

[2009] SAFETY, TOLERABILITY AND EVIDENCE OF EFFICACY OF INTRAVENOUS LY2439821 IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING BACKGROUND ORAL DMARDs

MC Genovese¹, F Van den Bosch², SA Roberson³, J Sloan-Lancaster^{3 1} Stanford University, Palo Alto, CA, USA; ² University Hospital Ghent, Ghent, Belgium; ³ Chorus, Eli Lilly & Co., Indianapolis, IN, USA.

Background: TNF α inhibitors and other biologic agents, though effective in rheumatoid arthritis (RA), do not work for all patients (pts), response may diminish, and safety issues have been identified with all agents. LY2439821 (LY) is an anti-IL-17 antibody that neutralizes the biologic activity of IL-17, a key cytokine in RA pathogenesis.

Objectives: This was an early phase clinical development study to investigate the safety, tolerability, PK, and evidence of efficacy of LY in pts with RA taking at least one disease-modifying anti-rheumatic drug (DMARD).

Methods: A randomized, placebo (PBO)-controlled, double-blind study, conducted in 2 parts. The study had dual primary endpoints: safety and tolerability after single and multiple dosing, and evidence of efficacy after multiple dosing. Part A was an initial single dose escalation, evaluating safety and tolerability, 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. Patients were evaluated for an additional 8 weeks (16 weeks total). The primary efficacy endpoint was the Disease Activity Score (DAS28) at Wk 10.

Results: In Part B, mean baseline characteristics were similar between groups. Most patients were caucasian women. 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 LY group compared to PBO) were detected as early as 1 week after the first dose of LY. At Week 10, statistical differences in the mean change from baseline in DAS28 were detected between the all LY combined group and PBO, between the 2.0 LY group and PBO, and between the 0.2 LY group and PBO. There were no deaths. Three LY pts (1 at 0.6 mg/kg, 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 the first dose had been administered. 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.

Summary of Efficacy Results

	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.

Conclusions: IL-17 is a novel cytokine target. IV administrations of LY improved the signs and symptoms of RA in this population of pts taking concomitant DMARDs early during treatment and confirms the rationale for targeting IL-17. In addition, LY was well-tolerated and not associated with any severe or significant adverse effects clearly attributable to study drug.

Abstract Session: Topic 11; Rheumatoid Arthritis - other biologic treatment