Presentation 2836

Effects of Blisibimod, an Inhibitor of B Cell Activating Factor, on Patient Reported Outcomes and Disease Activity in Patients with Systemic Lupus Erythematosus

Observations from the Placebo-Controlled PEARL-SC Study

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Disclosures

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M Petri	Investigator, Consultant to Anthera Pharmaceuticals
RS Martin	Employee and stock-holder of Anthera Pharmaceuticals
C Hislop	Employee and stock-holder of Anthera Pharmaceuticals
MA Scheinberg	Investigator
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Introduction

- To evaluate the effects of blisibimod on patient self-reported fatigue in subjects with SLE, the Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue scale was used in the Phase 2 PEARL-SC trial.

- Patient-reported wellness is an important treatment goal for patients with systemic lupus erythematosus (SLE).

> "We recognize that improvements in clinical outcome measures in patients with SLE may not always translate to improvements in how patients feel or function. Therefore, we encourage the use of patient-reported outcome (PRO) instruments to measure all relevant and important SLE symptoms and patient-perceived abilities to function and perform daily activities."
>
> *FDA Guidance for Industry Systemic Lupus Erythematosus — Developing Medical Products for Treatment (2010)*

The FACIT-Fatigue Scale

- The FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy) scale measures health-related quality of life with specific focus patient's self-evaluation of fatigue, tiredness, and weakness in the previous 7 days.

- The FACIT-Fatigue scale has been shown to have:
  - Good internal consistency (Cronbach's alpha = 0.86 to 0.87)
  - Concordance with the SF-36 vitality scale (r = 0.73 to 0.84)
  - Concordance with Multi-Assessment of Fatigue scale (r = –0.84 to –0.88)
  - Amongst patients with rheumatoid arthritis, an ability to differentiate patients according to clinical change using ACR response criteria (ACR 20, ACR50, ACR70).

- A change of 3-4 points in the FACIT-Fatigue scale is deemed to be minimally important based on a clinical trial in patients with rheumatoid arthritis randomized to adalimumab or placebo.

Cella *et al*. *J Rheumatol*. 2005

The FACIT-Fatigue Questionnaire

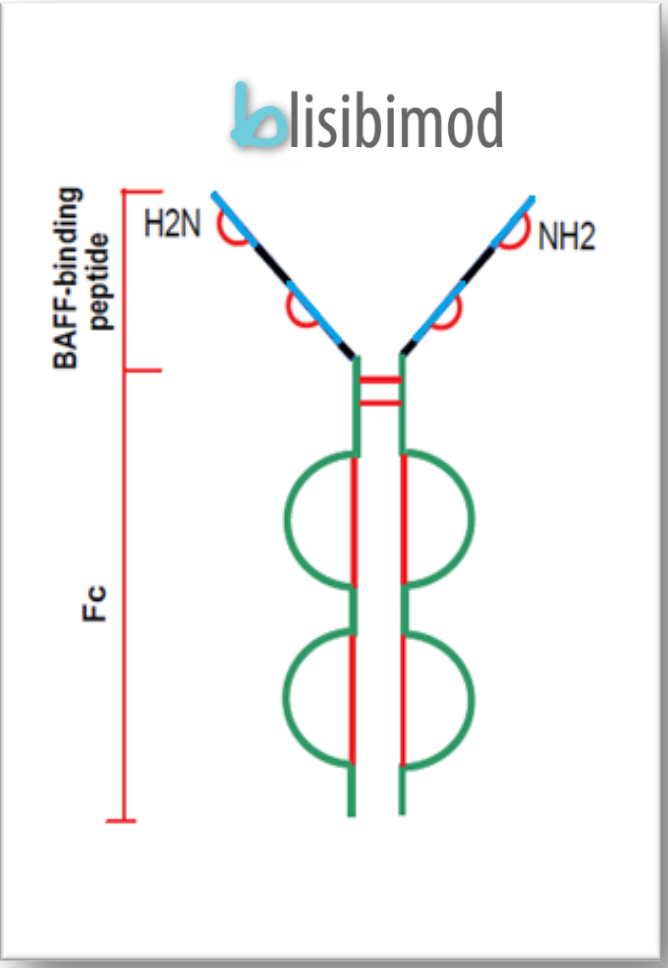
- 13-item questionnaire that asks patients to describe their level of fatigue

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel fatigued	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I feel listless (“washed out”)	0	1	2	3	4
I feel tired	0	1	2	3	4
I have trouble starting things because I am tired	0	1	2	3	4
I have trouble finishing things because I am tired	0	1	2	3	4
I have energy	0	1	2	3	4
I am able to do my usual activities	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I am too tired to eat	0	1	2	3	4
I need help doing my usual activities	0	1	2	3	4
I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
I have to limit my social activity because I am tired	0	1	2	3	4

High score identifies worsening

High score identifies improvement

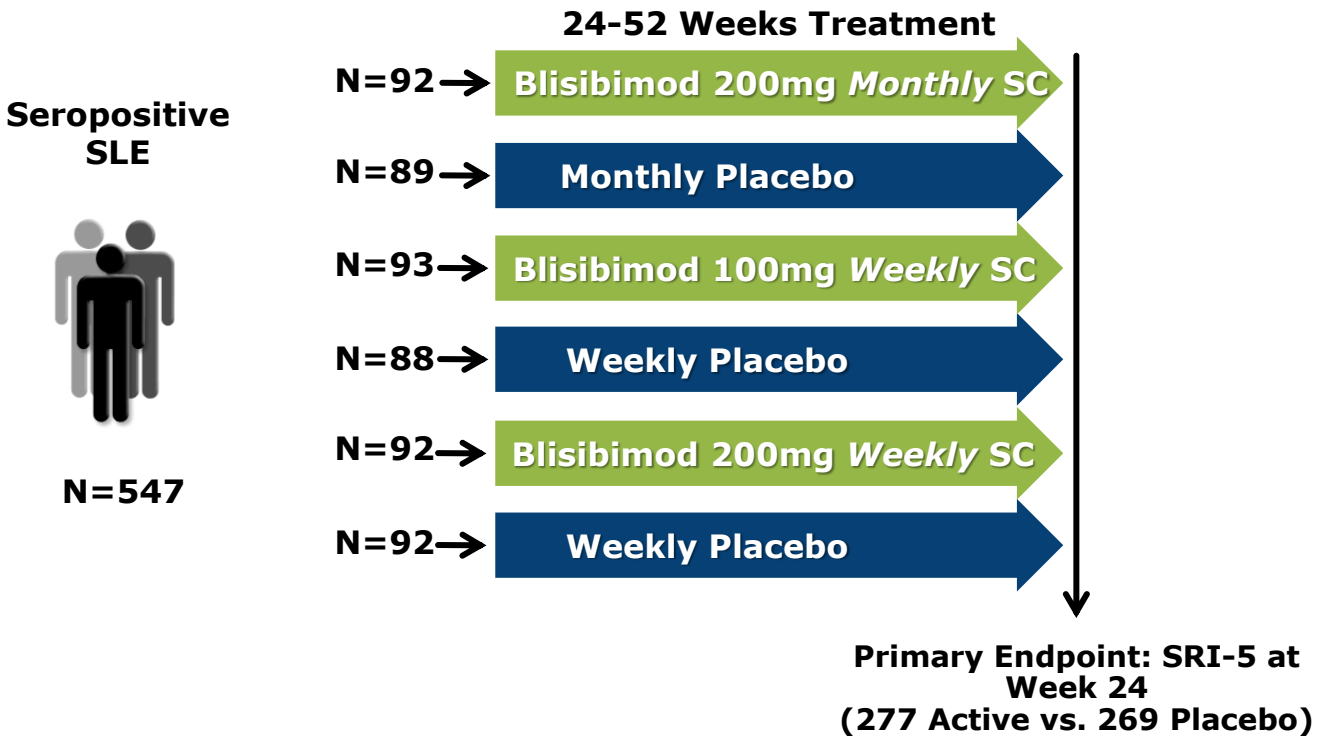
What is Blisibimod?



- A BAFF (BLyS) inhibitor that binds soluble and membrane-bound BAFF
- A peptibody, composed of two identical polypeptides
  - 4 BAFF binding peptides (blue) give rise to high affinity/avidity for BAFF (1 pM)
  - Human IgG_1 Fc domain (green)
  - Dimerizes via covalent disulfide bonds (red)
  - Lower molecular weight (64 kD) compared with monoclonal antibodies (140-150 kD)
- Human serum half-life (8-12 days)
- Administered subcutaneously

Design of the PEARL-SC Study

- The efficacy and safety of blisibimod were evaluated in the Phase 2b, double-blind, placebo-controlled, dose-ranging PEARL-SC study in subjects with seropositive SLE:



Key Entry Criteria for the PEARL-SC Study

- Key Inclusion Criteria:
  - Fulfill ≥ 4 ACR criteria for SLE
  - SELENA-SLEDAI ≥ 6
  - Receiving stable SLE treatment
  - Seropositive for ANA (≥ 1:80) or anti-dsDNA antibodies (≥ 30 IU)

- Key Exclusion Criteria:
  - Severe vasculitis, CNS lupus, lupus nephritis
  - Malignancy within past 5 years
  - Exposure to B cell depleting therapy in the past 18 months

Key Analyses in the PEARL-SC Study

- Key efficacy evaluations were based on the modified SLE Responder Index (mSRI)
  - ≥5 or ≥8 point improvements in the SELENA-SLEDAI, AND
  - No new BILAG 1A or 2B organ domain scores, AND
  - No worsening in Physician's Global Assessment (< 0.3 increase)
  - Subjects who withdrew for any reason, or were treatment failures were considered non-responders
  - Primary efficacy endpoint: SRI-5 at Week 24

- Additional evaluations
  - Patients-reported outcomes using FACIT-Fatigue
  - SLE biomarkers (autoantibodies, peripheral B cells, complement C3 and C4)
  - Proteinuria
  - Safety

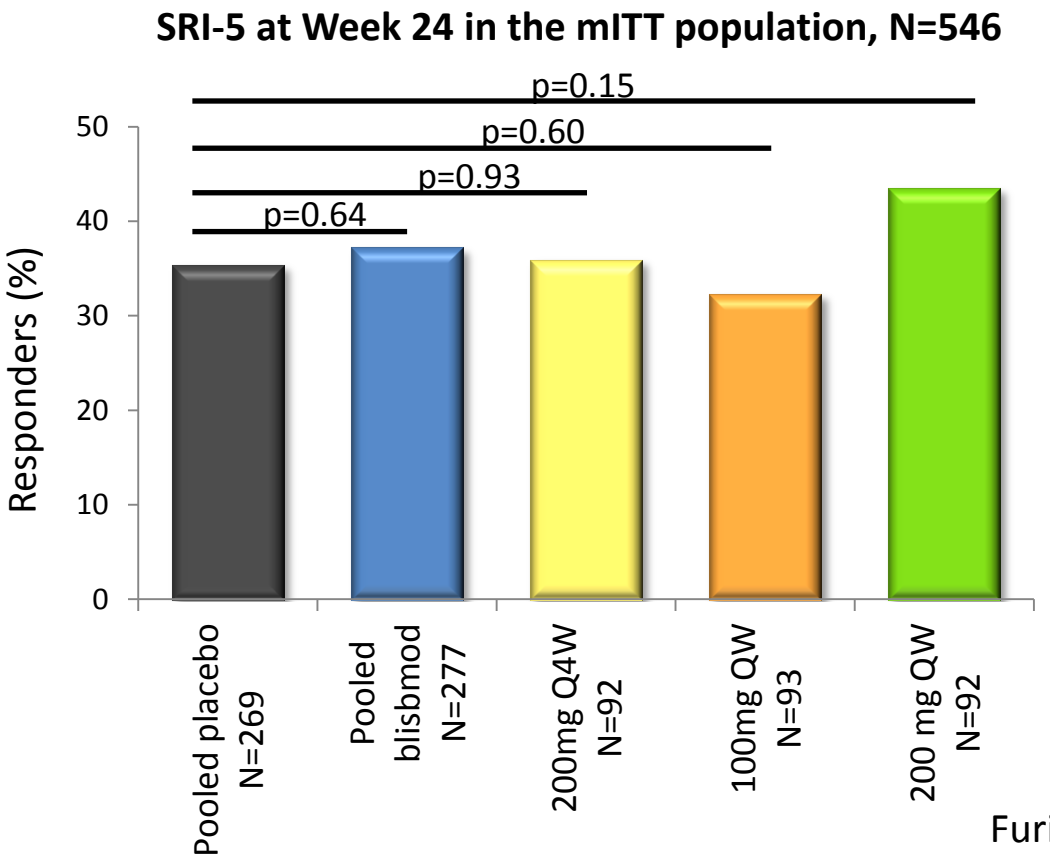
Demographics and Baseline Disease Characteristics

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)	10.1
BILAG 1A or 2B, %	50.3
PGA (mean score)	1.4
ANA >1:80, %	78.8
Anti-dsDNA ≥30 IU, %	68.4
Low C3 (< 90 mg/dL), %	42.4
Low C4 (<16 mg/dL), %	50.2
Urinary Pr/Cr > 1.0, %	9.9
Prednisone dose (mg/day)	12.0
Prednisone >7.5 mg/day, %	60.1
Immunosuppressive use, %	45.0
Anti-malarial use, %	70.9

mSRI Response at Week 24 in the PEARL-SC Study

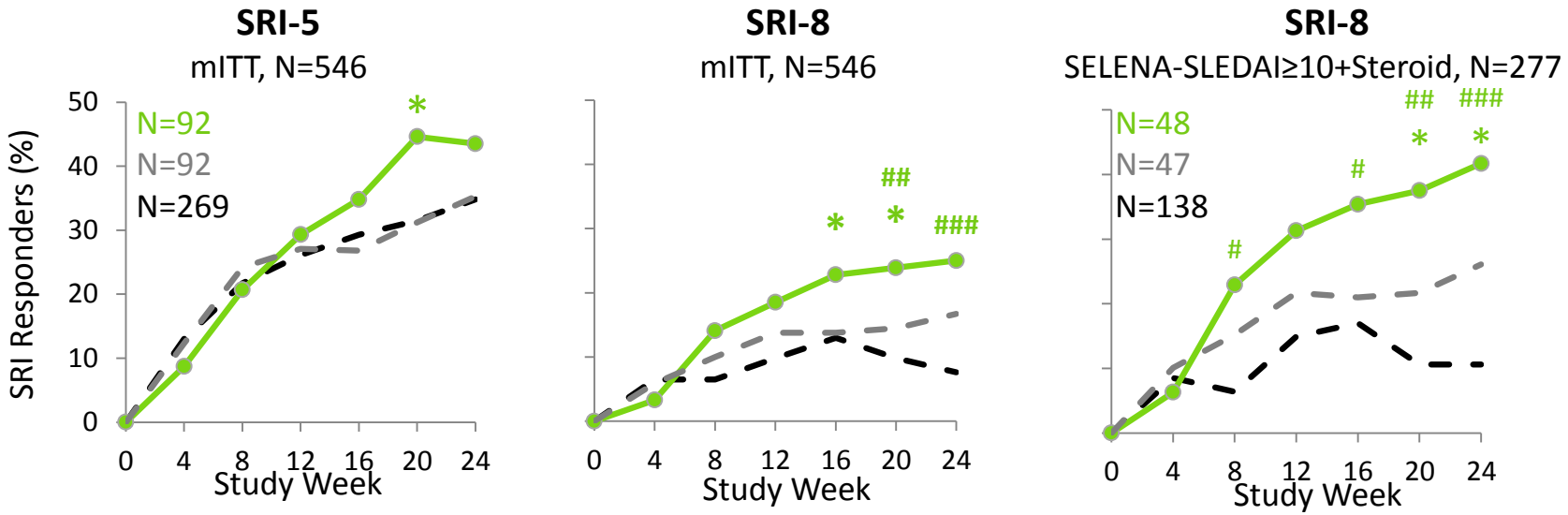
- The primary efficacy endpoint was not met: SRI-5 responder rates at Week 24 for pooled blisibimod vs pooled placebo.
- The highest dose, 200mg QW blisibimod, was the most effective.



Furie *et al*. *Ann Rheum Dis* 2014

mSRI Responses over 24 Weeks in the PEARL-SC Study

- The best mSRI responses to blisibimod were observed:
  - At the highest blisibimod dose (200mg QW)
  - Using a modified SLE Responder Index (SRI) defined by 8-point improvement from baseline in SELENA-SLEDAI
  - In the subgroup of subjects with severe disease at enrollment: SELENA-SLEDAI>10 and receiving systemic corticosteroid medication

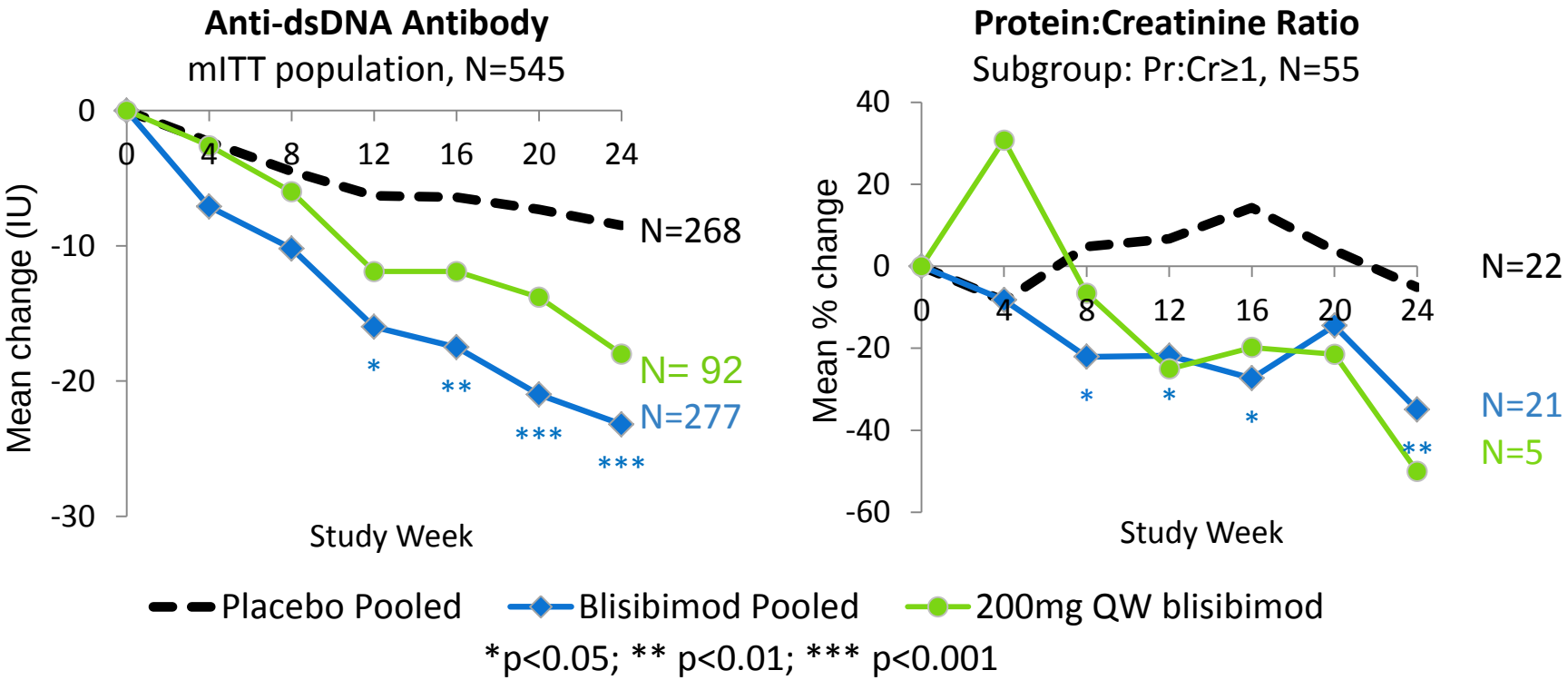


QW = Once weekly; *p<0.05 vs pooled placebo; #p<0.05; ##p<0.01; ###p<0.001 vs dose-matched placebo

Furie *et al*. *Ann Rheum Dis* 2014

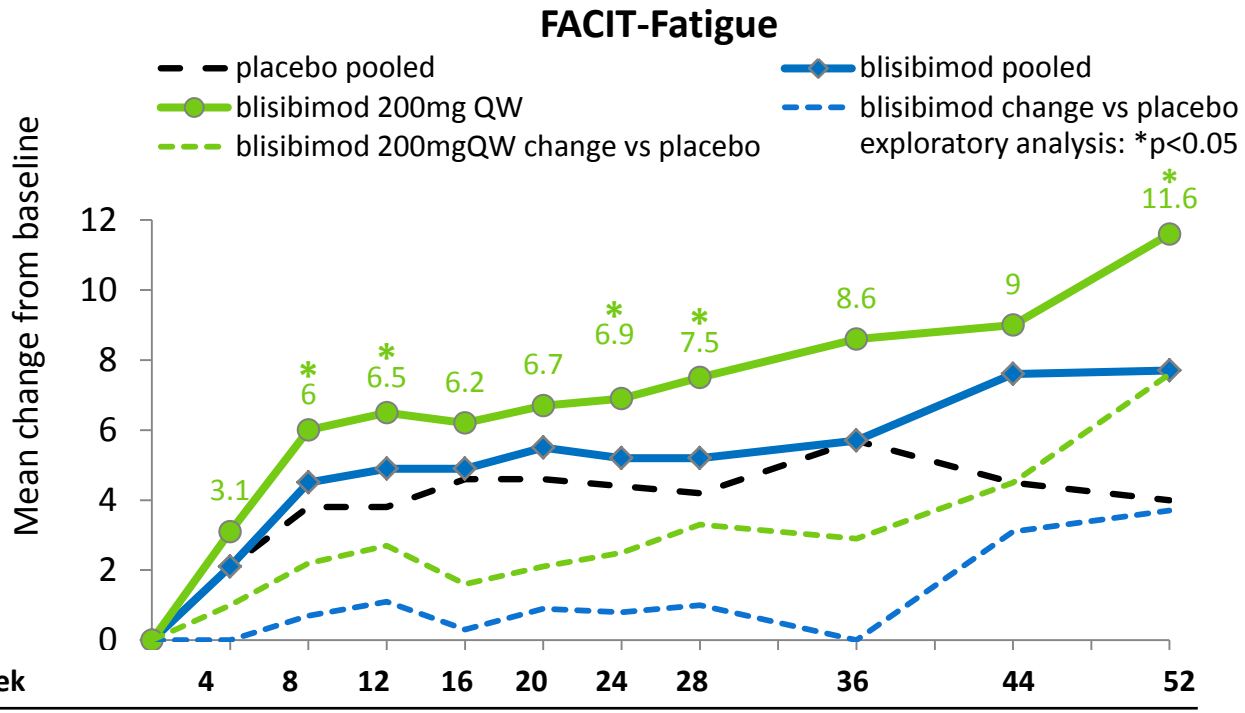
Effects on autoantibodies and proteinuria

- Treatment with blisibimod was associated with improvements in SLE-relevant lab parameters including anti-double stranded DNA autoantibodies and proteinuria



Blisibimod significantly improves FACIT-Fatigue score

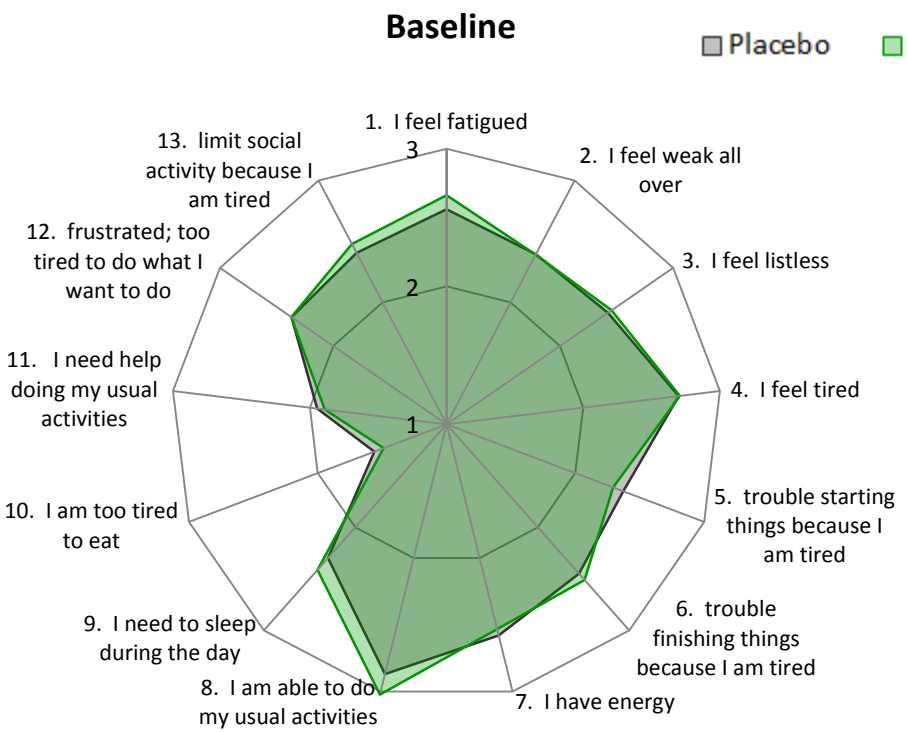
- Blisibimod was associated with clinically-meaningful improvement in patient-reported fatigue:
  - Meeting the criteria for minimally-important difference from baseline from Week 4 onward, and relative to placebo from Week 28 onward at the 200 mg QW dose
  - Over a similar time course to the effects on mSRI and SLE biomarkers

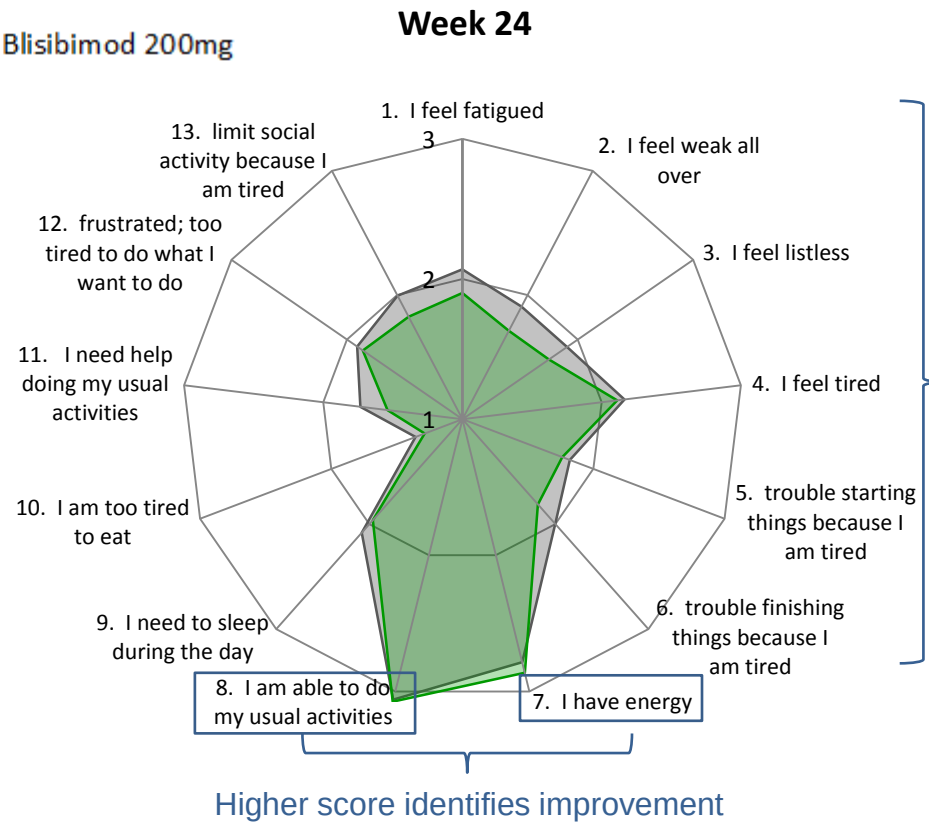


Number of subjects (mITT population)										
Placebo Pooled	258	245	240	236	232	229	189	142	73	37
Blisibimod Pooled	267	254	246	246	240	239	191	132	70	44
Blisibimod 200QW	87	85	83	81	79	80	64	45	25	14

FACIT-Fatigue domains

- Balanced incidence of fatigue in blisibimod and placebo arms at baseline
- Numerically greater improvement across all fatigue questions with blisibimod at Week 24 compared with placebo





Adverse Events

	PEARL-SC	
	Placebo N=266	Blisibimod N=280
Overview (% incidence)		
All Adverse Events (AEs)	85.0	82.5
Serious AEs	15.8	11.1
AEs Related to Study Drug	37.2	40.0
AEs Leading to Withdrawal	7.9	5.7
AEs Leading to Death*	1.1	1.4
Severe Infection AEs	1.1	1.4
Severe Injection Site Reactions	0.0	0.0
Serious Adverse Events Occurring in >1 Subject, n(%)		
Herpes zoster	2 (0.8)	2 (0.7)
Pneumonia	7 (2.7)	3 (1.1)
Urinary tract infections	2 (0.8)	2 (0.7)
SLE	3 (1.1)	2 (0.7)
Deep vein thrombosis	2 (0.8)	3 (1.1)

*4 deaths on blisibimod: Myocardial infarction (Day 39), Septic shock (Day 90), Respiratory failure on study day 100, Septic shock secondary to pneumonia (Day 200).

3 deaths on placebo: Cardiorespiratory arrest secondary to pneumonia (Day 301), Cardiac arrest (Day 258), Bronchopneumonia (Day 252).

Conclusions

- Patients randomized to blisibimod 200mg QW reported significantly better FACIT-fatigue scores compared with placebo
- These effects were consistent with:
  - Concurrent improvements in physician-evaluated disease activity
  - Concurrent improvements in SLE biomarkers
  - Observed safety and tolerability of blisibimod
- These data support further evaluation of blisibimod in SLE:
  - A Phase 3 trial in patients with SLE is currently enrolling

Acknowledgements

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  - Peru
  - Philippines
  - Taiwan
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