199 BARICITINIB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS FROM A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Background Baricitinib (Bari), an oral selective inhibitor of Janus kinase (JAK)1 and JAK2, has been approved for the treatment of rheumatoid arthritis (RA) in over 50 countries including the United States, European countries, and Japan. The purpose of this study was to report results from a 24 week global, Phase 2, double-blind, placebo (PBO)-controlled study of Bari in patients with systemic lupus erythematosus (SLE) receiving standard therapy.

Methods Patients with SLE (positive antinuclear antibody [ANA] or anti-double stranded DNA [anti-dsDNA], clinical SLE Disease Activity Index 2000 [SLEDAI-2K] 4, arthritis or rash required) receiving stable background SLE therapy were randomized 1:1:1 to PBO or Bari (2- or 4 mg) once-daily. The primary endpoint was resolution of arthritis or rash as defined by the SLEDAI-2K at Week 24.

Results Of 314 patients randomized, 79%, 82%, and 83% completed 24 weeks of treatment in the PBO, Bari 2 mg, and Bari 4 mg groups, respectively. At Week 24, a significantly greater proportion of patients in the Bari 4 mg group compared to PBO achieved resolution of arthritis or rash (67% vs 53%, $p<0.05$) and SLE Responder Index (SRI)−4 response (64% vs 48%, $p<0.05$). At Week 24, the proportions of patients achieving flare reduction (Safety of Estrogens in Lupus Erythematosus National Assessment [SELENA]-SLEDAI Flare Index [SFI]), Lupus Low Disease Activity State (LLDAS), Physicians Global Assessment, and tender joint count change from baseline were also significantly improved for Bari 4 mg compared to PBO (Table). No statistically significant differences were observed between Bari 2 mg and PBO in any of the above endpoints. There were no significant changes in anti-dsDNA or complement in patients treated with Bari. Rates of adverse events leading to treatment discontinuation and serious adverse events (SAEs) were higher for both Bari dose groups compared to PBO. There were no deaths, malignancies, major adverse cardiovascular events, tuberculosis, or serious herpes zoster infections; 1 SAE of deep vein thrombosis was reported in a patient with risk factors (Bari 4 mg group).

Conclusions In patients with SLE receiving standard background therapy, once-daily oral Bari 4 mg was associated with significant clinical improvements compared to PBO and an acceptable benefit/risk profile. These findings support further study of Bari as a potential therapy for patients with SLE.

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Abstract 199 Table 1 Efficacy and safety outcomes of patients with systemic lupus erythematosus in a phase 2 study of baricitinib

	PBO (n=105)	Bari 2 mg (n=105)	Bari 4 mg (n=104)
Efficacy measure	**Week 24**		
Resolution of arthritis or rash (SLEDAI-2K)	56 (53.3)	61 (58.1)	70 (67.3)*
SRI-4	50 (47.6)	54 (51.4)	67 (64.4)*
Flare (SFI, any severity)	54 (51.4)	45 (42.9)	34 (32.7)*
Flare (SFI, severe)	12 (11.4)	10 (9.5)	6 (5.8)
LLDAS	27 (25.7)	35 (33.3)	40 (38.5)*
Δ Tender joint count	−5.59	−6.50	−6.86*
Δ Swollen joint count	−4.60	−4.12	−4.76
Δ Physician's Global Assessment	−26.3	−25.9	−32.2*
Δ Complement C3, g/L	0	0	−0.02
Δ Complement C4, g/L	0.01	−0.01	−0.01
Safety measure	**Weeks 0–24‡**		
TEAEs	68 (64.8)	75 (71.4)	76 (73.1)
SAEs	5 (4.8)	11 (10.5)	10 (9.6)
Serious infections	1 (1.0)	2 (1.9)	6 (5.8)
Deep vein thrombosis	0	0	1 (1.0)

Δ=least squares mean change from baseline; Bari=baricitinib; LLDAS=Lupus Low Disease Activity State; n=number of patients in the analysis population; n=number of patients in the specified category; PBO=placebo; SAEs=serious adverse events; SFI=Safety of Estrogens in Lupus Erythematosus National Assessment [SELENA]-Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] Flare Index; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SRI-4=Systemic Lupus Erythematosus Responder Index-4; TEAEs=treatment emergent adverse events.
Data are n (%) patients, unless otherwise indicated.
*p≤0.05 vs placebo.
‡Includes up to 30 days post-treatment.
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200 EFFICACY AND SAFETY OF BELIMUMAB IN PATIENTS OF BLACK RACE WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS FROM THE EMBRACE STUDY

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Background Black patients have an increased prevalence and severity of systemic lupus erythematosus (SLE), alongside higher mortality rates. The efficacy and safety of intravenous (IV) belimumab has been demonstrated in several Phase 2/3 studies; however, the small number of black patients within these trials, and the conflicting results, have limited conclusions regarding efficacy in this population. The objective of this study was to specifically assess the efficacy and safety of IV belimumab plus standard of care (SoC) in black patients with active, auto antibody-positive SLE.

Methods EMBRACE (NCT01632241) is a randomized, multicenter, double-blind, placebo-controlled trial in patients of self identified black race, aged 18 years, with active SLE at

Abstract 200 Table 1 Primary, key secondary, and subgroup efficacy analyses (mITT population)

	Belimumab (n=299)[a]	Placebo (n=149)
SRI-S2K response[b] at Week 52, n (%)	145 (48.7)	62 (41.6)
Odds ratio (95% CI) vs placebo	1.40 (0.93–2.11)	
P-value	p=0.1068	
SRI response[c] at Week 52, n (%)	146 (49.0)	62 (41.6)
Odds ratio (95% CI) vs placebo	1.42 (0.94–2.15)	
Number of patients with severe SFI flare over 52 weeks, n/n (%)	58 (19.4)	37 (24.8)
Hazard ratio (95% CI) vs placebo	0.77 (0.51–1.17)	
Patients who experienced a reduction in prednisone dose[d], n/n (%)	27/184 (14.7)	12/95 (12.6)
Adjusted odds ratio (95% CI)	1.30 (0.61–2.80)	
SRI-S2K[a] response at Week 52 in subgroups		
Patients with baseline SS-S2K score≤9, n/n (%)	62/140 (44.3)	24/56 (42.9)
Odds ratio (95% CI) vs placebo	0.97 (0.51–1.85)	
P-value	p=0.9198	
Patients with baseline SS-S2K score≥10, n/n (%)	83/158 (52.5)	38/93 (40.9)
Odds ratio (95% CI) vs placebo	1.76 (1.03–3.00)	
P-value	p=0.0384	
Patients with low baseline C3 and/or C4 levels, n/n (%)	51/108 (47.2)	14/57 (24.6)
Odds ratio (95% CI) vs placebo	3.00 (1.45–6.23)	
P-value	p=0.0031	
Patients without low baseline C3 or C4 levels, n/n (%)	94/190 (49.5)	48/92 (52.2)
Odds ratio (95% CI) vs placebo	0.92 (0.55–1.54)	
P-value	p=0.7554	
Patients with low C3 and/or C4 and anti-dsDNA≥30 IU/mL, n/n (%)	41/91 (45.1)	12/50 (24.0)
Odds ratio (95% CI) vs placebo	3.00 (1.35–6.68)	
p-value	p=0.0072	
Patients without low C3, C4 or anti-dsDNA≥30 IU/mL, n/n (%)	104/207 (50.2)	50/99 (50.5)
Odds ratio (95% CI) vs placebo	1.01 (0.62–1.66)	
P-value	p=0.9556	
Patients from US/Canada, n/n (%)	49/131 (37.4)	25/65 (38.5)
Odds ratio (95% CI) vs placebo	0.97 (0.52–1.81)	
P-value	p=0.9334	
Patients from the rest of the world, n/n (%)	96/167 (57.5)	37/84 (44.0)
Odds ratio (95% CI) vs placebo	1.81 (1.05–3.13)	
P-value	p=0.0324	

[a]One patient in the belimumab group was excluded from the analyses as they did not have a baseline or screening PGA score; [b]modified S2K scoring for proteinuria; [c]with SELENA-SLEDAI scoring of proteinuria; [d]reduction in prednisone dose, in patients initially treated with >7.5 mg/day, by ≥25% to≤7.5 mg/day during Weeks 40–52.
Anti-dsDNA, anti-double-stranded deoxyribonucleic acid; C, complement; CI, confidence interval; mITT, modified intent-to-treat; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus-SLE Disease Activity Index; SFI, SLE flare index; SRI-S2K, SLE Responder Index-SLEDAI-2000; SS, SELENA-SLEDAI.

screening. Patients were randomized (2:1) to monthly belimumab 10 mg/kg IV or placebo, plus SoC. The primary endpoint was the SLE Responder Index (SRI) response rate with modified SLEDAI-2K (S2K) scoring for proteinuria at Week 52 (SRI-S2K response required a 4 point reduction in the SELENA-SLEDAI (SS)-S2K, no worsening [increase of <0.3] in Physician's Global Assessment (PGA), and no new BILAG A or 2 new B organ domain scores). Key secondary endpoints included SRI response rate with SS scoring of proteinuria at Week 52, time to first severe SFI flare, and reductions in prednisone dose by 25% to 7.5 mg/day during Weeks 4052. Subgroup analyses of the primary endpoint were also conducted. Step-down sequential testing was utilized to control the overall type 1 error rate (2-sided, alpha=0.05). Safety was assessed by monitoring adverse events (AEs).

Results The mITT population comprised 448 patients; 96.9% were female and mean (SD) age was 38.8 (11.42) years. Although the study did not achieve the primary endpoint, numerical trends were observed in favor of belimumab, and significant improvements were observed in subgroups with characteristics of high disease activity (HDA; table). Study withdrawals were similar between groups (belimumab 22.4%; placebo 24.2%) and AEs were the primary reason for withdrawals (belimumab 5.4%; placebo 6.7%). The percentage of patients who experienced an AE (belimumab 83.7%; placebo 87.3%) or serious AE (belimumab 10.9%; placebo 18.8%) was similar between groups. Two deaths occurred within the belimumab group (0.6%; pneumonia and meningitis); neither were established as directly related to belimumab.

Conclusions Whilst the primary endpoint of this study in black patients with SLE was not achieved, improvements in favor of belimumab were observed, with significant benefits in patients with HDA. The safety profile was acceptable and consistent with previous studies.

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201 USTEKINUMAB TARGETS A NOVEL MECHANISM OF ACTION TO TREAT PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Both IL-12 and IL-23 have been implicated in the pathogenesis of human and experimental lupus,[1–6] and in a drug repositioning analysis, the anti-IL-12/23 monoclonal antibody ustekinumab (UST) was identified as a high-priority candidate for the treatment of patients with SLE.[7] We evaluated the efficacy, safety, and molecular effects of UST in a Ph2 trial.[8]

Methods A Ph2, placebo (PBO)-controlled study was conducted in 102 adults with seropositive (ANA, anti-dsDNA, and/or anti-Smith autoantibodies) SLE by SLICC criteria and active (SLEDAI 6 and 1 BILAG A and/or 2 BILAG B) disease. Patients were randomized (3:2) to receive UST IV~6 mg/kg or PBO at wk0, followed by SC injections of UST 90 mg q8w or PBO, both added to standard care. PBO patients crossed over to SC UST at wk24. The primary endpoint was proportion of patients achieving SLE Responder Index (SRI)−4 response at wk24. Circulating levels of type I (IFN-I) and type II interferon (IFN-) were assessed by microarray of whole blood RNA samples and serum protein ELISA analyses.

Results SRI-4 response at wk24 was significantly greater (p=0.0057) in the UST group (62%) vs PBO (33%). UST also demonstrated greater improvement in musculoskeletal and mucocutaneous disease features vs PBO at wk24. The risk of a new BILAG flare (1 new BILAG A or 2 new BILAG B) was significantly lower in the UST group vs. PBO (HR 0.11 [95% CI 0.01–0.94]; p=0.0078; wk12 to wk24 prespecified