Effects of Chronic Treatment with Sub-cutaneous Blisibimod on Renal and Inflammation Biomarkers in Subjects with Systemic Lupus Erythematosus from the Multicenter, International, Placebo-controlled Pearl-SC and Open-label Extension Studies

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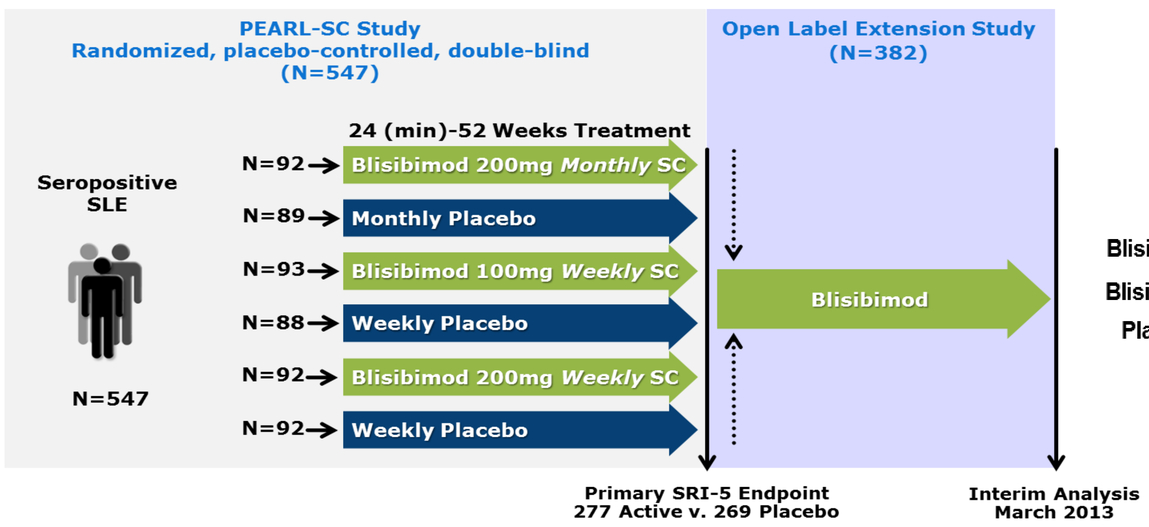
Introduction

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

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



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 18 months

Subjects were invited to participate in the Open-Label Extension study after completion of the placebo-controlled PEARL-SC trial

PEARL-SC Demographics and Baseline Disease Characteristics

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

Results

Adverse Events in the PEARL and Open-Label Extension Studies

	PEARL-SC		Open-Label
	Placebo	Blisibimod	Blisibimod
	N=266	N=280	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

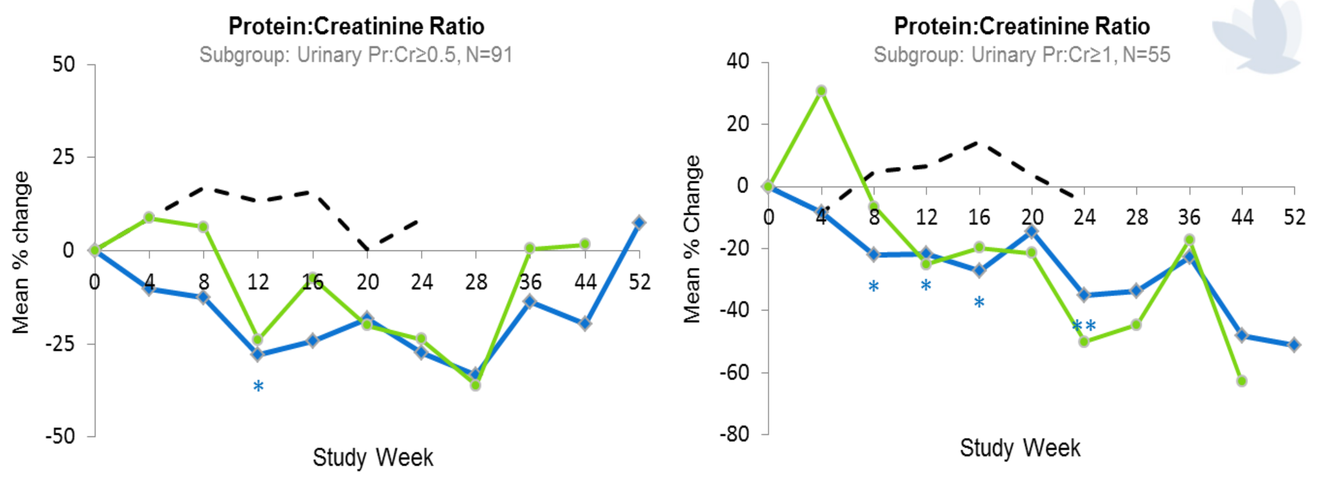
Adverse Events: Infections in the PEARL and Open-Label Extension Studies

	PEARL-SC		Open-Label*
	Placebo	Blisibimod	Blisibimod
	N=266	N=280	N=380
Infections occurring in > 3% of subjects, n (%)			
Gastroenteritis	18 (6.8)	9 (3.2)	4 (1.0)
Influenza	17 (6.4)	22 (7.9)	16 (4.2)
Nasopharyngitis	18 (6.8)	21 (7.5)	11 (2.9)
Pharyngitis	17 (6.4)	11 (3.9)	7 (1.8)
Pneumonia	6 (2.3)	6 (2.1)	2 (0.5)
Sinusitis	6 (2.3)	12 (4.3)	12 (3.1)
Upper respiratory tract infection	31 (11.7)	34 (12.1)	18 (4.8)
Urinary tract infection	38 (14.3)	40 (14.3)	23 (6.1)

*Safety data at Feb 2013, ≥10 months exposure (data are not adjusted for exposure duration)

Results

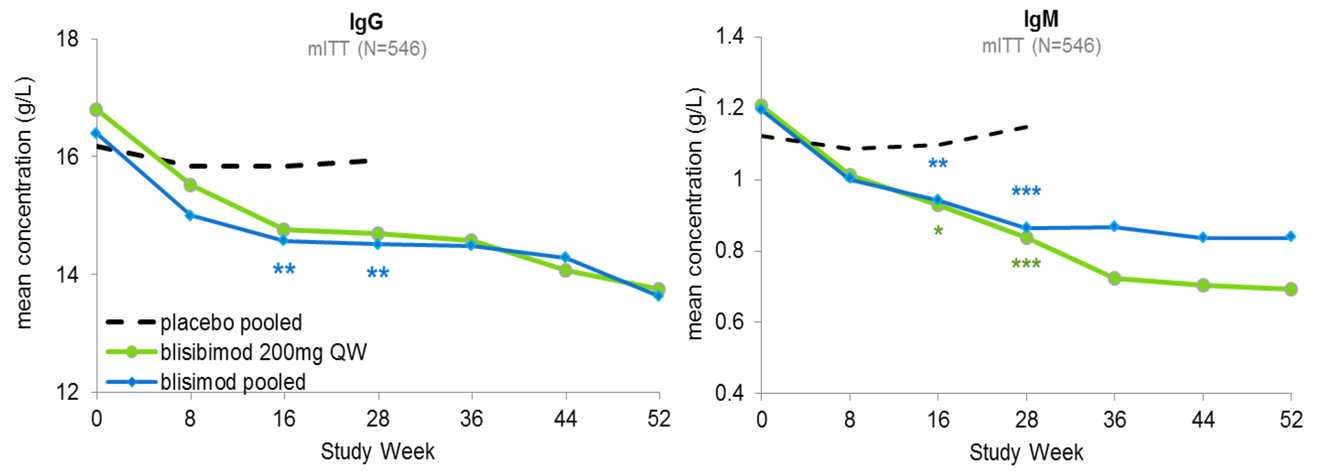
Durability of Blisibimod Effect on Protein:Creatinine Ratio Amongst Patients with Elevated Urinary Protein at Baseline



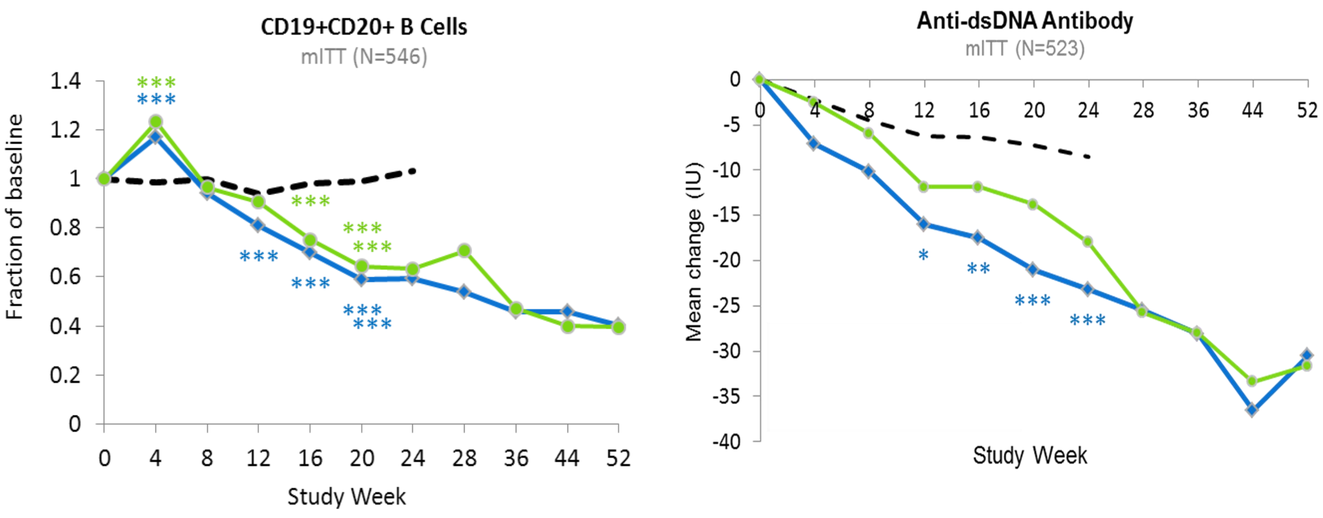
N	4	8	12	16	20	24	28	36	44	52
Blisibimod Pooled	39	39	37	37	38	36	37	32	28	17
Blisibimod 200QW	8	10	10	10	10	10	10	9	6	4
Placebo Pooled	47	46	45	43	42	38				

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

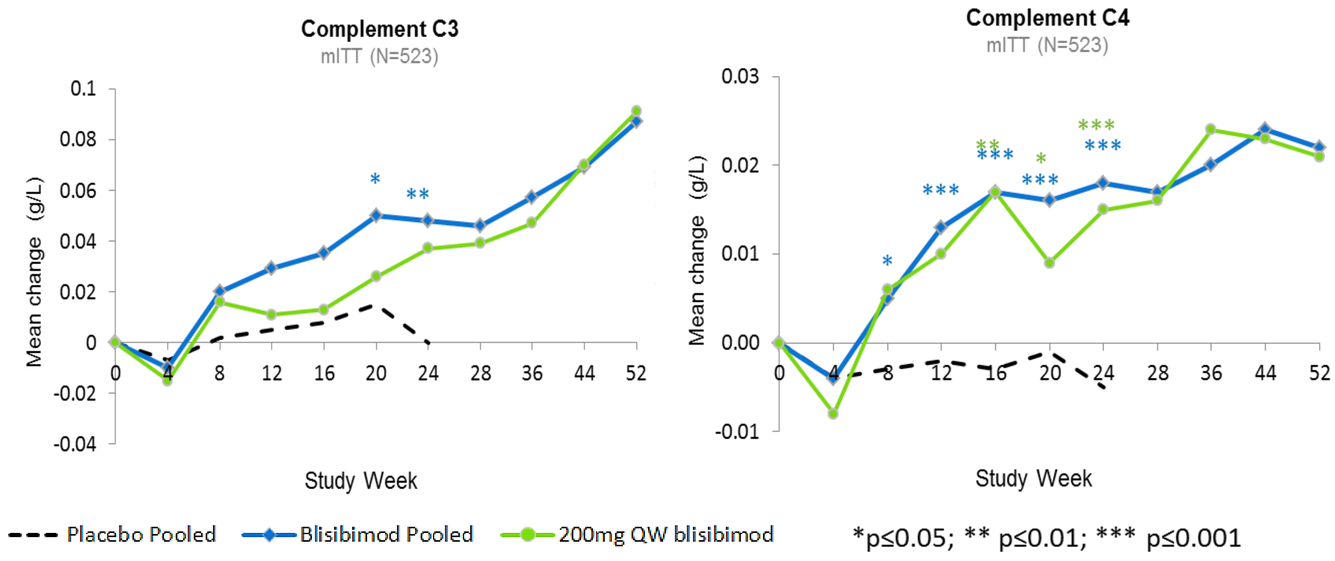
Durability of Blisibimod Effect on Serum Immunoglobulins IgG and IgM



Durability of Blisibimod Effect on Total Peripheral B Cell Counts and Serum anti-dsDNA Autoantibodies



Durability of Blisibimod Effect on Complement C3 and C4



Conclusions

- At the time of the 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.
- There was no increased risk of infection despite reductions in immunoglobulins and B cells, nor were effects of blisibimod observed on peripheral counts of white blood cells including monocytes, lymphocytes, and neutrophils compared with placebo in the PEARL-SC study or over the course of long-term therapy in the Open-Label study.
- Improvements in proteinuria, complement, anti-dsDNA suggest that blisibimod, through its effect to inhibit binding of BAFF to its receptors on B cells and plasma cells, may attenuate renal inflammation.
- The Phase 3 clinical development program with blisibimod is currently enrolling patients with SLE.

References

- Furie RA, et al.Arthritis Rheum. 64(12), 4169 (2012).
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