LUPUS 2019, the 13th International Congress on SLE, April 5–8, 2019, San Francisco, California, USA

Efficacy and safety of belimumab in patients of black race with systemic lupus erythematosus: Results from the EMBRACE study

David P D'Cruz[1], Kathleen Maksimowicz-McKinnon[2], Jim C Oates[3], Mittermayer Barreto Santiago[4], Damon Bass[5], Susan Burriss[5], Jennifer Gilbride[6], James Groark[5], Michelle Miller[5], Beulah Ji[7]

[1]Louise Coote Lupus Unit, Guys Hospital, London, UK; [2]Henry Ford Hospital, Wayne State University, Detroit, MI, USA; [3]Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC, USA; [4]Bahia School of Medicine and Public Health, Salvador, Bahia, Brazil; [5]GSK, Collegeville, PA, USA; [6]GSK, Stevenage, Hertfordshire, UK; [7]GSK, Uxbridge, Middlesex, UK

Disclosures

- Damon Bass, Susan Burriss, Jennifer Gilbride, James Groark, Michelle Miller and Beulah Ji are employees of GlaxoSmithKline (GSK) and hold shares in the company
- David P D'Cruz reports participation in advisory boards and consultancies for GSK and Roche, and has received consulting fees and/or has participated in clinical trials for GSK, Bristol-Myers Squibb, TEVA, Merck Serono, and Eli Lilly
- Kathleen Maksimowicz-McKinnon reports participation in an advisory board for ChemoCentryx and has participated in clinical trials for AstraZeneca, Gilead, GSK, and Merck
- Jim C Oates reports grant funding from the National Institutes of Health and the Department of Veterans Affairs and participation in clinical trials for Gilead, GSK, Merck Serono, and Takeda
- Mittermayer Barreto Santiago reports participation in clinical trials for AstraZeneca, BMS, GSK, Pfizer, and Roche
- Study (BEL115471; NCT01632241) funded/conducted by GSK. Editorial assistance was provided by Louisa McKay, PhD, of Fishawack Indicia Ltd, UK, funded by GSK

Background

- Black patients have an increased prevalence and severity of systemic lupus erythematosus (SLE), alongside higher mortality rates[1]
- The efficacy and safety of belimumab has been demonstrated in three previous Phase 3 intravenous (IV) trials and one Phase 3 subcutaneous trial[2–5]
  - The small number of black patients in these trials, along with the conflicting results, made it difficult to draw conclusions regarding efficacy in this population
- In this Phase 3/4, randomized, multicenter, double-blind, placebo-controlled, 52-week trial (EMBRACE study) we evaluated the efficacy and safety of IV belimumab plus standard of care (SoC) in black patients with active, autoantibody-positive SLE
  - Reporting results from 52-week double-blind treatment period
  - Open-label extension is complete (January 28, 2019)

1. Pons-Estel GJ et al. Semin Arthritis Rheum 2010;39:257–68; 2. Furie R et al. Arthritis Rheum 2011;63(12):3918–30;
3. Navarra S et al. Lancet 2011;377(9767):721–31; 4. Zhang F et al. Ann Rheum Dis 2018;77(3):355–63; 5. Stohl W et al. Arthritis Rheumatol 2017;69(5):1016–27.

Design and study population

Key selection criteria

Inclusion

- ≥18 years of age
- Self-identified black race
- SLE by ACR criteria
- Active SLE: Screening SELENA-SLEDAI score ≥8
- Autoantibody-positive from two time points
- Stable SoC SLE treatment regimen ≥30 days before Day 0 (first dose)

Exclusion

- Prior belimumab
- Abatacept, B-cell–targeted therapies or any other investigational biologic in the last year

Randomized 2:1 (N=503)

Subjects stratified by:

- Screening SELENA-SLEDAI (8–9 vs ≥10)
- Complement level (C3 or C4 low vs other)
- Region (US/Canada vs Rest of World)

Weeks 0–52

Placebo IV + SoC

Belimumab 10 mg/kg IV + SoC

Dosing schedule:

- Days 0, 14, 28
- Then every 28 days through Week 48
- Final evaluation at Week 52

SoC:

- Corticosteroids
- Immunosuppressives
- Anti-malarials
- Non-steroidal anti-inflammatories

ACR, American College of Rheumatology; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus-National Assessment Trial-Systemic Lupus Erythematosus Disease Activity Index; US, United States.

Primary endpoint

- Efficacy analyses performed on modified intent-to-treat (mITT) population: defined as all patients from remaining sites* who were randomized and received at least 1 dose of study agent

Primary endpoint
SRI response at Week 52 • ≥4-point SELENA-SLEDAI reduction (with modified SLEDAI-2K scoring for proteinuria) • No worsening in PGA (defined as an increase of <0.3 points from baseline) • No new BILAG A or 2 new BILAG B organ domain scores
Responders must meet all 3 criteria Drop out/treatment failure = Non-responder

*Three sites (n=48) excluded from efficacy analyses due to non-compliance.
BILAG, British Isles Lupus Assessment Group; PGA, Physician Global Assessment; SRI, Systemic lupus erythematosus (SLE) Responder Index.

Secondary endpoints and safety

A priori sub-group analyses of primary endpoint

- Baseline SELENA-SLEDAI score, low complement, low complement and anti-dsDNA ≥30 IU/mL, and region

Major secondary endpoints

1. SRI response rate with SELENA-SLEDAI scoring at Week 52
2. Time to severe flare over 52 weeks
3. Proportion of patients with a reduction in prednisone dose by ≥25% to ≤7.5 mg/day during Weeks 40–52

Safety

- Adverse events (AEs)
- AEs of special interest (AESIs): mortality, serious and/or severe infections, opportunistic infections, malignant neoplasms, selected serious psychiatric AEs, suicidality, infusion/hypersensitivity reactions, immunogenicity

- Testing for statistical significance per pre-specified sequence

Primary endpoint

↓

Major secondary endpoint 1

↓

Major secondary endpoint 2

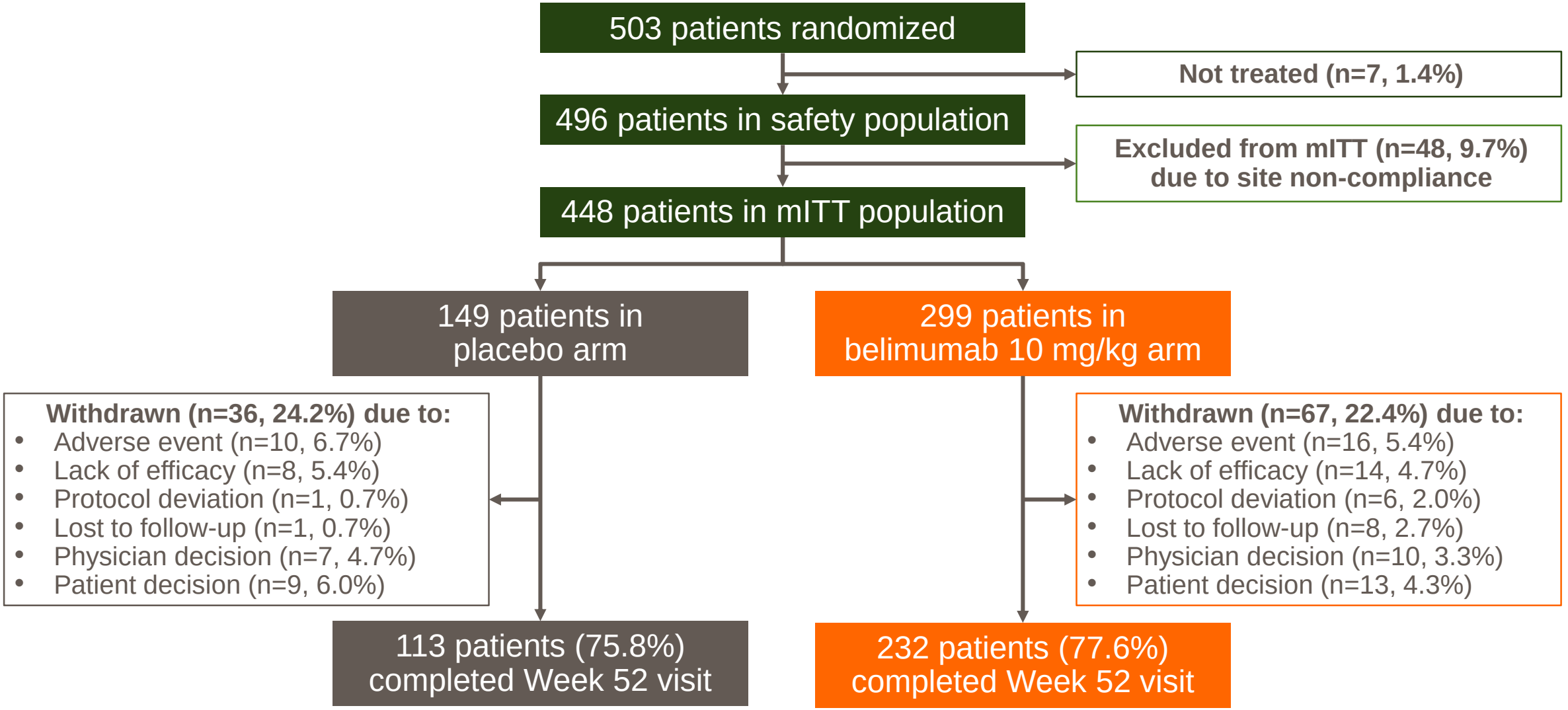
↓

Major secondary endpoint 3

- Step-down sequential testing was utilized to control the overall type-1 error rate (2-sided, alpha=0.05)

dsDNA, double-stranded deoxyribonucleic acid.

Patient disposition



Baseline demographics and disease characteristics

	Placebo (n=149)	Belimumab 10 mg/kg (n=299)
Female, n (%)	144 (96.6)	290 (97.0)
Age, years (mean, SD)	39.3 (12.15)	38.6 (11.05)
Region, n (%)		
US/Canada	65 (43.6)	131 (43.8)
Rest of World	84 (56.4)	168 (56.2)
SELENA-SLEDAI-S2K (mean, SD)	10.5 (3.08)	10.2 (3.68)
SELENA-SLEDAI-S2K category ≥10, n (%)	93 (62.4)	158 (52.8)
Presence of flare, n (%)*	22 (14.8)	67 (22.4)
Presence of severe flare, n (%)*	0	4 (1.3)
Low C3 and/or C4, n (%)	57 (38.3)	108 (36.1)
Low C3 and/or C4 and anti-dsDNA ≥30 IU/mL, n (%)	50 (33.6)	91 (30.4)
Daily prednisone category, n (%)		
0 mg/day	22 (14.8)	53 (17.7)
>0 to ≤7.5 mg/day	32 (21.5)	62 (20.7)
>7.5 mg/day	95 (63.8)	184 (61.5)
Daily prednisone dose, mg/day (mean, SD)	12.2 (9.95)	12.1 (10.71)
SLE disease duration, years (mean, SD)	6.9 (7.38)	7.3 (7.08)

*Anytime during the screening period (Day –35 to 0)
SD, standard deviation; SELENA-SLEDAI-S2K, SELENA-SLEDAI with modified SLEDAI-2K scoring for proteinuria.

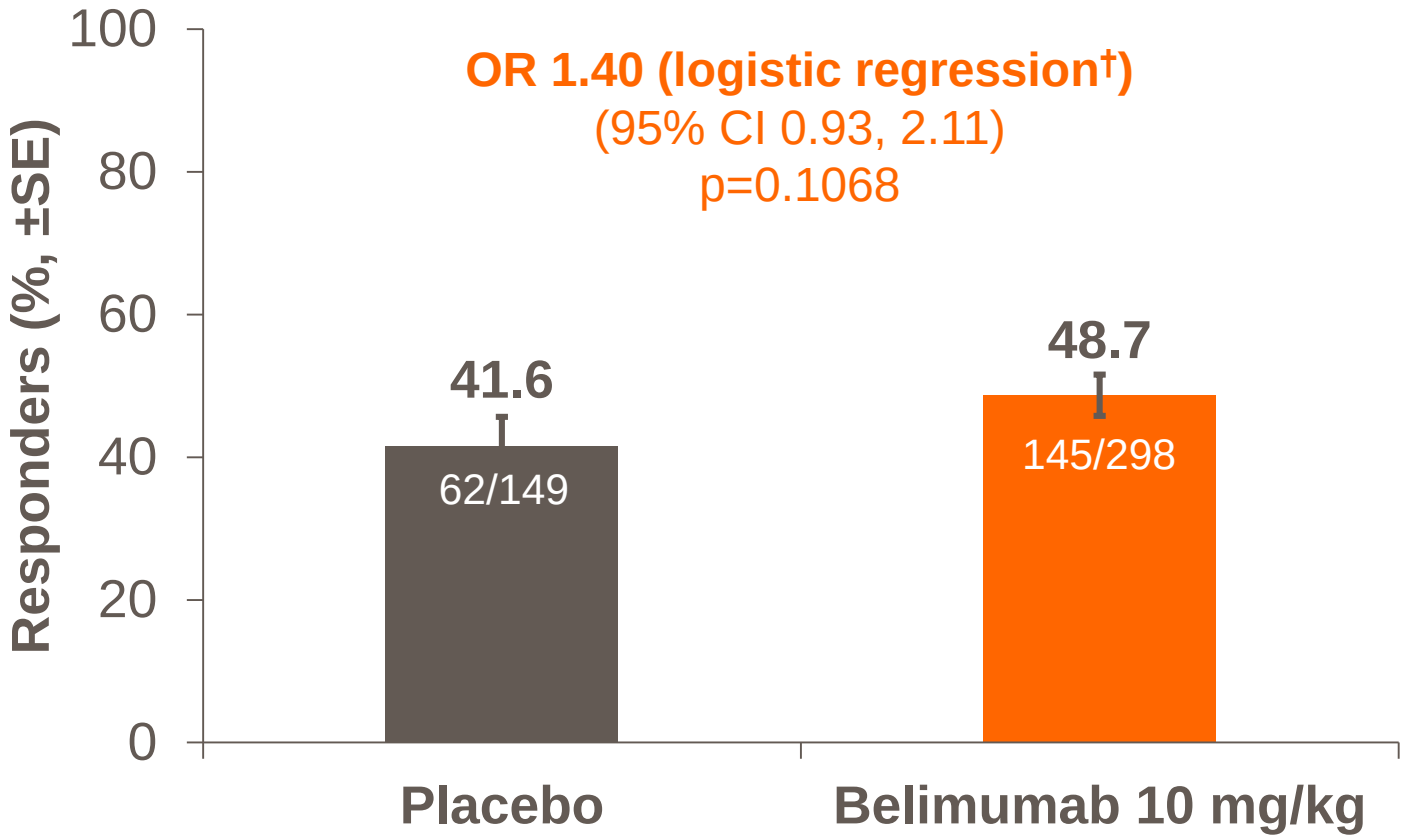
Baseline demographics and disease characteristics by region

	US/Canada (n=196)	Rest of World (n=252)
Age, years (mean, SD)	40.0 (11.49)	37.9 (11.29)
SLE disease duration, years (mean, SD)	7.8 (7.35)	6.6 (7.01)
SLE disease duration, years (median; min, max)	6.2 (0, 36)	4.1 (0, 35)
SELENA-SLEDAI-S2K category ≥10, n (%)	125 (63.8)	126 (50.0)
SLICC/ACR damage index score = 0, n (%)	110 (56.1)	180 (71.4)
Proteinuria ≤0.5 g/24 hr, n (%)	167 (85.2)	195 (77.4)
Any steroid, n (%)	141 (71.9)	232 (92.1)
Average daily prednisone dose >7.5 mg/day, n (%)	101 (51.5)	178 (70.6)
Low C3 (<90 mg/dL), n (%)	59 (30.1)	91 (36.1)
Low C4 (<10 mg/dL), n (%)	25 (12.8)	59 (23.4)
Low C3 and/or C4, n (%)	63 (32.1)	102 (40.5)
Low C3 and/or low C4 and anti-dsDNA ≥30 IU/mL, n (%)	53 (27.0)	88 (34.9)

SLICC, Systemic Lupus International Collaborating Clinics.

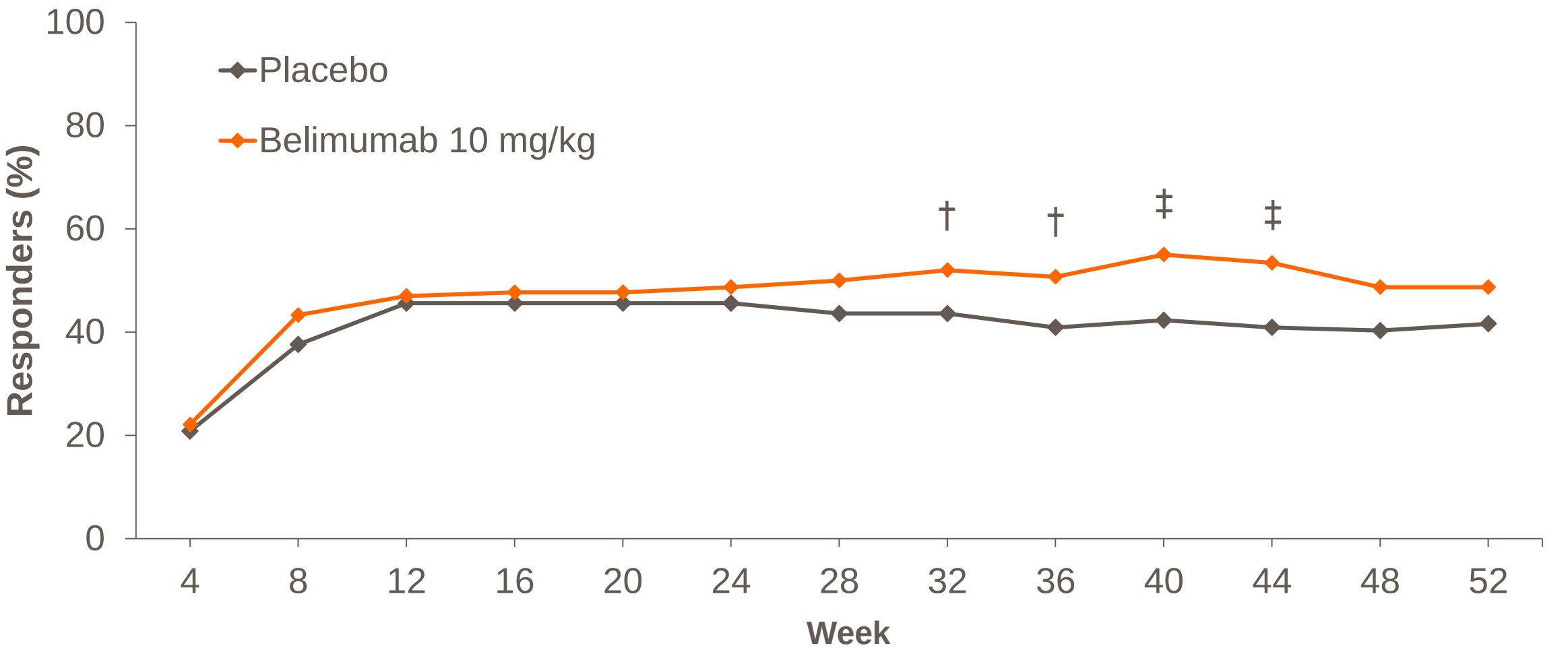
Primary endpoint: SRI-S2K response at Week 52*

- SRI-S2K response was numerically greater in belimumab compared with placebo patients



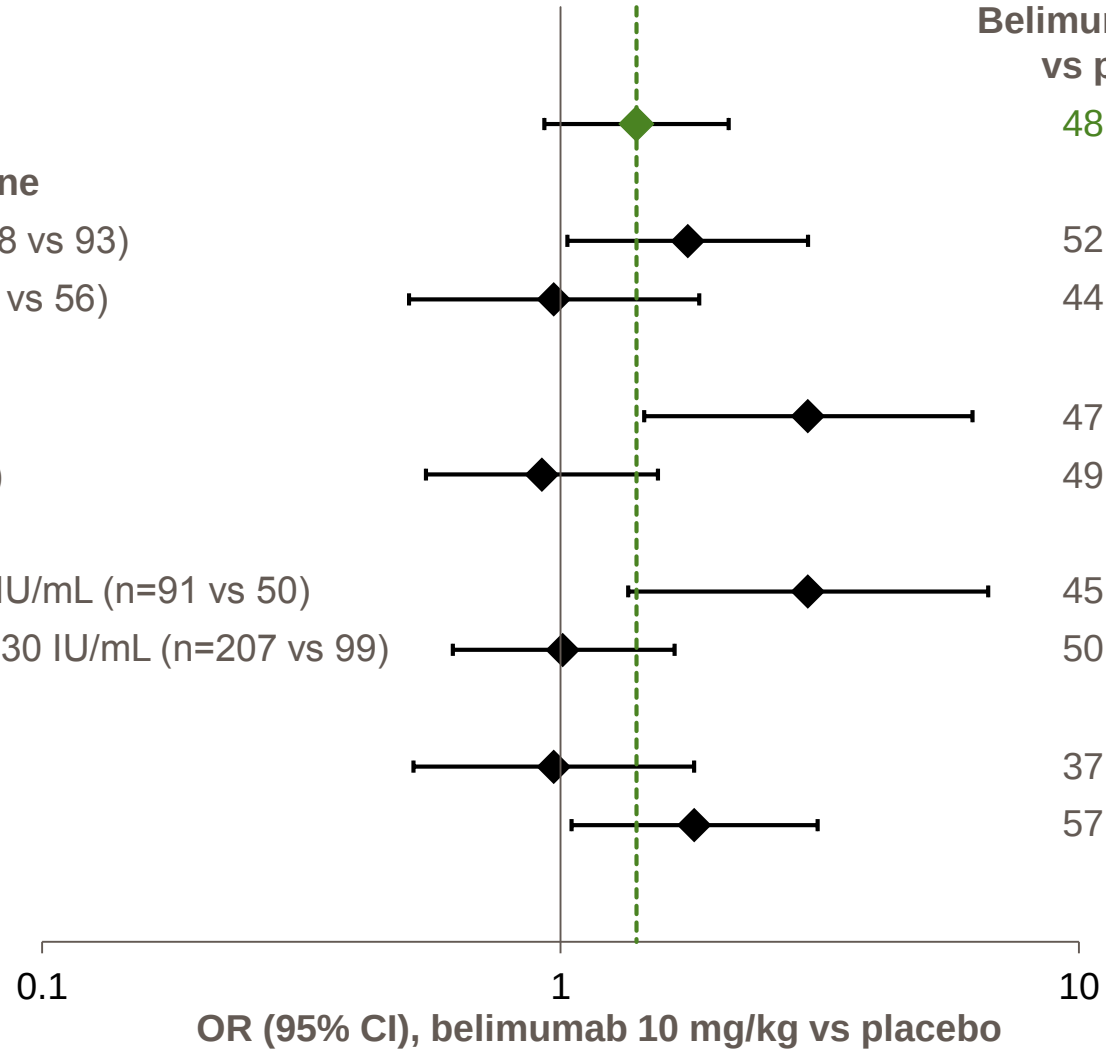
*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †covariates were treatment group, baseline SELENA-SLEDAI-S2K score (≤9 vs ≥10), baseline complement levels (at least one C3/C4 low vs no C3/C4 low) and region (US/Canada vs Rest of World). CI, confidence interval; OR, odds ratio; SE, standard error.

Primary endpoint: SRI-S2K response over time*



*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †p<0.05 vs placebo; ‡p<0.01 vs placebo.

Subgroup analyses: SRI-S2K response at Week 52*

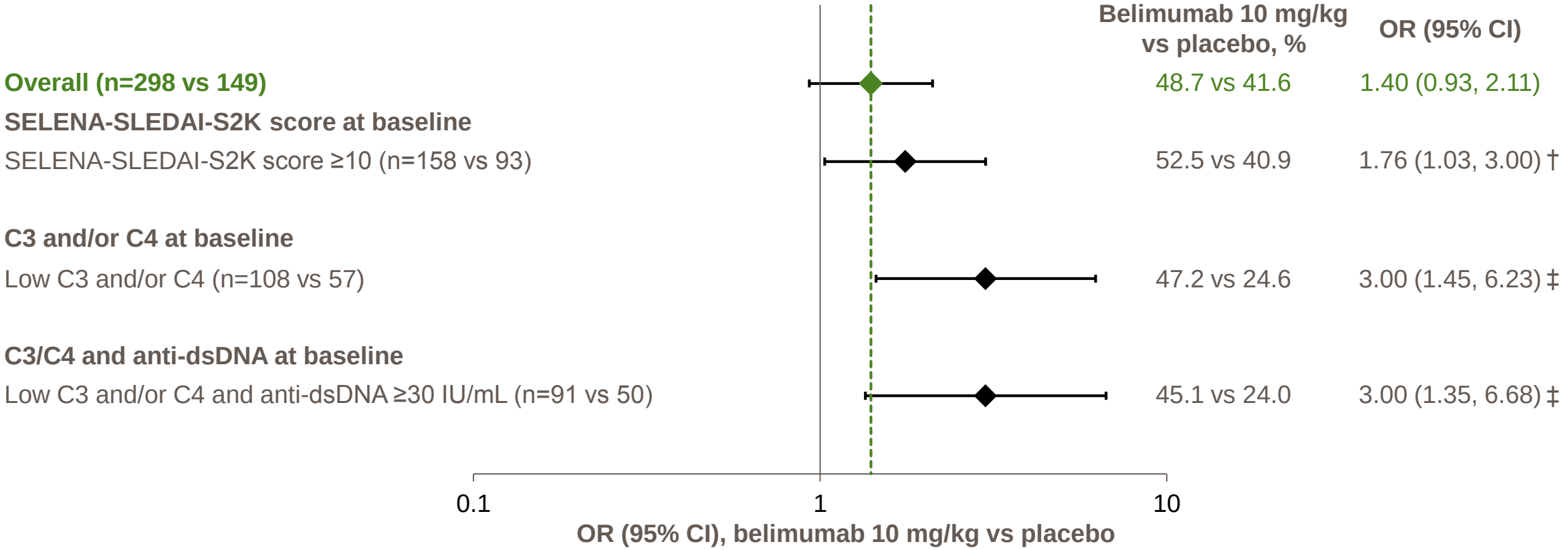


	Belimumab 10 mg/kg vs placebo, %	OR (95% CI)
Overall (n=298 vs 149)	48.7 vs 41.6	1.40 (0.93, 2.11)
SELENA-SLEDAI-S2K score at baseline		
SELENA-SLEDAI-S2K score ≥10 (n=158 vs 93)	52.5 vs 40.9	1.76 (1.03, 3.00) †
SELENA-SLEDAI-S2K score ≤9 (n=140 vs 56)	44.3 vs 42.9	0.97 (0.51, 1.85)
C3 and/or C4 at baseline		
Low C3 and/or C4 (n=108 vs 57)	47.2 vs 24.6	3.00 (1.45, 6.23) ‡
Without low C3 and/or C4 (n=190 vs 92)	49.5 vs 52.2	0.92 (0.55, 1.54)
C3/C4 and anti-dsDNA at baseline		
Low C3 and/or C4 and anti-dsDNA ≥30 IU/mL (n=91 vs 50)	45.1 vs 24.0	3.00 (1.35, 6.68) ‡
Without C3 and/or C4 and anti-dsDNA ≥30 IU/mL (n=207 vs 99)	50.2 vs 50.5	1.01 (0.62, 1.66)
Region		
US/Canada (n=131 vs 65)	37.4 vs 38.5	0.97 (0.52, 1.81)
Rest of World (n=167 vs 84)	57.5 vs 44.0	1.81 (1.05, 3.13) †

*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †p<0.05 vs placebo; ‡p<0.01 vs placebo.

Subgroup analyses: SRI-S2K response at Week 52*

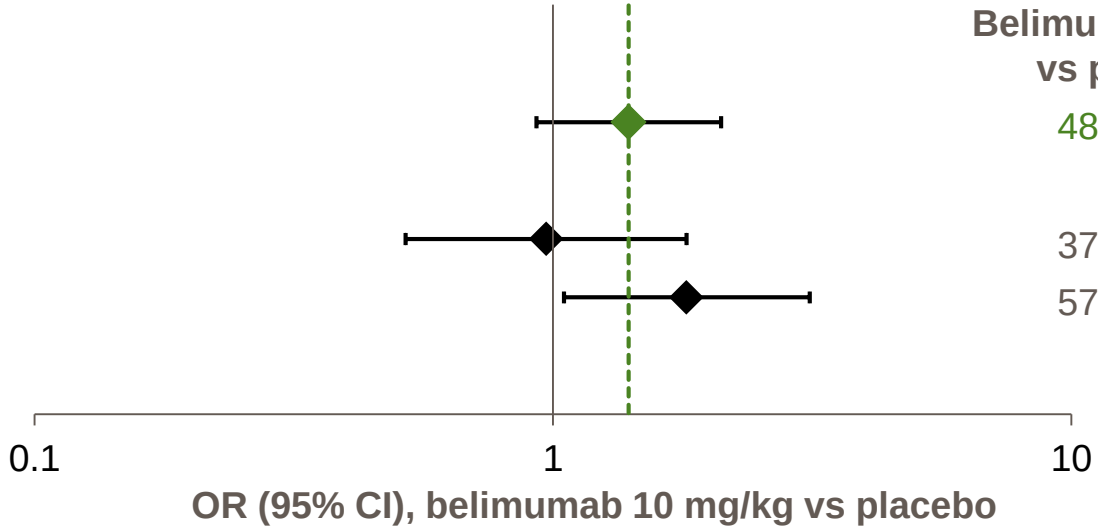
High disease activity subgroups



*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †p<0.05 vs placebo; ‡p<0.01 vs placebo.

Subgroup analyses: SRI-S2K response at Week 52*

Region



	Belimumab 10 mg/kg vs placebo, %	OR (95% CI)
Overall (n=298 vs 149)	48.7 vs 41.6	1.40 (0.93, 2.11)
Region		
US/Canada (n=131 vs 65)	37.4 vs 38.5	0.97 (0.52, 1.81)
Rest of World (n=167 vs 84)	57.5 vs 44.0	1.81 (1.05, 3.13) †

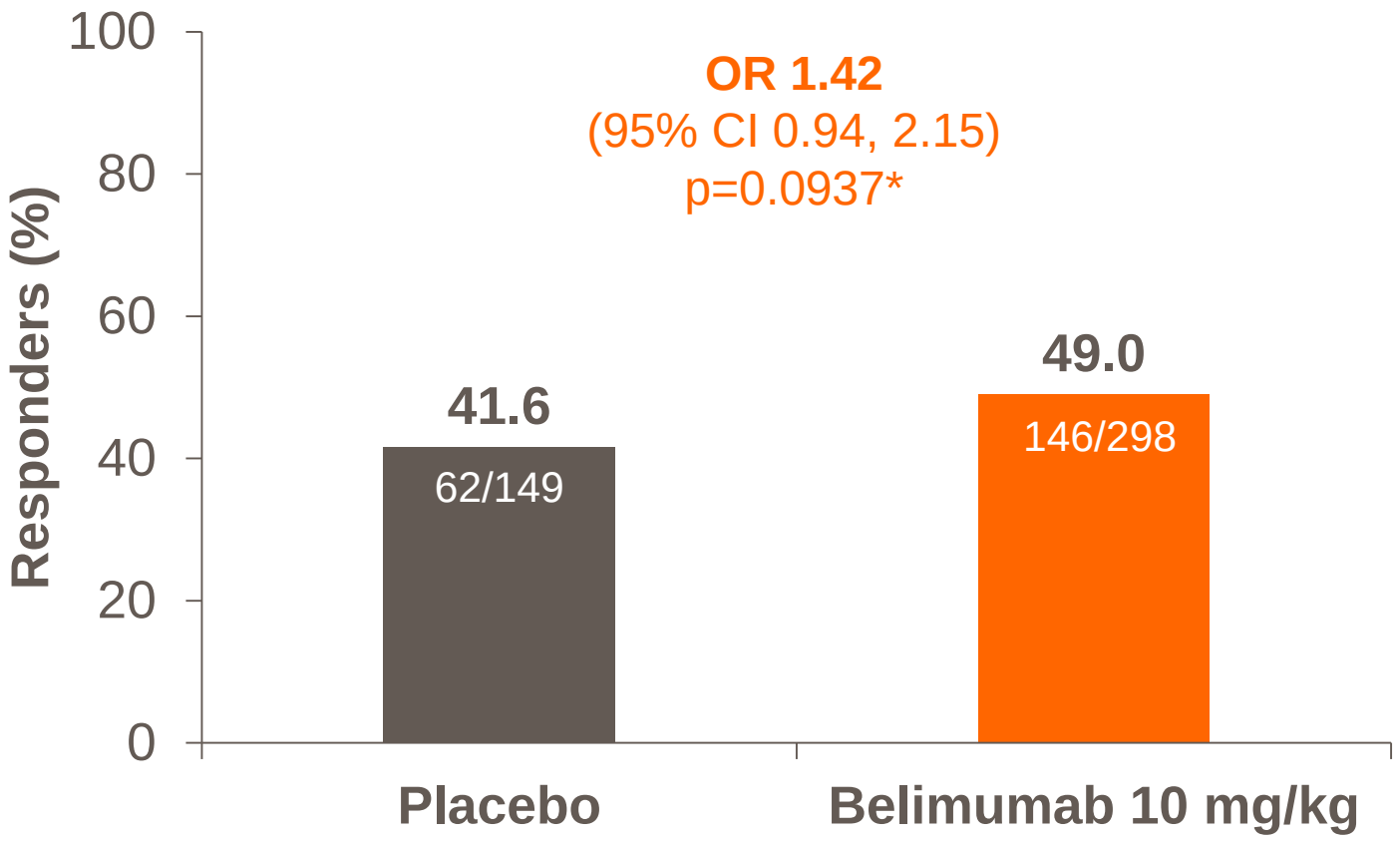
- At baseline (no statistical analyses completed):
  - Longer SLE disease duration, fewer patients with SLICC/ACR score of 0 and more patients with SELENA-SLEDAI-S2K ≥10 in US/Canada versus Rest of World
  - Greater steroid use and higher levels of serological activity in Rest of World versus US/Canada

*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †p<0.05 vs placebo.

Major secondary endpoint: SRI response at Week 52

SELENA-SLEDAI proteinuria scoring rule

- SRI response was numerically greater in belimumab compared with placebo patients

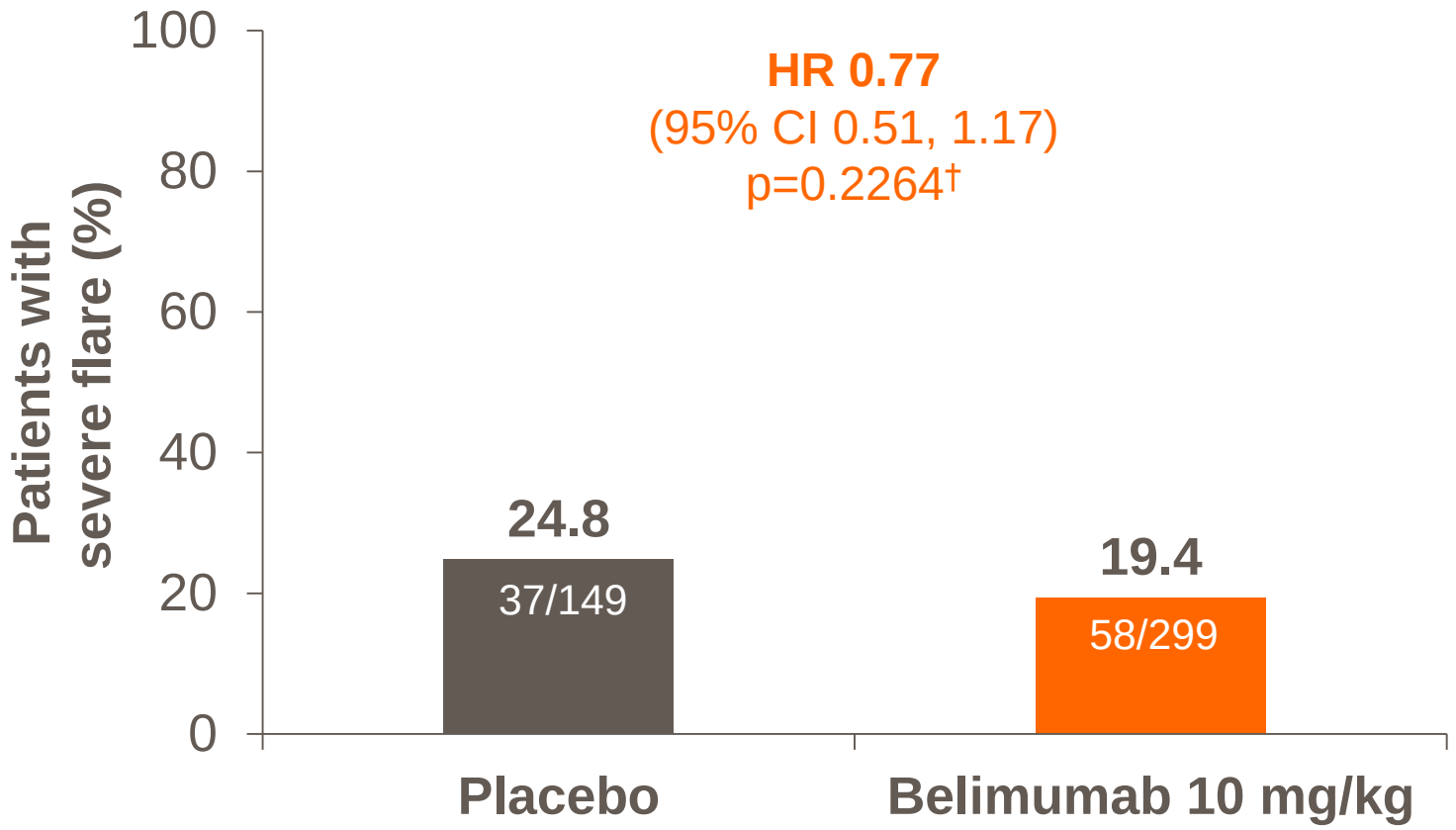


*Sequential testing; therefore, nominal p-value.

Major secondary endpoint: time to severe flare over 52 weeks

Modified SFI*

- Patients who received belimumab had a 23% lower risk of experiencing a severe flare, at any time point, compared with placebo

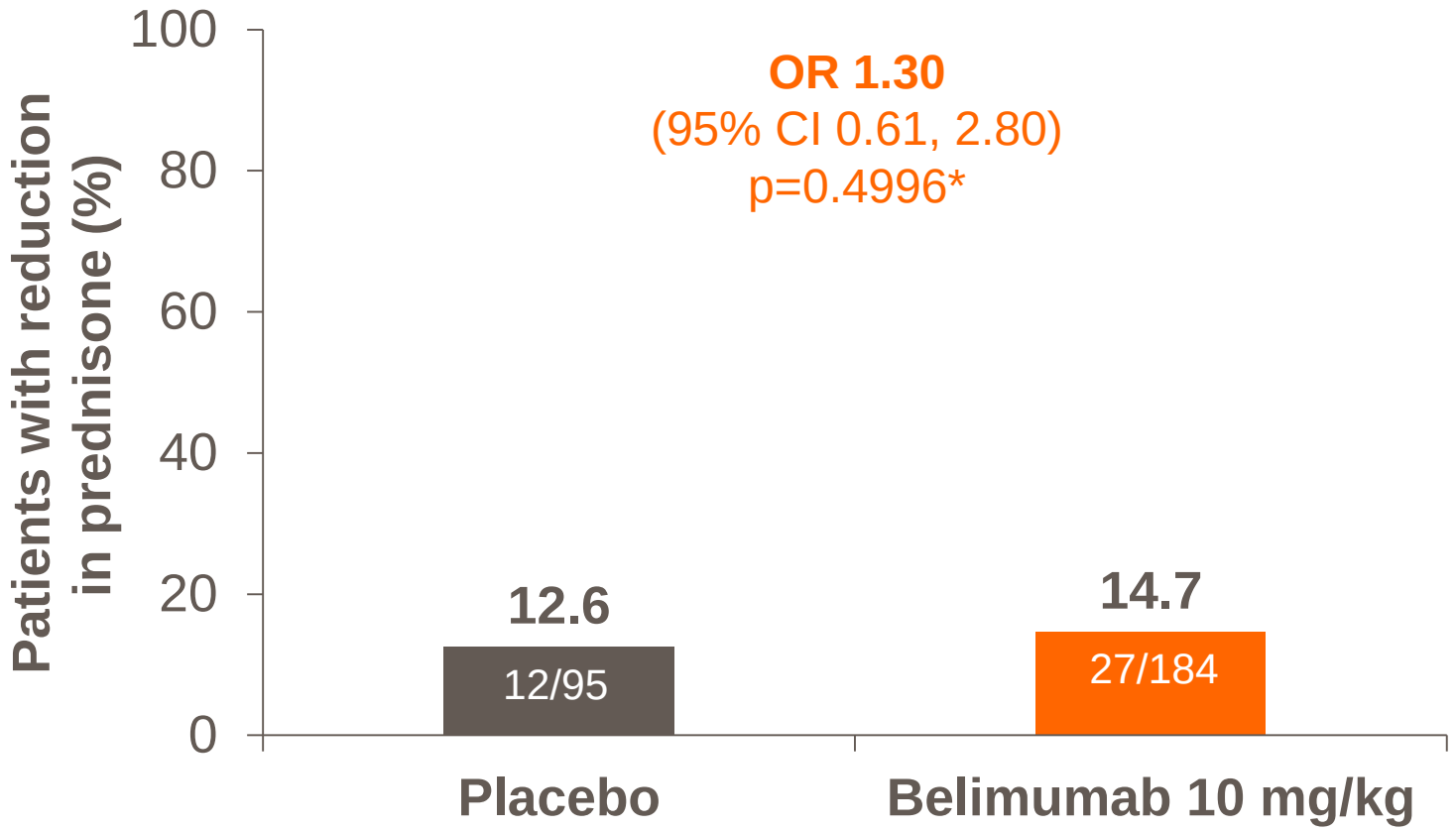


*SFI, SELENA-SLEDAI Flare Index (excludes severe flares triggered only by an increase in SELENA-SLEDAI to >12); †sequential testing; therefore, nominal p-value.
HR, hazard ratio.

Major secondary endpoint: prednisone dose reduction

Reduction of ≥25% from baseline to ≤7.5 mg/day, during Weeks 40 through 52

- There was a numerically greater proportion of patients with a prednisone dose reduction in the belimumab group compared with placebo



*Sequential testing, therefore nominal p-value.

Safety: AEs

- The percentage of patients who experienced an AE or SAE was similar between groups

Adverse events	Placebo (N=165) n (%)	Belimumab 10 mg/kg (N=331) n (%)
Patients with ≥1 AE	**144 (87.3)**	**277 (83.7)**
Patients with an SAE by system organ class (≥2%)*	**31 (18.8)**	**36 (10.9)**
Infections and infestations	13 (7.9)	11 (3.3)
Musculoskeletal and connective tissue disorders	7 (4.2)	9 (2.7)
Renal and urinary disorders	3 (1.8)	7 (2.1)
Respiratory, thoracic, and mediastinal disorders	3 (1.8)	7 (2.1)
Cardiac disorders	4 (2.4)	3 (0.9)
General disorders and administration site conditions	4 (2.4)	3 (0.9)
AEs leading to discontinuation by system organ class (≥1%)*	**12 (7.3)**	**22 (6.6)**
Infections and infestations	2 (1.2)	6 (1.8)
Renal and urinary disorders	2 (1.2)	6 (1.8)
Musculoskeletal and connective tissue disorders	2 (1.2)	2 (0.6)

*Patients only counted once per system organ class.
SAE, serious adverse event.

Safety: AESI

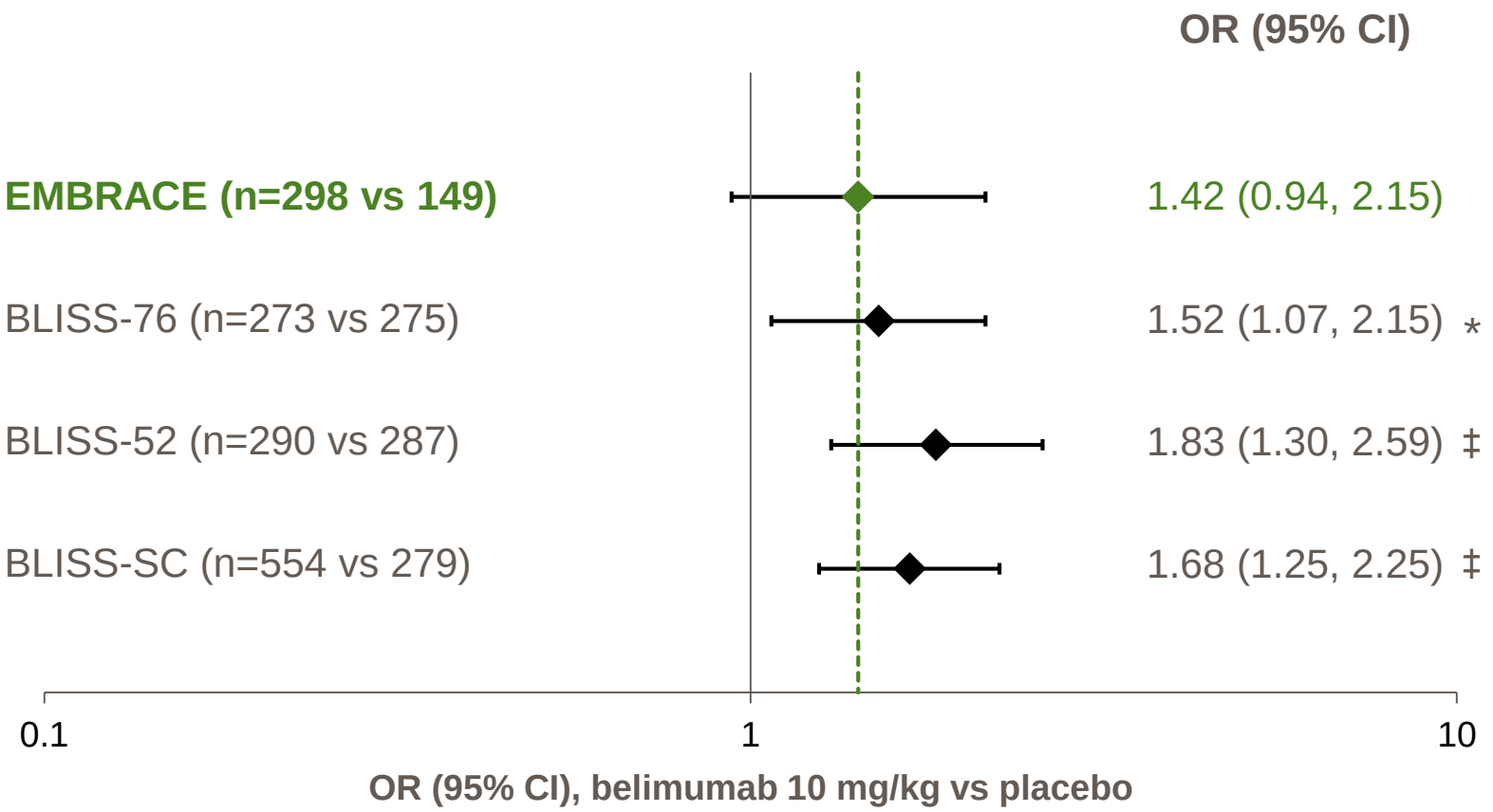
AESIs	Placebo (N=165) n (%)	Belimumab 10 mg/kg (N=331) n (%)
All malignancies (no cases of NMSC)	0	1 (0.3)
Post-infusion systemic reactions per anaphylactic reaction CMQ broad search	8 (4.8)	21 (6.3)
Serious acute post-infusion systemic reactions/hypersensitivity*†	0	0
All infections of special interest (serious: 1 each)	13 (7.9)	19 (5.7)
All opportunistic infections (none serious)*	2 (1.2)	2 (0.6)
Active tuberculosis	1 (0.6)	0
All herpes zoster‡ (none serious)	4 (2.4)	7 (2.1)
Opportunistic	2 (1.2)	1 (0.3)
Sepsis	2 (1.2)	1 (0.3)
Depression/suicide/self-injury	17 (10.3)	26 (7.9)
Suicide/self-injury	2 (1.2)	2 (0.6)
Suicide/self-injury per GSK adjudication	2 (1.2)	0
Deaths	0	2 (0.6)

- Reasons for deaths: pneumonia and meningitis, neither established as directly related to belimumab

*Per sponsor adjudication; †acute: onset ≤1 day; delayed acute: onset 2–3 days; ‡not all herpes zoster recurrent or disseminated.
CMQ, Custom Medical Dictionary for Regulatory Activities Queries; NMSC, non-melanoma skin cancer.

EMBRACE and other Phase 3 studies: SRI response at Week 52

SELENA-SLEDAI proteinuria scoring rule (major secondary endpoint in EMBRACE)



*p<0.05 vs placebo; †p<0.01 vs placebo; ‡p<0.001 vs placebo.

Summary

- The study did not achieve the primary endpoint
  - Numerical trends were observed in favor of belimumab
  - Significant improvements were observed in subgroups with characteristics of high disease activity at baseline (SELENA-SLEDAI-S2K ≥10, low C3 and/or C4, and low C3/C4 and anti-dsDNA ≥30 IU/mL), which is consistent with previous studies
- There were numerical trends in favor of belimumab for secondary endpoints (SRI response at Week 52, time to severe flare over 52 weeks, and prednisone dose reduction)
- Study withdrawals were similar between groups (placebo 24.2%; belimumab 22.4%)
  - AEs were the primary reason for withdrawals (placebo 6.7%; belimumab 5.4%)
- The percentage of patients who experienced an AE or SAE was similar between groups
  - AEs: placebo 87.3%; belimumab 83.7%
  - SAEs: placebo 18.8%; belimumab 10.9%
- The safety profile was consistent with previous studies
  - Low numbers of opportunistic infections and psychiatric events

Thank you

Questions?