LB0005

ORELABRUTINIB, AN IRREVERSIBLE INHIBITOR OF BRUTON'S TYROSINE KINASE (BTK), FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE IB/IIA DOSE-FINDING STUDY

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Background: Orelabrutinib is an oral, highly-selective, irreversible inhibitor of Bruton's tyrosine kinase (BTK). Orelabrutinib has been approved for the treatment of B cell malignancies in China. Two distinct lupus animal models showed significant efficacy of orelabrutinib in reducing disease activity, which supported the clinical development of orelabrutinib in Systemic Lupus Erythematosus (SLE).
Objectives: This phase Ib/IIa, randomized, double-blind, placebo-controlled, dose-finding study aimed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), preliminary efficacy and biomarkers of orelabrutinib in patients with mild to moderate SLE who received standard of care (SoC) therapy.
Methods: Patients diagnosed with SLE by the ACR classification criteria for ≥ 6 months, who had a SLEDAI-2K score ≥5 at screening, and were autoantibody-positive, were randomized 1:1:1:1 to receive oral orelabrutinib at 50mg, 80mg, 100mg or placebo once daily for 12 weeks, respectively.
Results: This study randomized 60 patients with 55 patients who completed 12-week treatment. Age at baseline was 33.7±9.8 years and 96.7% were female. Baseline disease characteristics were generally balanced across treatment groups. Adverse events (AEs) were reported in 80%, 93.3% and 100% of orelabrutinib treated patients at doses of 50mg, 80mg and 100mg QD respectively versus 85.5% in placebo group. AEs were mostly mild or moderate. Treatment-related SAEs were reported in 3 patients treated with orelabrutinib, only 1 of which was grade 3. No deaths were reported. The plasma exposure of orelabrutinib (AUC and Cmax) was proportionally increased with doses. Nearly complete BTK occupancy was achieved at all dose levels, and the occupancy lasted for 24 hours without any decrease compared to that at 4 hour post-dosing. In all evaluable patients, the SLE Response Index (SRI)-4 response rates at week 12 were 50.0%, 61.5% and 64.3% in patients treated with orelabrutinib at 50mg (n=14), 80mg (n=13) and 100mg (n=14) respectively, compared with 35.7% in patients treated with placebo (n=14), which indicated the trend of dose-dependent improvement. Among the subgroup of patients with SLEDAI-2K≥8 at screening, SRI-4 response occurred in 70%, 70% and 66.7% of patients treated with orelabrutinib at 50mg (n=10), 80mg (n=10) and 100mg (n=9), respectively, compared with 30% who received placebo (n=10). Trends of reduced proteinuria, anti-dsDNA and IgG, total B cells and increased complements C4 were also observed following orelabrutinib treatment.
Conclusion: Orelabrutinib was generally safe and well tolerated in patients with SLE. Preliminary results also suggested encouraging efficacy which supports further development of orelabrutinib in larger and longer trials for SLE.

Table 1. Efficacy results at week 12.

	Placebo	Orelabrutinib	Orelabrutinib	Orelabrutinib
All Evaluable Patients		**50 mg**	**80 mg**	**100 mg**
N=55	14	14	13	14
SRI-4 response, n (%)	5 (35.7%)	7 (50.0%)	8 (61.5%)	9 (64.3%)
Treatment difference vs. PBO (%)		14.3%	25.8%	28.6%
SLEDAI-2K≥8, N=39	10	10	10	9
SRI-4 response, n (%)	3 (30.0%)	7 (70.0%)	7 (70.0%)	6 (66.7%)
Treatment difference vs. PBO (%)		40.0%	40.0%	36.7%

Note: All evaluable patients at week 12 efficacy data were included in the efficacy analysis.

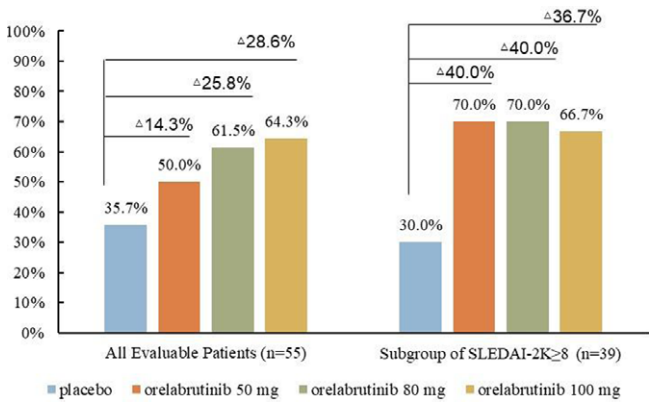

Figure 1. SRI-4 response rates at week 12.

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LB0006

SARILUMAB IN PATIENTS WITH RELAPSING POLYMYALGIA RHEUMATICA: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL (SAPHYR)

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Background: Interleukin-6 (IL-6) is elevated in patients with active polymyalgia rheumatica (PMR) and is associated with disease activity, relapse and severity. Clinical trials with IL-6 receptor (IL-6R) inhibitors in PMR showed higher remission rates and reduced glucocorticoid (GC) use vs GC alone.[1-4]
Objectives: The SAPHYR study (NCT03600818) assessed the efficacy and safety of sarilumab (SAR), a fully human anti IL-6Rα monoclonal antibody, with a 14 week (wk) GC taper in patients with steroid resistant active PMR who flared on ≥7.5 mg/day prednisone or equivalent.
Methods: Patients were randomized (1:1) to 52 wks of treatment with SAR 200 mg every 2 wks (Q2W) + 14 wk GC tapered regimen (SAR arm) OR placebo Q2W + 52 wk GC tapered regimen (comparator arm). The primary endpoint was the proportion of patients achieving sustained remission at wk 52, defined as disease remission by wk 12, absence of disease flare, CRP normalization from wks 12 to 52 and adherence to the per protocol GC taper from wks 12 to 52.
Results: The study was terminated early due to protracted recruitment timelines during the COVID-19 pandemic, resulting in 118 of the intended 280 patients recruited between Oct 2018 and Jul 2020, and 117 were treated (SAR n=59, comparator n=58). The demographics were balanced; patients were primarily female, Caucasian, and a median age of ~70 years (Table 1). Overall, 78 patients completed the treatment (SAR n=42; comparator n=36). Primary reasons for treatment discontinuation were adverse events (AEs; SAR n=7, comparator n=4) and lack of efficacy (SAR n=4, comparator n=9). Sustained remission rate was significantly higher in the SAR arm vs the comparator arm (28.3% vs 10.3%; P=0.0193). Results of a sensitivity analysis excluding CRP from the sustained remission definition was consistent with the primary analysis (31.7% vs 13.8%; P=0.0280). All sustained remission components favored SAR (Figure 1). Patients in the SAR arm were 44% less likely to have a flare after

achieving clinical remission vs the comparator arm (16.7% vs 29.3%; HR 0.56; 95% CI 0.35–0.90; P=0.0158). The comparator arm required more additional GCs vs the SAR arm, mainly due to PMR flare (median difference in actual and expected cumulative dose 199.5 mg vs 0.0 mg; P=0.0189). The cumulative GC toxicity index scores numerically favored SAR but the difference was not statistically significant. PMR activity scores improved in the SAR arm vs the comparator arm (LS mean -15.57 vs -10.27, nominal P=0.0002). Patient reported outcomes (eg, physical and mental health component scores, disability index, etc) favored SAR (Figure 1). Incidence of treatment-emergent AEs (TEAEs) was numerically higher in the SAR arm vs the comparator arm (94.9% vs 84.5%) and included neutropenia (15.3%) and arthralgia (15.3%) in the SAR arm, and insomnia (15.5%) in the comparator arm. Conversely, the frequency of serious AEs was higher in the comparator arm vs the SAR arm (20.7% vs 13.6%). No deaths were reported.

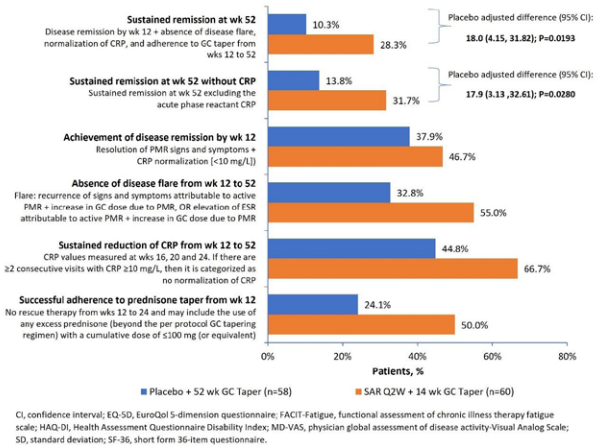
Table 1. Demographics and baseline characteristics

Parameter	SAR + 14 wk GC taper (n=60)	Placebo + 52 wk GC taper (n=58)
Age, median years (range)	69 (51–88)	70 (52–88)
Sex (female), n (%)	45 (75.0)	37 (63.8)
Race, n (%)		
Caucasian	50 (83.3)	48 (82.8)
Asian	1 (1.7)	2 (3.4)
Not reported	9 (15.0)	8 (13.8)
PMR duration (diagnosis date to baseline),* median days (range)	292 (78–3992)	310 (66–2784)
Any prior disease modifying anti rheumatic drugs, n (%)		
Methotrexate	5 (8.3)	10 (17.2)
Leflunomide	2 (3.3)	1 (1.7)
Azathioprine	0	1 (1.7)
Hydroxychloroquine	1 (1.7)	1 (1.7)
Adalimumab	1 (1.7)	0
Tocilizumab	0	1 (1.7)
CRP (mg/L), median (range)	6.8 (0.5–38.2)	5.7 (0.1–62.3)
Erythrocyte sedimentation rate (mm/h), median (range)	25.0 (2.0–115.0)	22.0 (5.0–85.0)

*SAR n = 54; comparator n= 50.

Conclusion: SAR + 14 wk GC taper demonstrated significant efficacy vs the comparator arm in steroid refractory PMR patients, including clinically meaningful improvement in quality of life. Safety was consistent with the known safety profile of SAR.

Figure. Summary of disease remission, disease flare, CRP reduction, and adherence to prednisone taper



CI, confidence interval; EQ-5D, EuroQol 5-dimension questionnaire; FACIT-Fatigue, functional assessment of chronic illness therapy fatigue scale; HAQ-DI, Health Assessment Questionnaire Disability Index; MD-VAS, physician global assessment of disease activity-Visual Analog Scale; SD, standard deviation; SF-36, short form 36-item questionnaire.

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