

Phase 2 Study of Safety and Efficacy of a novel anti-BAFF monoclonal antibody, in Patients (Pts) with RA Treated with Methotrexate (MTX)

MC Genovese¹, E. Mociran², M. Biagini³, S. Bojin⁴ and J. Sloan-Lancaster⁵

¹Stanford U, Palo Alto; ²County Hospital, Baia Mare, Romania; ³County Hospital, Bacau, Romania; ⁴County Hospital, Covasna, Romania; ⁵Eli Lilly, Indianapolis, IN

Purpose: B cell activating factor (BAFF) is a survival factor for peripheral B lymphocytes which exists in both cell surface and soluble forms. Dysregulated BAFF expression may contribute to autoimmune diseases via effects on abnormal B lymphocyte activation, proliferation, survival, and immunoglobulin secretion. LY2127399 is a novel monoclonal antibody binding both cell surface and soluble BAFF. This study was designed to explore the tolerability and efficacy of LY2127399 in Pts with active RA.

Method: This was a 24-week, randomized, placebo-controlled, double-blind study which enrolled 136 Pts with active RA despite treatment with MTX. Pts continued stable doses of MTX and received 1 of 3 dose levels (30, 60, or 160 mg) of LY2127399 or placebo (PBO) intravenously for a total of 3 doses at 3-week intervals (Weeks 0, 3, 6). Response was assessed for efficacy, PK/PD and safety. The primary endpoint was ACR20 response vs. PBO at Week 16.

Results: ACR20/50/70 and DAS28 responses showed that RA signs and symptoms improved more in Pts at each LY2127399 dose as compared with PBO. The primary objective was achieved at all LY2127399 treatment levels (Table; one-sided χ^2 test no adjustment for multiplicity), and ACR20 treatment differences remained significant at end of study (69.7%, 67.6% and 63.6% for 30, 60, 160mg respectively vs. 26.5% for PBO, $p \leq 0.001$). Initial transient increases were shown in total (CD20⁺) B cells in all LY2127399 treatment groups, followed by significant reductions. Importantly, B cells were not completely depleted. Mean reductions at Week 24 were 33.5%, 50.8% and 33.3% for CD20⁺ B cells, and 35.8%, 66.9% and 63.6% for IgD⁺/CD27⁻ B cells, for the 30, 60 and 160 mg treatment groups respectively, vs. 18.3% and 17.7% respectively for placebo. Memory (IgD⁻/CD27⁺) B cells also increased in all LY2127399 groups compared with PBO by Week 1, with a return toward baseline by end of study. The nature and frequency (41% to 44%) of AEs were similar across groups; serious AEs were reported in 5 (4.9%) LY2127399- Pts and 3 (9.1%) PBO- Pts; serious infection was reported in 1 (1.0%) LY2127399- Pts and 1 (3.0%) PBO- Pts. IgM levels decreased significantly more in all LY2127399 groups combined vs. PBO; decreases in mean IgG and IgA levels were not significant compared with PBO.

Wk 16 results	LY2127399 (30 mg) n=34	LY2127399 (60 mg) n=34	LY2127399 (160 mg) n=34	PBO n=34
ACR20 (Primary) % (p value)	57.6 (0.010)	67.6 (<0.001)	51.5 (0.033)	29.4
ACR50	42.4	32.4	21.2	8.8

% (p value)	(<0.001)	(0.008)	(0.077)	
ACR70	12.1	8.8	3.0	0.0
% (p value)	(0.018)	(0.038)	(0.153)	
Mean ACR-N	35.1	34.8	25.8	14.1
% (p value)	(0.001)	(0.001)	(0.101)	
Pts with DAS28 <2.6	9.1	14.7	0.0	0.0
%				
Change in DAS28	-1.54	-1.84	-1.41	-0.58
LS Mean (p value)	(<0.001)	(<0.001)	(0.001)	
Change in CD20 B Cells	-75.7	-48.4	-40.5	-3.6
(Cells/uL)	[129.7]	[197.1]	[152.8]	[173.9]
LS Mean [baseline]				
(p value)	(<0.001)	(0.012)	(0.040)	

Conclusions: LY2127399 given intravenously as 3 infusions was well-tolerated and reduced the signs and symptoms of RA. Reduction of RA symptoms was not contingent upon complete B cell depletion. These results support further dose exploration of LY2127399 in RA.