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Background: Atacicept is a fusion protein that blocks B-lymphocyte stimulator and a proliferation-inducing ligand, which are increased in patients with SLE. APRIL-SLE was a double-blind, placebo-controlled, Phase 2 study that randomized patients with moderate-to-severe systemic lupus erythematosus (SLE) to atacicept 75 mg, atacicept 150 mg, or placebo twice-weekly for 4 weeks, then weekly for 48 weeks.

Objectives: The primary results of the APRIL-SLE study – the effect of atacicept compared to placebo in preventing new flares in patients with moderate-to-severe SLE – have been reported (Isenberg et al., 2013). We performed a post hoc analysis to describe the effect of atacicept compared to placebo on measures of renal function in patients with SLE; this effect has not been reported previously.

Methods: The APRIL-SLE study excluded patients with moderate to severe glomerulonephritis, as defined by either of the following: urinary protein/creatinine ratio (UPCR)>1 mg/mg and/or hematuria or a significant renal impairment as defined by estimated glomerular filtration rate (eGFR)<50 mL/min/1.73 m2. Patients with proteinuria and mild to moderate chronic kidney disease, as assessed by KDIGO criteria were eligible. UPCR and eGFR were measured at baseline, week 2, and then every 4 weeks until week 52. The median change from baseline to each of these timepoints was calculated for eGFR and UPCR using the Safety Analysis Set, comprised of all randomized patients who received at least 1 dose of study medication. Enrollment in the atacicept 150 mg group was discontinued prematurely due to 2 deaths from pneumonias. When treatment was discontinued, 62 of 144 patients in this group had completed 52 weeks of treatment; 27 other patients had already been withdrawn for various reasons; and, in the remaining 55 patients, treatment was stopped early as a safety precaution. Patients in the other two groups completed the protocol.

Results: In total, 111 patients in the placebo group, 112 patients in the atacicept 75 mg group, and 62 patients in the atacicept 150 mg group completed 52 weeks of treatment. The eGFR time course was stable for the atacicept groups compared to a 4.4% decline in the placebo group from baseline at week 52 (Figure 1 and Table 1). UPCR from baseline at week 52 declined in the atacicept groups and increased in the placebo group.

Table 1. Median Percent Change from Baseline of Estimated Glomerular Filtration Rate (eGFR) and Proteinuria at Week 52 – Safety Analysis Set

Variable	Placebo	Atacicept 75 mg	Atacicept 150 mg
eGFR (mL/min)	n=110	n=111	n=62 [b]
median	-4.35	-1.49	0.57
UPCR (mg/mg)	n=108	n=108	n=63
median	6.29	-6.27	-12.72
UPCR (mg/mg) [a]	n=12	n=15	n=8
median	26.11	-54.42	-12.15

eGFR=estimated glomerular filtration rate; UPCR=urinary protein/creatinine ratio. [a]Among patients with screening UPCR ≥0.2 mg/mg. [b]Enrollment in the atacicept 150 mg arm was discontinued prematurely (described in Isenberg et al., 2015).

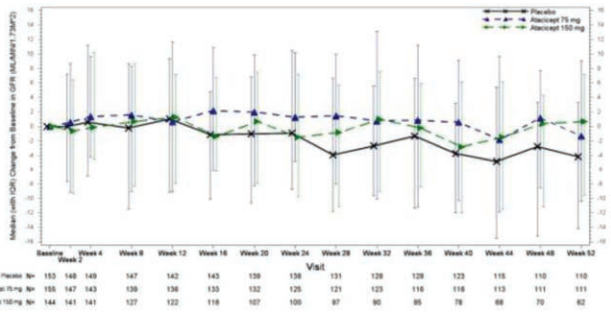

Figure 1. Median Change from Baseline in eGFR. eGFR= estimated glomerular filtration rate; IQR=interquartile range

Conclusion: Results from this double-blind, placebo-controlled, Phase 2 study suggest a potential for improved renal function with atacicept treatment of patients with moderate-to-severe SLE.

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POS0190 EFFICACY AND SAFETY OF BARICITINIB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS FROM TWO RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, PHASE 3 STUDIES

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Background: In a 24-week, phase 2 clinical study (NCT02708095) in patients with systemic lupus erythematosus (SLE), baricitinib (BARI), an oral selective inhibitor of Janus kinase 1 and 2 approved for the treatment of rheumatoid arthritis and atopic dermatitis, inhibited the type I interferon gene signature, multiple other cytokine pathways, and improved disease activity (1) (2).

Objectives: To further evaluate the efficacy and safety of BARI in patients with SLE.

Methods: Patients with active SLE receiving stable background therapy were randomised 1:1:1 to BARI 2-mg, 4-mg, or placebo (PBO) once daily in two identically designed, 52-week, phase 3 randomised, PBO-controlled studies. In SLE-BRAVE-I (NCT03616912) and -II (NCT03616964), 760 and 775 patients, respectively were enrolled in a balanced manner across regions, although different countries per region participated in each study. The primary endpoint for both studies was the proportion of patients achieving an SLE Responder Index-4 (SRI-4) response at week 52. Glucocorticoid tapering was encouraged but not required per protocol.

Results: The mean Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) at baseline was 10.1 for both SLE-BRAVE-I and -II participants; musculoskeletal and mucocutaneous domains were the most common domains involved at baseline. In SLE-BRAVE-I, the proportion of SRI-4 responders at week 52 among patients treated with BARI 4-mg (56.7%), but not BARI 2-mg (49.8%), was significantly greater than in patients treated with PBO (45.9%, p = 0.016) (Table 1). No difference was seen in SLE-BRAVE-II (47.1%, 46.3%, and 45.6%, BARI 4-mg, 2-mg, and PBO, respectively). None of the key secondary endpoints, including glucocorticoid tapering or time to first severe flare (SFI), were met in either study. The proportions of patients with serious adverse events (SAEs) were 7.1% and 8.6% for PBO, 9.4% and 13.4% for BARI 2-mg and 10.3% and 11.2% for BARI 4-mg in SLE-BRAVE-I and II, respectively.

Table 1. Efficacy and safety of baricitinib in patients with SLE-BRAVE-I and -II

	SLE-BRAVE-I			SLE-BRAVE-II		
Efficacy measure	PBO (N=253)	BARI 2-mg (N=255)	BARI 4-mg (N=252)	PBO (N=256)	BARI 2-mg (N=261)	BARI 4-mg (N=258)
SRI-4 (W52)	116 (45.9)	126 (49.8)	142 (56.7)*	116 (45.6)	120 (46.3)	121 (47.1)
SRI-4 (W24)	99 (39.1)	114 (44.8)	117 (46.5)	98 (38.6)	104 (40.0)	108 (42.1)
Severe Flares (n, events)	38 (15.0)	34 (13.3)	26 (10.3)	26 (10.2)	29 (11.1)	29 (11.2)
HR for time to first severe flare (SFI) HR [CI]	NA	0.8 [0.52, 1.32]	0.65 [0.40, 1.08]	NA	1.1 [0.65, 1.89]	1.1 [0.67, 1.94]
Glucocorticoid sparing	36 (30.8)	31 (29.2)	36 (34.0)	33 (31.7)	34 (29.8)	36 (34.3)
LLDAS (W52)	66 (26.2)	65 (25.7)	74 (29.7)	59 (23.2)	62 (24.0)	65 (25.4)
Safety measure						
TEAE	210 (83.0)	210 (82.4)	208 (82.5)	198 (77.3)	199 (76.2)	200 (77.5)
SAE	18 (7.1)	24 (9.4)	26 (10.3)	22 (8.6)	35 (13.4)	29 (11.2)

Data are n (%) patients, unless otherwise indicated. BARI=baricitinib; CI=confidence interval; HR=hazard ratio compared with PBO; LLDAS=lupus low disease activity state; N=number of patients in the analysis population; n=number of patients in the specified category; PBO=placebo; TEAE=treatment-emergent adverse event; SAE=serious adverse event; W=week. *p≤0.05 vs PBO.

Conclusion: Although phase 2 data suggested BARI as a potential treatment for patients with SLE (2), the SLE-BRAVE-I and -II phase 3 study results were discordant for the primary outcome measure, with only SLE-BRAVE-I positive, making it difficult to elucidate benefit. Additional analyses are being performed to understand this discordance. No new safety signals were observed.

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POS0191

ANTIMALARIAL DRUGS AND ELECTROCARDIOGRAPHIC ALTERATIONS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS.

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Background: During the first months of the Sars-CoV-2 pandemic, antimalarial drugs were the central axis of the treatment of patients with acute respiratory infection. After that, several studies reported a risk of prolongation of corrected QT interval (QTc) at the electrocardiogram (ECG).
Historically, these drugs, have been the common denominator in the treatment of patients with Systemic Lupus Erythematosus (SLE).

Objectives: To analyze the possible relationship between the use of antimalarial drugs ant the electrocardiographic alterations in patients diagnosed with SLE.

Methods: Cross-sectional study in patients diagnosed with SLE (SLICC 2012). In all of them, we performed a 12-lead ECG at rest. We measured the QT interval: manually and automatically, ant its correction was made according to the Hodge formule (QTc).

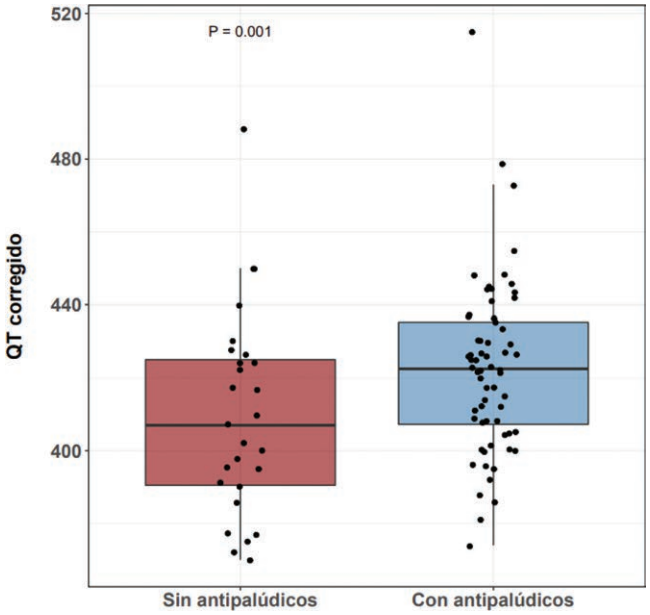
Results: 91 patients diagnosed with SLE were included in the study. Of the total of patients included in the study, 64 were in current treatment with an antimalarial drug, with a mean of 9.09 (5.73) years of treatment, and a mean cumulative dosage of 813.16 (436.12) gr.
Of the patients on current treatment with antimalarial drugs, 4.69% had a prolonged QTc, compared to 3.7% of the patients without current treatment with these drugs.

Table 1.

	NO antimalarial n= 27	YES antimalarial n= 64
Heart disease	7 (25,93%)	5 (7,81%)
Cumulative dosage HCQ (gr)	316,41 (457,28)	813,16 (436,12)
ECG disorders	5 (18,52%)	12 (18,75%)
Structural disorders	1 (3,7%)	6 (9,38%)
Electrical conduction disorders	2 (7,41%)	6 (9,38%)

We analyzed the possible relationship between the QTc interval, the current treatment with antimalarial drugs, and the cumulated dosage of this medication. We corrected the lineal regression models by the years of disease evolution, the presence or absence of known heart disease, the women gender, and other treatments such as antiarrhythmics or beta-blockers.
We found a statistically significant association between taking antimalarial drugs and the elongated QTc interval (p= 0,001). Nevertheless, in the multivariate analysis, we did not found a significant relationship between the ECG alterations and the treatment with antimalarial drugs.

Figure 1.



Conclusion: In our study, we did not observe a direct relationship between the intake of antimalarial drugs and the alteration of the corrected QT interval.

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N/A