

LY2439821, a novel anti-IL-17 mAb: Safety, tolerability and efficacy in patients with RA on background DMARDs.

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Purpose: LY2439821 (LY) is an anti-IL-17 antibody that neutralizes the biologic activity of IL-17, a key cytokine in RA pathogenesis.

Method: This was an early phase clinical study to investigate the safety, tolerability, PK, and evidence of efficacy of LY in pts with RA taking at least one DMARD. The study was a randomized, placebo (PBO)-controlled, double-blind study, conducted in 2 parts. The study had dual primary endpoints: safety after single and multiple dosing, and efficacy after multiple dosing. Part A was an initial single dose escalation evaluating safety, which was used to enable multiple dosing. In Part B, 4 treatment groups were dosed IV in parallel every 2 wks for 8 wks (5 treatments per pt), at 0.2, 0.6, or 2.0 mg/kg of LY or PBO, and were evaluated for an additional 8 weeks. The primary efficacy endpoint was the DAS28 at Wk 10.

Results: In Part B, mean baseline characteristics were similar between groups. Mean baseline findings include : age 54.4 to 59.6 yrs; disease duration 6.1 to 10.9 yrs; DAS28 5.8 to 6.1; CRP 1.80 to 2.47 mg/dL; ESR 61.0 to 69.1 mm/hr; Tender Joint Counts (28) 15.7 to 18.2; Swollen Joint Count (28) 11.8 to 13.7; HAQ-DI 1.4 to 1.8. 77 pts were randomized to PBO (18), or LY at 0.2 mg/kg (19), 0.6 mg/kg (20), or 2.0 mg/kg (20). Multiple administrations of LY improved the signs and symptoms of RA (Table). Statistical differences in the mean change from baseline in DAS28 (each dose level compared to PBO) and ACR20 responses (0.2 mg/kg and all LY groups compared to PBO) were detected as early as 1 week after the first dose. At Week 10, statistical differences in the mean change from baseline in DAS28 were detected between the 0.2, 2.0 mg/kg, and all LY combined groups vs. PBO. There were no deaths. Three LY pts (1 at 0.6 and 2 at 2.0 mg/kg) were discontinued from study drug treatment due to AEs, and 1 LY pt was discontinued due to pre-treatment laboratory abnormalities discovered after administration of the first dose. There was 1 reported SAE (skin ulcer in a 0.6 mg/kg pt), classified as unrelated to study drug. No serious infections or malignancies were noted. The incidence of AEs was generally similar between groups.

	PBO	LY 0.2 mg/kg	LY 0.6 mg/kg	LY 2.0 mg/kg
Week 2				
DAS28	-0.5	-1.1*	-1.0*	-1.2*
ACR20 (%)	0	26.3*	30.0*	45.0*
ACR50 (%)	0	5.3	5.0	5.0
ACR70 (%)	0	0	0	0
Week 10				
DAS28	-1.7	-2.3*	-2.2	-2.4*
ACR20 (%)	55.6	73.7	70.0	90.0*
ACR50 (%)	16.7	42.1	40.0	35.0
ACR70 (%)	5.6	26.3	20.0	25.0

NOTE: DAS28 values represent change from baseline.

* Significant at the 0.05 level compared to placebo.

Week refers to number of weeks on active treatment.

Conclusion: IL-17 is a novel cytokine target. IV administrations of LY improved the signs and symptoms of RA early during treatment and confirms the rationale for targeting IL-17. In addition, LY was well-tolerated.