SAT0237

EFFICACY OF BARICITINIB IN PATIENTS WITH RHEUMATOID ARTHRITIS WHO FAILED 2 OR MORE DMARDS

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Background: Baricitinib (Bari) is an oral Janus Kinase (JAK)1/JAK2 inhibitor in development for patients with active rheumatoid arthritis (RA). In Phase 3 studies, Bari has demonstrated clinical efficacy and has a favorable safety profile.

Objectives: To evaluate Bari 2- and 4-mg in patients who have failed multiple DMARDs, across several studies.

Methods: Data from the subgroup of patients who had failed ≥ 2 DMARDs, including approx. one-half of patients in RA-BUILD (csDMARD-IR) and RA-BEAM (MTX-IR) and all patients from RA-BEACON (bDMARD-IR) were assessed, post hoc, for comparison of Bari 2-mg and 4-mg to placebo across time points using the following measures: ACR20, ACR50, ACR70, SDAI, CDAI, DAS28-CRP, HAQ-DI, and radiographic assessment of structural damage (mTSS), as well as safety. For patients who had failed ≥ 2 DMARDs from RA-BEAM, a comparison was also made between Bari 4-mg and adalimumab.

Results: In the ≥ 2 DMARD-IR populations from RA-BEACON, RA-BUILD, and RA-BEAM, $>95\%$ had failed MTX as one of the DMARDs. Compared to PBO in this population, Bari resulted in statistically significantly greater improvement in efficacy measures at Week 24, including physical function (Table). In the ≥ 2 DMARD-IR population from RA-BEAM (all patients received background MTX), Bari 4-mg was associated with greater improvements compared to adalimumab (table 1 and figure 1). Compared to PBO, Bari 4-mg statistically significantly inhibited structural progression at Week 24 in the ≥ 2 DMARD-IR subsets of RA-BEAM and RA-BUILD. The overall safety profile of Bari 4-mg in the ≥ 2 DMARD-IR population was consistent with findings from the overall baricitinib-treated population.

^{*}Data are the proportion (%) of pts who achieved the response at Week 24 (non-responder imputation), unless otherwise indicated. [§]Approximately 56% of patients in RA-BUILD and 54% of patients in RA-BEAM failed ≥ 2 DMARDs. ^Δleast squares mean change from baseline (modified last observation carried forward). [¶]mTSS data are as randomized using last observation carried forward. ^{*} $p \leq 0.05$, ^{**} $p \leq 0.01$, ^{***} $p \leq 0.001$ for Bari 4-mg or Bari 2-mg vs. PBO; [†] $p \leq 0.05$ Bari 4-mg vs. ADA

Conclusions: These data demonstrate that a dose response is present between Bari 2-mg and Bari 4-mg, with both doses providing benefit in the patients who failed multiple DMARDs in the phase 3 program by improving signs and symptoms, physical function, and structure.

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SAT0238

RAPID ELEVATION OF ERYTHROCYTE METHOTREXATE-POLYGLUTAMATE3 (MTX-PG3) LEVELS RELATED TO THE EFFICACY OF MTX IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA).

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Background: MTX is transported into cells and retained long after polyglutamation. Recently, it has been described that the response to MTX treatment is related to the intracellular MTX-polyglutamate (MTX-PG) levels, but little is known about its details and determinants¹.

Objectives: To clarify the association of erythrocyte concentrations of MTX-PGs (PG1 to PG4) with the efficacy of MTX in 35 MTX naïve patients with RA.

Methods: We measured erythrocyte MTX-PGs at 4, 12, 24, and 48 weeks after administration of MTX using liquid chromatography (LC)-mass spectrometry (MS)/MS assay. The associations of MTX-PG concentrations with disease activity and the 9 SNPs including 5 SNPs reported for associations with MTX-efficacy were analyzed.

Results: As shown in the figure, MTX-PG1 and PG2 elevated at week 4, and total MTX-PGs as well as MTX-PG3 and MTX-PG4 increased until week 12. The MTX-PG2 fraction (as percentage of total) was 26% to 29% and almost constant throughout the course. MTX-PG3 and MTX-PG4 fractions were gradually elevated over time, although MTX-PG1 fraction was decreased. A negative association of Disease Activity Score in 28 joints (DAS28) at week 4, 12 and 24 was observed with levels of MTX-PG2 ($p=0.008$), MTX-PG3 ($p=0.0045$), MTX-PG4 ($p=0.0142$) and total MTX-PG ($p=0.023$). On the other hand, Δ DAS28 (change in DAS28 scores from baseline) was positively correlated to fraction of MTX-PG3 ($p=0.011$) but negatively correlated to that of MTX-PG1 ($p=0.0071$). At week 12 and 24, MTX-PG2 fraction was higher ($p=0.0783$) in the patients who achieved the EULAR good response criteria than in those who did not.

MTX-PG3 levels were associated with SLC19A1c.80G>A and FMO2_c.585A>G, and the fraction of MTX-PG2 in total MTX-PGs was associated with GGH c.452C>T and with FMO2_c.585A>G.

Erythrocyte concentrations (nmol/ml) of total MTX-PGs and the PG2 fractions (%) in total MTX-PGs

Conclusions: This study suggests that rapid elevation of erythrocyte MTX-PG3 levels from MTX-PG1 through MTX-PG2 and higher distribution of MTX-PG3 is

important to exert certain efficacy of MTX. We previously reported in retrospective study that MTX-PG concentration in RA patients keeping remission for long time was associated with several SNPs²), and some of the results were confirmed in this prospective study.

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SAT0239

RAPID RESPONSE WITH UPADACITINIB TREATMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO CSDMARDS OR bDMARDS

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Background: Upadacitinib (UPA), an oral JAK inhibitor selective for JAK1, demonstrated efficacy in patients (pts) with moderate to severe rheumatoid arthritis (RA) with an inadequate response (IR) to csDMARDs or bDMARDs in the SELECT-NEXT¹ and SELECT-BEYOND² trials, respectively.

Objectives: To investigate the speed of response to UPA across disease measures in csDMARD- and bDMARD-IR pts.

Methods: 661 pts in NEXT and 498 in BEYOND received UPA 15 mg or UPA 30 mg once daily (QD) or placebo (PBO) for 12 weeks (wks)^{1,2}. Time to first achievement of clinically meaningful outcomes, including ACR20/50, DAS28-CRP≤3.2 and Low Disease Activity (LDA) measures of CDAI (≤10) and SDAI (≤11) was evaluated. The cumulative incidences of ACR20/50, DAS28-CRP≤3.2 and LDA by CDAI and SDAI over 12 wks were estimated. Hazard ratios between UPA and PBO were obtained using Cox proportional hazards model with treatment group, corresponding baseline values and main stratification factors, without control for multiple comparisons. All analyses were based on observed data without imputation.

Table 1. Summary of Median Time (in Weeks) to Achieve First Response Over 12 Weeks

		csDMARD-IR			bDMARD-IR		
		N	Median (Q1, Q3)	HR	N	Median (Q1, Q3)	HR
ACR20	PBO	221	12.1 (3.9, NE)		169	11.9 (2.3, NE)	
	UPA 15	219	4.1 (2, 12.1)	2.1***	164	4.1 (1.3, 12.1)	2.0***
	UPA 30	216	2.4 (1.3, 8.1)	2.5***	164	2.7 (1.6, 12.1)	2.0***
ACR50	PBO	221	12.9 (4.2, NE)		169	NE (NE, NE)	
	UPA 15	219	12.3 (4.3, NE)	2.4***	164	12.7 (8, NE)	2.8***
	UPA 30	216	8.6 (4.1, 13.4)	3.4***	165	12.1 (4.1, NE)	3.6***
DAS28-CRP ≤3.2	PBO	221	NE (12.1, NE)		166	NE (12.2, NE)	
	UPA 15	214	12.1 (4.1, 13)	2.9***	163	12.2 (4.1, NE)	2.8***
	UPA 30	215	8.1 (2.6, 12.7)	3.9***	163	8.7 (4.1, 13)	3.2***
CDAI LDA	PBO	210	NE (12.1, NE)		159	NE (NE, NE)	
	UPA 15	206	12.3 (8, 13)	2.2***	156	13.1 (8.1, NE)	2.1***
	UPA 30	209	12.1 (4.1, 13.3)	2.6***	156	12.3 (4.3, NE)	2.5***
SDAI LDA	PBO	210	NE (12.1, NE)		160	NE (12.3, NE)	
	UPA 15	206	12.3 (4.1, 13)	2.6***	156	12.4 (7.7, NE)	2.2***
	UPA 30	209	12 (4.1, 13.4)	3.2***	156	12.1 (4.1, NE)	2.7***
TK68 50% Improvement	PBO	221	8.1 (2.3, NE)		169	8.1 (2.1, 12.4)	
	UPA 15	220	4.1 (2, 12.1)	1.6***	164	4.1 (1.3, 12.1)	1.5**
	UPA 30	216	4.1 (2.1, 8.6)	1.7***	165	4.1 (2, 8.4)	1.5**
SK66 50% Improvement	PBO	221	4.4 (2.1, 12.9)		169	4.1 (2.1, 12.3)	
	UPA 15	220	4.0 (1.4, 8.1)	1.5***	164	2.3 (1.3, 8.4)	1.4**
	UPA 30	216	2.2 (1.3, 8.1)	1.6***	165	3.9 (1.4, 8.1)	1.4**

HR, hazard ratio; NE (not estimable) indicates that the response was not reached within the 12-week period. ***p<0.001

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Results: Pts had a disease duration of 7 and 13 years in NEXT and BEYOND respectively.^{1,2} In BEYOND, pts were treatment-refractory as evidenced by 53% having received ≥2 prior bDMARDs². Median times to achieve ACR20 were similar, irrespective of pt population, being 4 wks for UPA 15 mg QD and 2–3 wks for

UPA 30 mg QD vs 12 wks on PBO (p<0.001). In general, the median times to achieve ACR50 and DAS28-CRP≤3.2 for UPA 15 mg and 30 mg QD were ~12 wks and ~8 wks for both csDMARD-IR and bDMARD-IR pts, whereas the median was not reached for pts on PBO during the first 12 wks (p<0.001, table 1). The median time to LDA by CDAI and SDAI was ~12 wks across UPA doses and populations, but was not reached for pts receiving PBO within that time. Pts receiving UPA were 2–4 times more likely to achieve clinical responses vs pts receiving PBO. In general, both UPA doses performed similarly across pt populations, with numerically quicker responses observed in pts receiving UPA 30 mg vs UPA 15 mg QD. Median times to achieve 20% and 50% improvements in tender and swollen joint counts were 1–2 wks and 2–4 wks respectively, for both UPA doses, irrespective of pt population. Median times to achieve 20% improvements in morning stiffness duration and severity were approximately 2 wks in each of the UPA arms vs 4 wks on PBO (p<0.001).

Conclusions: Pts receiving UPA at either 15 mg or 30 mg QD were more likely to achieve clinical responses at significantly earlier time points when compared with pts receiving PBO. Irrespective of being csDMARD-IR or bDMARD-IR, times to achieve various clinical responses were consistent between pt populations.

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SAT0240

VAGUS NERVE STIMULATION IN PATIENTS WITH RHEUMATOID ARTHRITIS: TWO-YEAR SAFETY AND EFFICACY

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Background: Rheumatoid arthritis (RA) is a debilitating chronic disease with an unmet need for additional therapeutic approaches. Activating neuro-immune reflex pathways by stimulation of the vagus nerve (VNS) could represent a novel means of treating RA [1] and other immune-mediated inflammatory diseases. Last year we reported a 12-week proof-of-concept study using a VNS device, approved for drug-resistant epilepsy, showing reduction in the DAS28-CRP clinical disease activity score, with concomitant reductions in TNF and IL-6 levels [2].

Objectives: To understand the long term safety and efficacy of this novel treatment approach, we followed the patients in a 24 months long-term extension study and report on the safety and clinical efficacy data.

Methods: VNS devices were implanted into 17 RA patients, mostly with insufficient response to multiple conventional and biologic disease-modifying antirheumatic drugs (DMARDs), on stable background of methotrexate (≤25 mg weekly) therapy. The devices electrically stimulated the vagus nerve, 1–4 min/day, over a 12 week open label period. On completion, subjects were offered to enroll into a follow-up study, where the study physicians were given flexibility to alter VNS dosing parameters and/or to add a biologic DMARD to the treatment regimen. DAS28-CRP and Health Assessment Questionnaire-Disability Index (HAQ-DI) were collected over 2 years.

Results: All subjects electively continued on VNS treatment through 24 months of the long term follow-up study. Biologic DMARDs were started in 1 and restarted in 8 of 17 subjects; of these, 4 were non-responders to VNS, and 5 had stable improvement but had not yet achieved disease remission on VNS alone (table 1). At the start of the follow-up study, the mean DAS28–28 and HAQ-DI were significantly reduced compared to the pre-implant baseline (mean difference±SE in DAS28-CRP = -1.60±0.37, p<0.0001; mean difference±SE in HAQ-DI = -0.44±0.21, p<0.037), and the depth of effect was retained through 24 months. At 24 months, there was no significant difference in DAS28-CRP between the subjects using VNS monotherapy or those using a combination of VNS and biologic