim analysis, approximately 300 subjects with SLE had completed 52 weeks of treatment with blisibimod, 47 of whom had completed approximately over 104 weeks of blisibimod treatment.
- Blisibimod was safe and well-tolerated through the PEARL-SC and open-label extension studies.
- The significant decreases in peripheral B cells and anti-dsDNA autoantibodies, and significant increases in complement C3 and C4 observed with blisibimod during the placebo-controlled PEARL-SC study persisted through 52 weeks in the open-label extension study.
- The Phase 3 clinical development program with blisibimod is currently enrolling patients with SLE.
- The significant and durable reductions in proteinuria observed with blisibimod additionally support evaluation of drug efficacy in patients with autoimmune renal diseases such a lupus nephritis and IgA nephropathy.

References

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) (2008). Arthritis Rheum 2008;:58:S565.

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.

Furie RA, Scheinberg MA, Leon G, Ramiterre EB, Thomas M, Martin RS, Petri MA. Blisibimod, an Inhibitor of B Cell Activating Factor, in Patients with Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheum.* 64(12), 4169 (2012).

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