Presentation 1742

Effects of Blisibimod, an Inhibitor of B Cell Activating Factor, on Serum Immunoglobulins and Infection Risk in Patients with Systemic Lupus Erythematosus:

Observations from the Placebo-Controlled PEARL-SC and Open-Label Extension Studies

RA Furie*, M Thomas, AD Chu, RS Martin, C Hislop, MA Scheinberg

*North Shore-LIJ Health System; Hofstra North Shore-LIJ School of Medicine

Disclosures

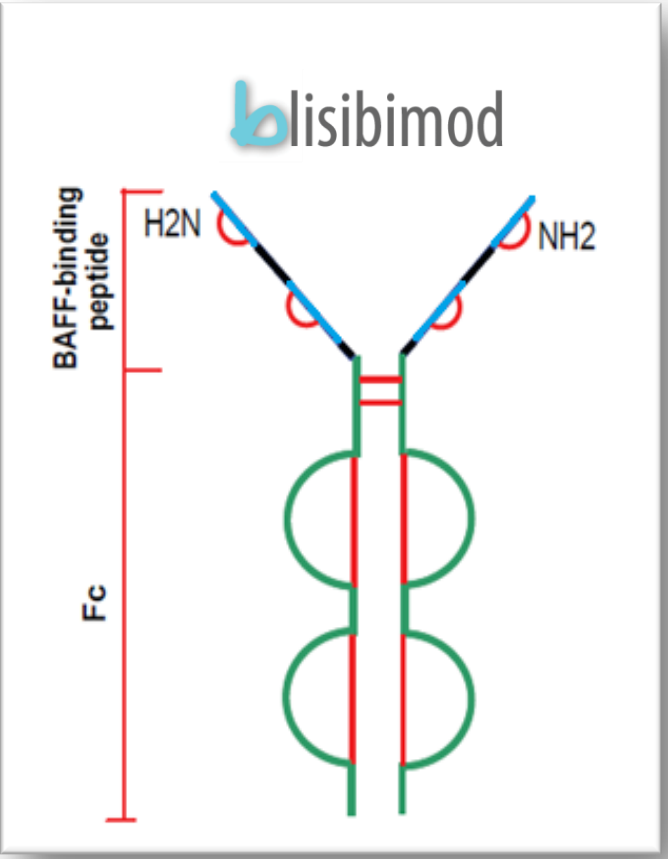
This study was sponsored by Anthera Pharmaceuticals, Inc.

RA Furie	Investigator, Consultant to Anthera Pharmaceuticals
M Thomas	Investigator
AD Chu	Employed by Anthera Pharmaceuticals, Stock-holder
RS Martin	Employee of Anthera Pharmaceuticals, Stock-holder
C Hislop	Employee of Anthera Pharmaceuticals, Stock-holder
MA Scheinberg	Investigator

Introduction

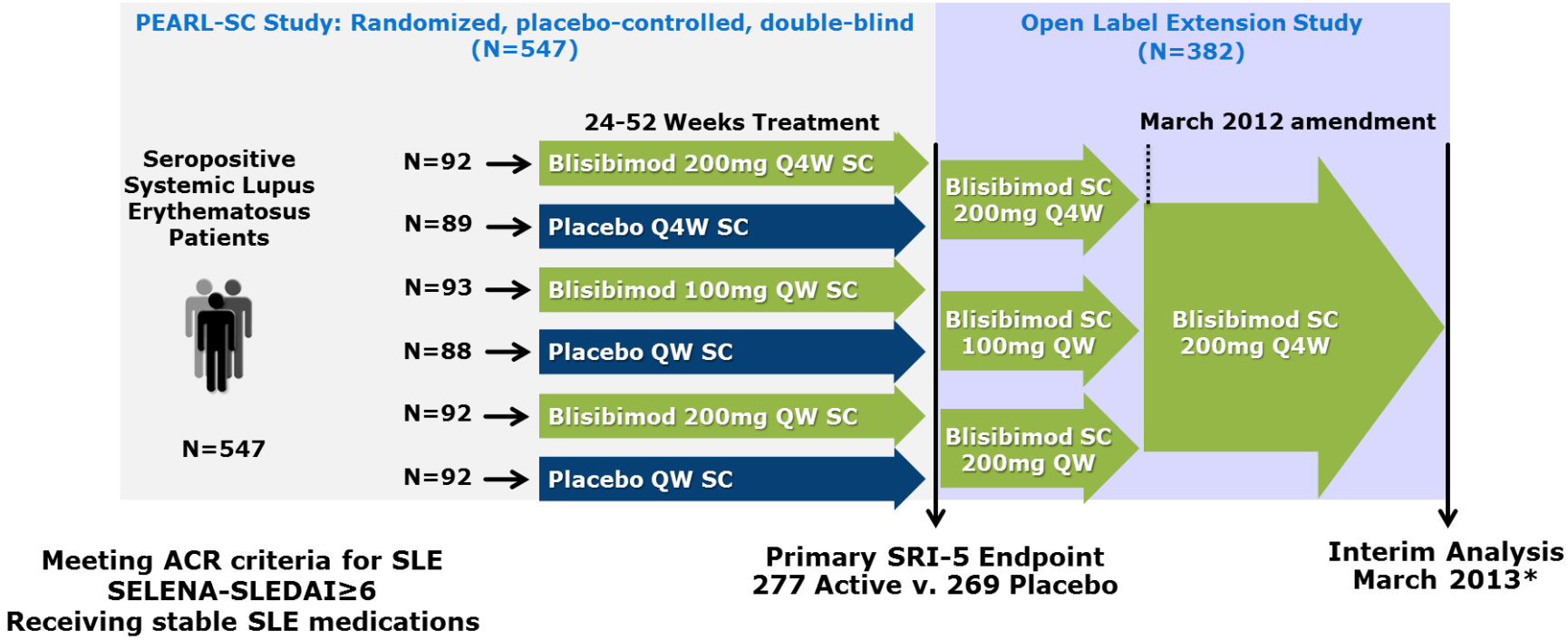
- With some exceptions, the safety of B cell targeted agents has been relatively favorable
- The purpose of this analysis was to evaluate whether blisibimod increased the infection risk over placebo
- Correlations between infectious serious adverse events with immunoglobulins and hematologic parameters were performed

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)
  - Human IgG_1 Fc domain (green)
  - Dimerizes via covalent disulfide bonds (red)
- Low molecular weight – 64 kD compared with monoclonal antibodies (140-150 kD)
- High affinity for human BAFF (K_D=1 pM)
  - Belimumab K_D = 250-350 pM
  - Tabalumab K_D = 120 pM
  - Atacicept K_D = 20 pM
- Human serum half-life (8-12 days)
- Administered subcutaneously

Design of the PEARL-SC and Open-Label Extension Studies



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

Key PEARL-SC Entry Criteria

- Key Inclusion Criteria:
  - Fulfill ≥ 4 ACR criteria for SLE
  - SELENA-SLEDAI ≥ 6
  - Receiving stable SLE treatment
  - Seropositive:
    - 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

- Completers of PEARL-SC were eligible for the Open-Label Extension study

Analyses in the PEARL-SC and Open-Label Studies

- Clinical Endpoints
  - Modified SLE Responder Index, mSRI (evaluated in PEARL-SC only)
    - ≥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)
  - SRI-5 at 24 weeks: primary endpoint
    - Subjects who withdrew for any reason, or were treatment failures were considered non-responders for the SRI-5
- Laboratory parameters
  - Immunoglobulins
  - Proteinuria
  - B cells
  - Anti-dsDNA autoantibodies
  - Complement C3 and C4
- 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

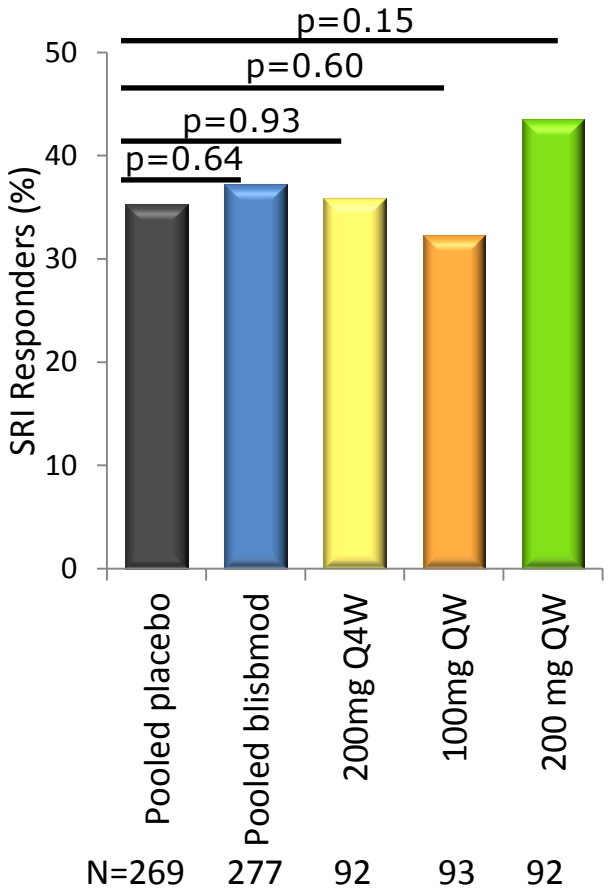
Baseline Disease Characteristics	
SELENA-SLEDAI (mean)	10.1
BILAG 1A or 2B, %	50.3
PGA (mean score)	1.4
ANA >1:80, %	78.8
Anti-dsDNA ≥30 IU, %	68.4
Low C3 (< 90 mg/dL), %	42.4
Low C4 (<16 mg/dL), %	50.2
Urinary Pr/Cr > 1.0, %	9.9
Prednisone dose (mg/day)	12.0
Prednisone >7.5 mg/day, %	60.1
Immunosuppressive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

Primary Endpoint (SRI-5) at Week 24

	PEARL-SC		
	Placebo	**Blisibimod (all doses)**	**Blisibimod 200mg QW**
	N=269	**N=277**	**N=92**
	Responders (%)		
SRI-5	**35.3**	**37.2**	**43.5**
≥5 reduction in SS	36.8	37.5	43.5
No new BILAG A or 2B	74.7	77.3	78.3
No worsening of PGA	72.9	76.2	76.1

SRI Responses at 24 Weeks in the PEARL-SC Study

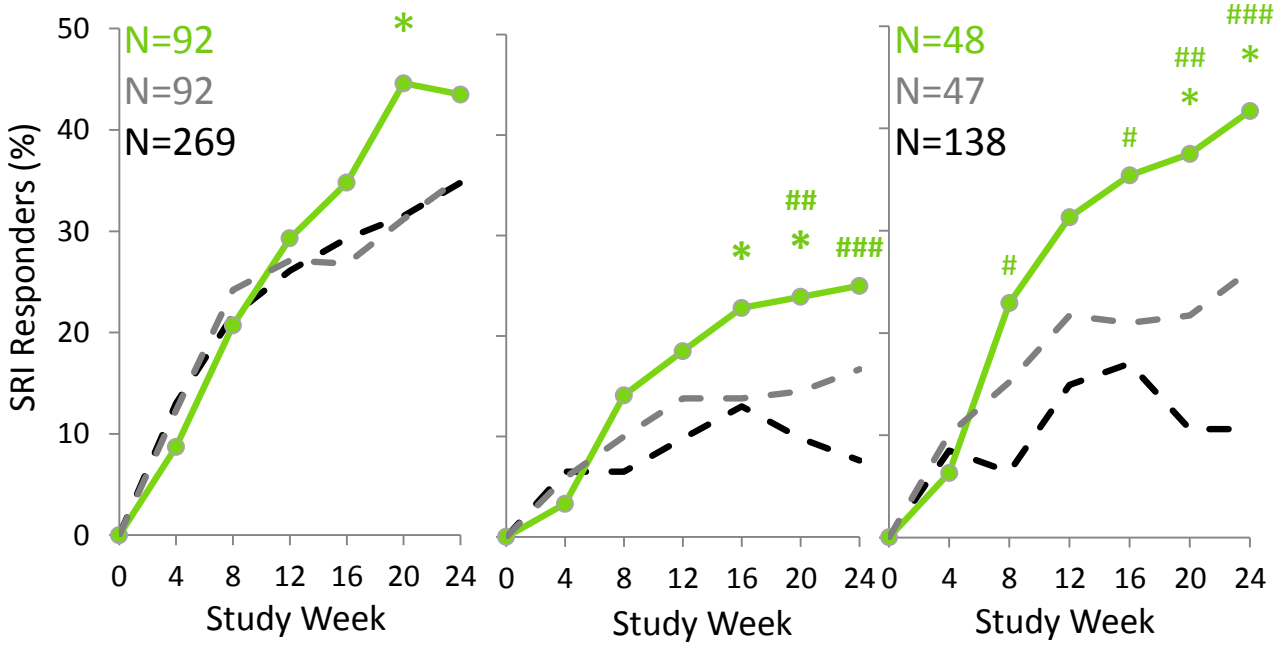
SRI-5 at Week 24
mITT population , N=546



SRI-5
mITT, N=546

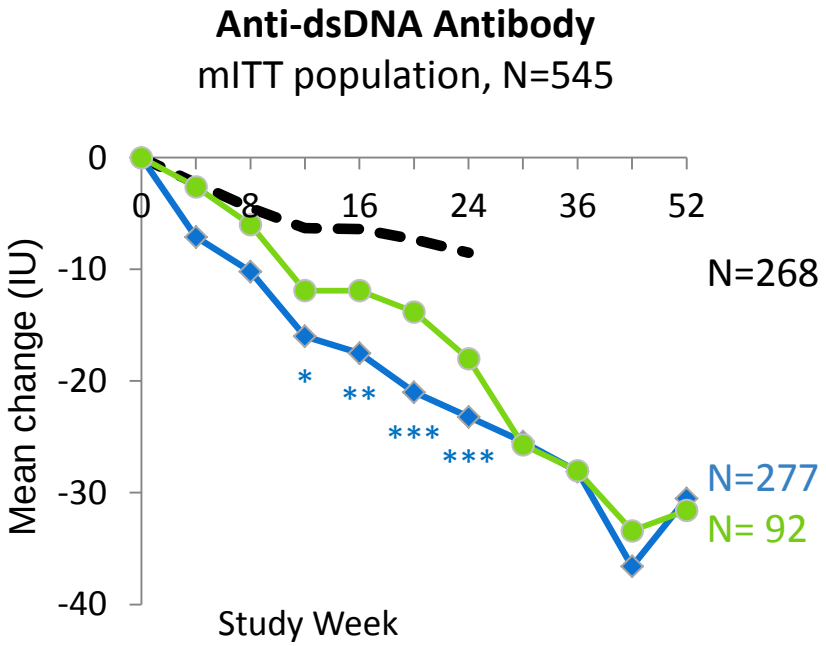
SRI-8
mITT, N=546

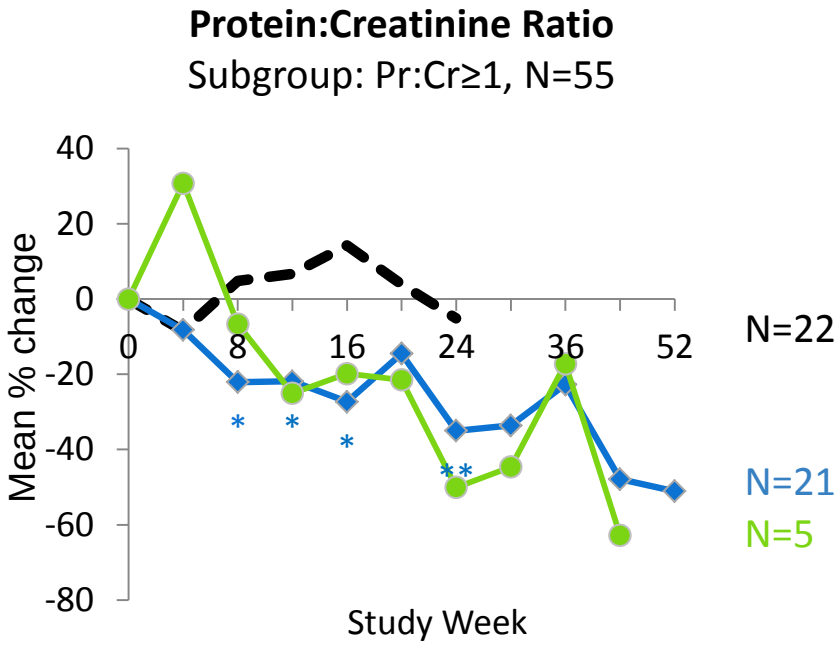
SRI-8
Subgroup: SELENA-SLEDAI≥10 + Steroid, N=277



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

Effects on Autoantibodies and Proteinuria





Placebo Pooled — Blisibimod Pooled — 200mg QW blisibimod

p<0.05; ** p<0.01; *** p<0.001

Includes interim data through Feb 2013 from the Open-Label Extension Study

Adverse Events

	PEARL-SC		Open-Label*
	Placebo N=266	Blisibimod N=280	Blisibimod N=380
Overview (% incidence)			
All Adverse Events (AEs)	85	82.5	46.2
Serious AEs	15.8	11.1	4.5
AEs Related to Study Drug	37.2	40	15.9
AEs Leading to Withdrawal	7.9	5.7	0.8
AEs Leading to Death	1.1	1.4	0
Severe Infection AEs	1.1	1.4	1.5
Severe Injection Site Reactions	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)	
Cellulitis			2 (0.5)

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

Adverse Events: Infections

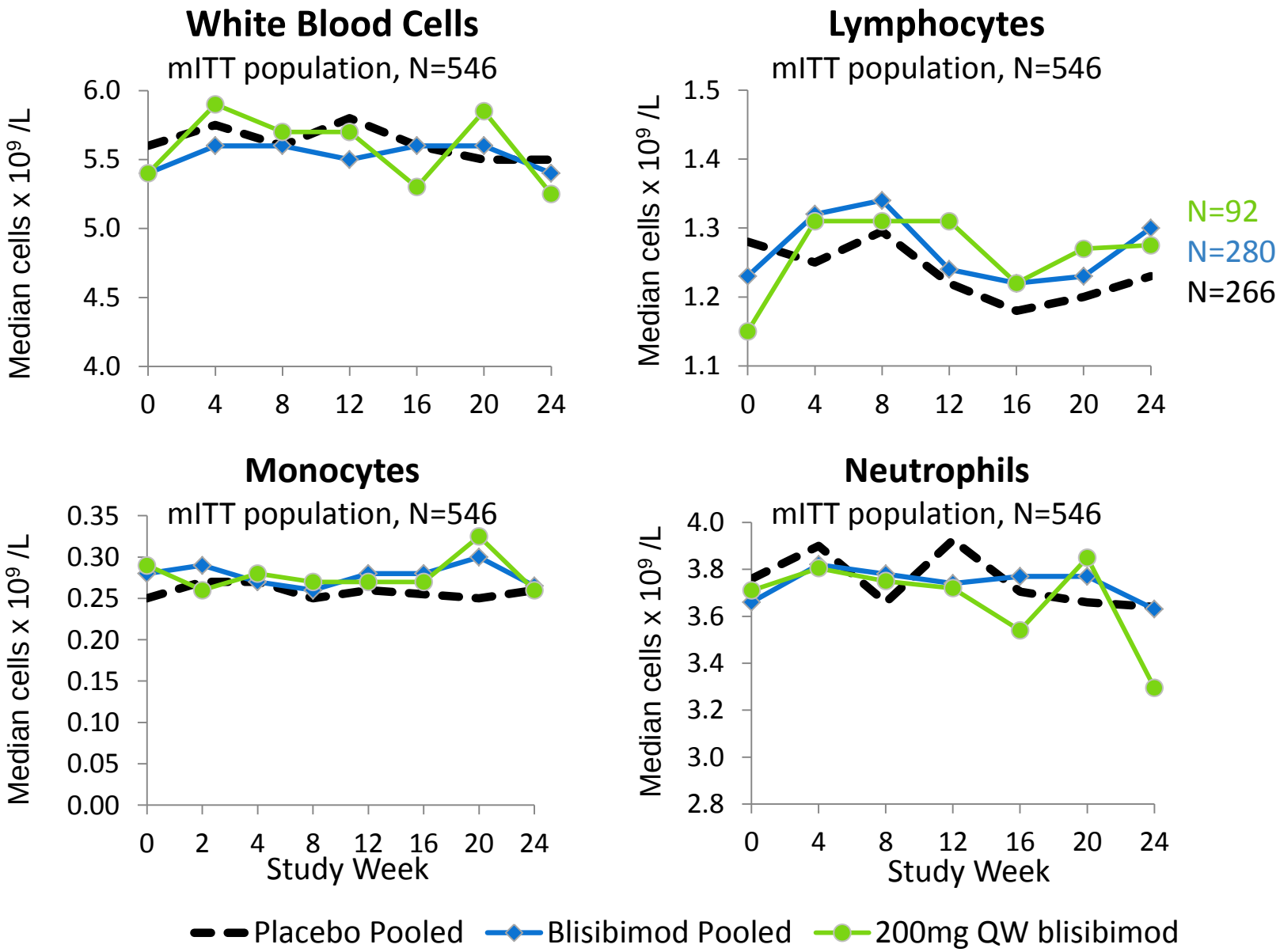
	PEARL-SC		Open-Label*
	Placebo N=266	Blisibimod N=280	Blisibimod N=380
Infections occurring in > 3% of subjects, n (%)			
Gastroenteritis	18 (6.8)	9 (3.2)	4 (1.0)
Influenza	17 (6.4)	22 (7.9)	16 (4.2)
Nasopharyngitis	18 (6.8)	21 (7.5)	11 (2.9)
Pharyngitis	17 (6.4)	11 (3.9)	7 (1.8)
Pneumonia	6 (2.3)	6 (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)

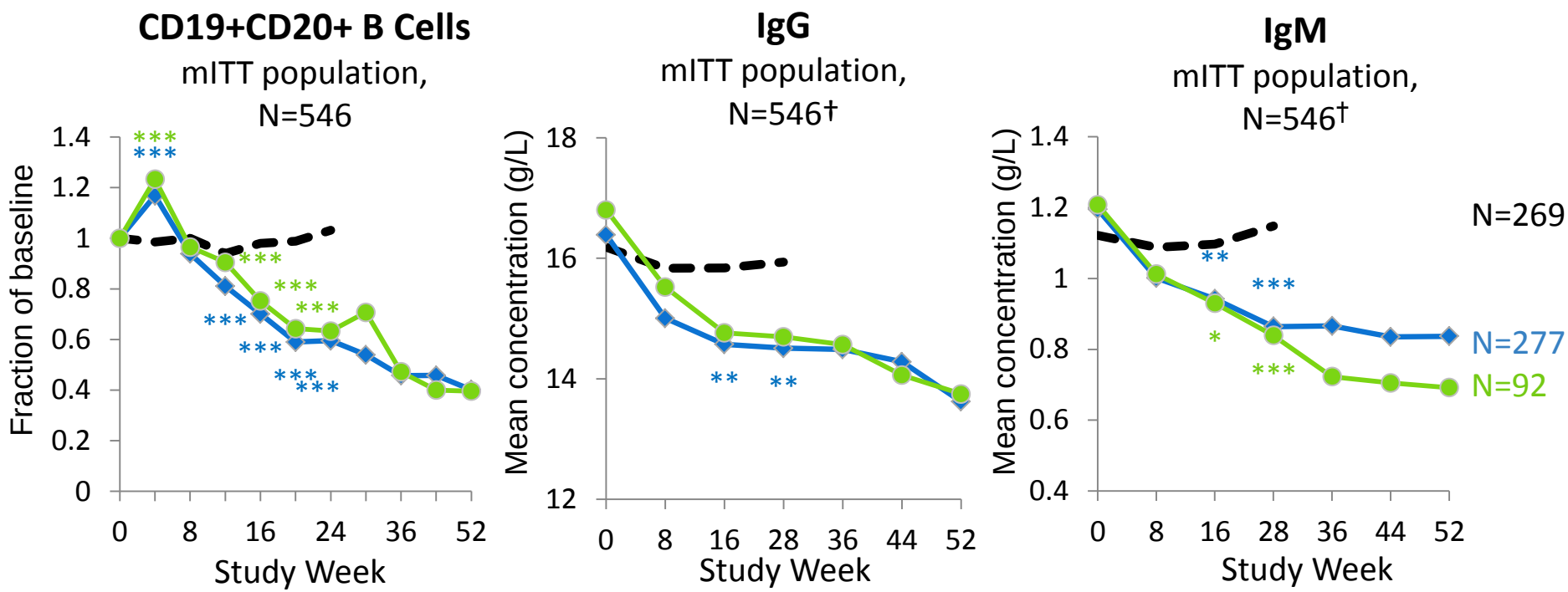
Effects on IgG and White Blood Cells

	PEARL-SC	
	Placebo	**Blisibimod**
	N=266	**N=280**
Proportion of subjects, n(%)		
IgG (<400 mg/dL)	0	1 (0.4)
White Blood Cells (<$2x10^9$/L)	15 (5.6)	4 (1.4)
Neutrophils (<$1x10^9$/L)	10 (3.8)	6 (2.1)
Lymphocytes (<$5x10^8$/L)	63 (23.7)	56 (20.0)

Hematological Effects in the PEARL-SC Study



Effects on Peripheral B cells and Immunoglobulins



Placebo Pooled — Blisibimod Pooled — 200mg QW blisibimod

p<0.05; ** p<0.01; *** p<0.001

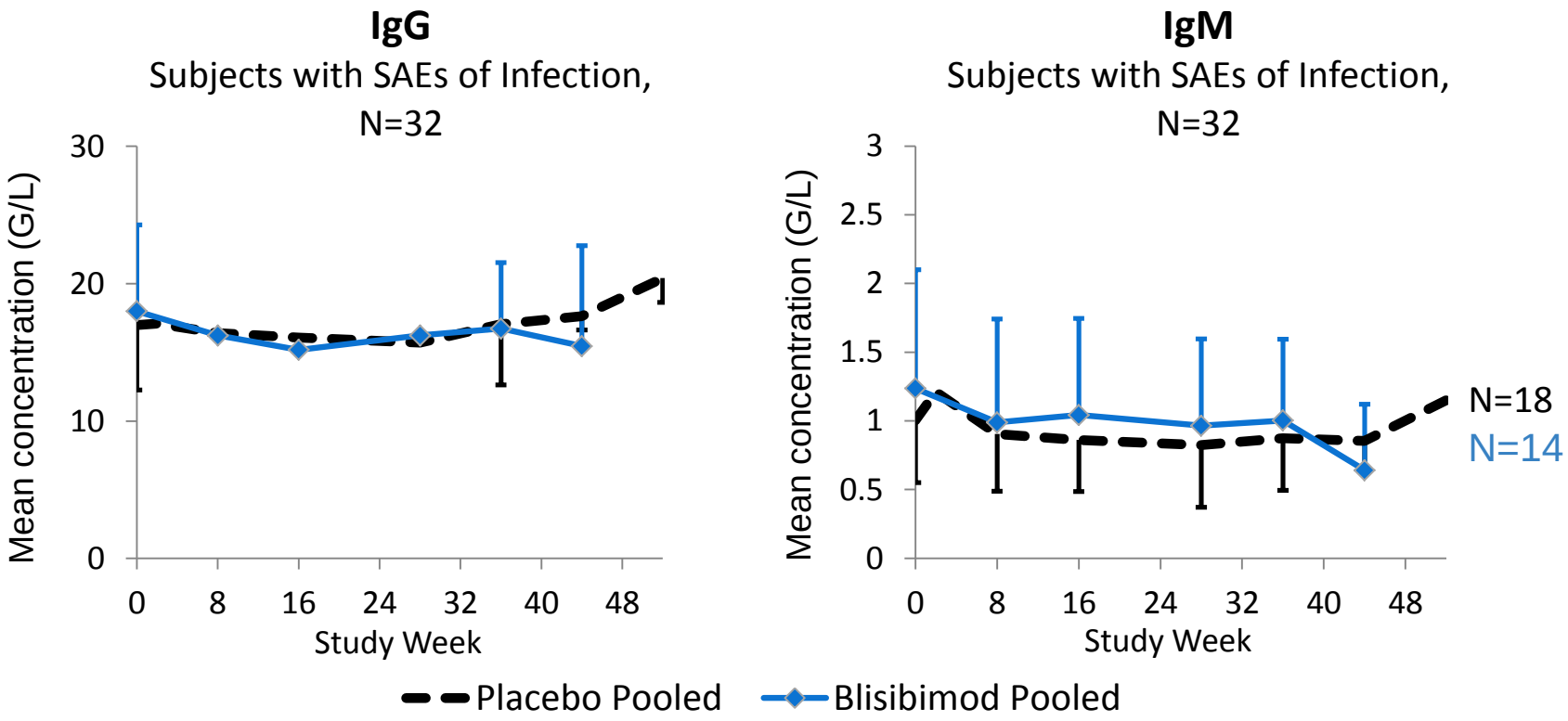
†Includes interim data through Feb 2013 from the Open-Label Extension Study

SAEs of Infections

	PEARL-SC		Open-Label*
	Placebo N=266	Blisibimod N=280	Blisibimod N=380
Serious Infections, n (%)			
Bacterial arthritis		1 (0.4)	
Cellulitis	1 (0.4)		2 (0.5)
Dengue Fever	1 (0.4)		
Diverticulitis			1 (0.3)
Gastroenteritis		2 (0.7)	1 (0.3)
Herpes Zoster	2 (0.8)	2 (0.7)	1 (0.3)
Meningitis	1 (0.4)	1 (0.4)	
Periodontal Infection	1 (0.4)		
Pneumonia	7 (2.7)	3 (1.1)	
Pyelonephritis	1 (0.4)	1 (0.4)	
Septic Shock		1 (0.4)	
Superinfection		1 (0.4)	
Subcutaneous Abscess	1 (0.4)	1 (0.4)	
Urinary Tract Infection	2 (0.8)	2 (0.7)	
Tuberculosis	1 (0.4)		1 (0.3)
Total	**18**	**15**	

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

Serum IgG in Patients with SAEs of Infection in PEARL-SC



Serious adverse events include death, life-threatening, hospitalization, persistent or significant incapacity, congenital anomaly/birth defect

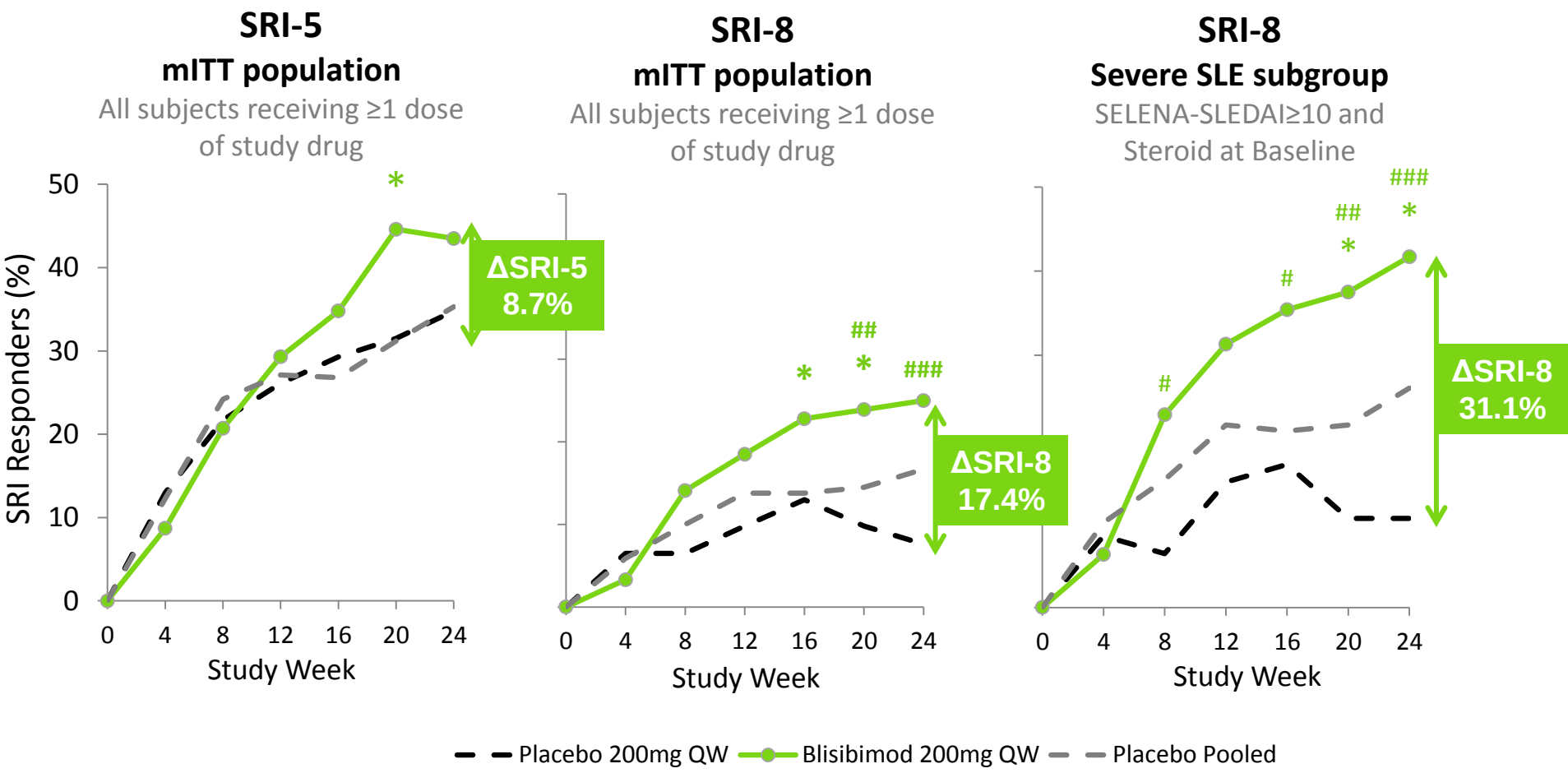
Conclusions

- During the placebo-controlled trial, blisibimod induced significant changes in serum Ig's, peripheral B cells, dsDNA Ab, and complement
- These effects were durable through the interim analysis of the Open Label Extension study (at Feb 2013).
- There was no increased risk of infection despite reductions in Ig's and B cells
- These data support further evaluation of blisibimod in SLE and other diseases:
  - A Phase 3 trial in patients with SLE is currently enrolling
  - A Phase 2 trial in patients with IgA nephropathy is currently enrolling

Questions?

SRI-5, SRI-8, SRI-8 in Severe SLE: Good, Better, Best

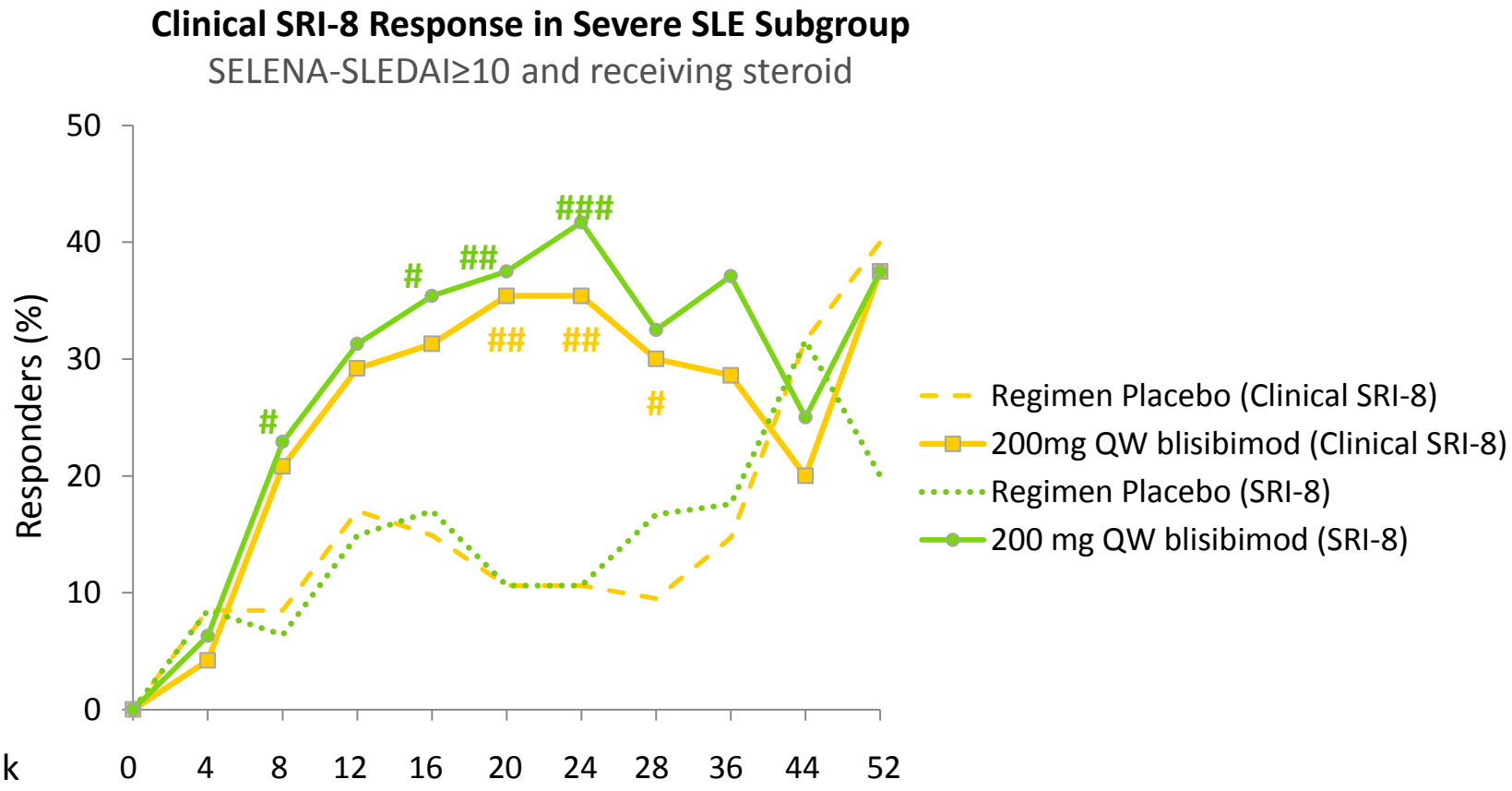
Effects of the highest dose of blisibimod (200mg QW)



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

SRI-8 is Driven by Clinical Improvement

Clinical SRI-8: Ignores Improvements in C3, C4, dsDNA, Thrombocytopenia, Leukopenia



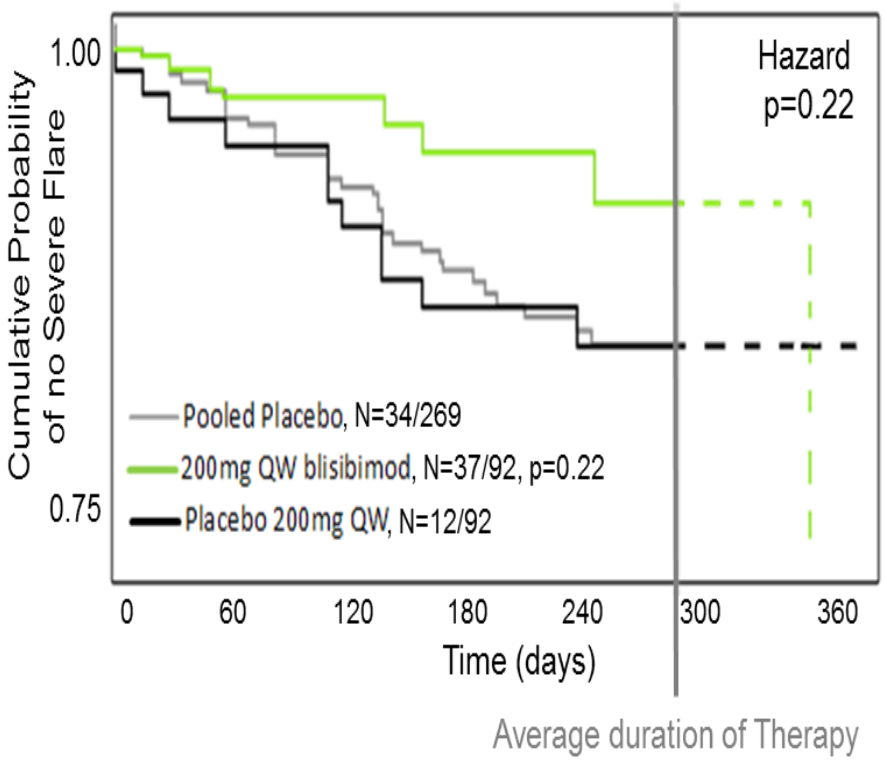
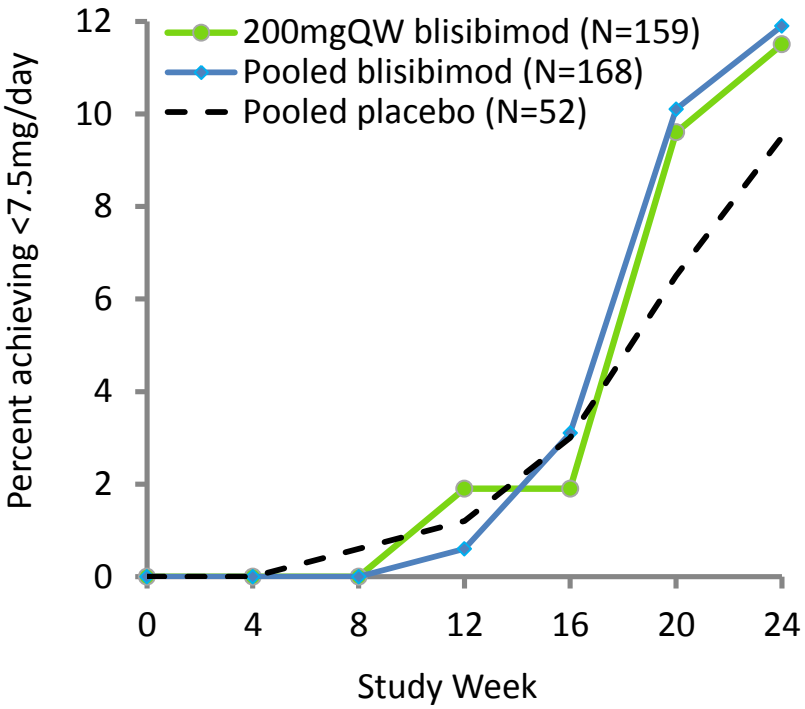
N (subjects with baseline SELENA-SLEDAI >10 and steroids)											
Regimen placebo	47	47	47	47	47	47	47	42	34	19	5
200mg QW blisbmod	48	48	48	48	48	48	48	40	35	20	8

#p≤0.05; ##p<0.01; ###p<0.001 vs regimen-matched placebo

SLE Flare and Background Steroid Dose

mITT Population

Probability of No Severe Flare



Subjects Achieving ≤ 7.5mg/day Prednisone (or equivalent)