SAT0244

IMPACT OF 12 WEEKS OF UPADACITINIB TREATMENT ON INDIVIDUAL AND COMPOSITE DISEASE MEASURES IN PATIENTS WITH RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO CONVENTIONAL SYNTHETIC OR BIOLOGIC DMARDS

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Background: Upadacitinib (UPA), an oral, JAK1-selective inhibitor, demonstrated efficacy through 12 and 24 weeks (wks) in phase 3 trials of patients (pts) with active rheumatoid arthritis (RA) and inadequate response (IR) to csDMARDs and bDMARDs, respectively.^{1,2} Efficacy evaluations at Wk 12 are an important assessment point according to T2T recommendations.³

Objectives: To assess the impact of UPA at 12 wks on individual and composite measures of RA disease activity.

Methods: Pts received UPA 15 mg or 30 mg once daily (QD) or PBO for 12 wks in two phase 3 trials. SELECT NEXT¹ and SELECT BEYOND² enrolled csDMARD- and bDMARD-IR pts, respectively. For this investigation, responses at Wk 12, were defined as $\geq 50\%$ improvement in ACR components. Among ACR50 responders, the proportions of pts achieving $\geq 50\%$ improvement in all 7 components of the ACR response criteria [Tender Joint Count (TJC68), Swollen Joint Count (SJC66), Pt Global Assessment (PtGA), Physician Global Assessment (PhGA), Pt Pain, Health Assessment Questionnaire-Disability Index (HAQ-DI), and high sensitive C-reactive protein (hsCRP)] were assessed. Differences in the cumulative distributions of CDAI, DAS28-CRP, and SDAI between baseline (BL) and Wk 12 were assessed. All analyses were based on observed data without imputation.

Results: Pts in both studies, on average, had established, moderate to severe RA at BL, with (mean) disease durations of 7.3 and 13.2 years, CDAI of 38.2 and 40.9, in csDMARD-IR and bDMARD-IR pts, respectively; 53% of bDMARD-IR pts had exposure to ≥ 2 bDMARDs.^{1,2} In both populations, significantly more pts on UPA vs PBO achieved $\geq 50\%$ improvement in each ACR component at Wk 12 (Table). Among pts who achieved ACR50 at Wk 12, approximately one-half of the csDMARD-IR and one-third of the bDMARD-IR pts achieved $\geq 50\%$ improvement in all 7 ACR components. While there were no differences at BL, cumulative distributions of CDAI, DAS28-CRP, and SDAI separated by treatment at Wk 12 ($p < 0.001$); for the lowest quartiles for UPA 15 mg and 30 mg vs PBO, CDAI levels dropped to 6.2 and 5.1 vs 12.5 in csDMARD-IR; and 7.2 and 8.2 vs 13.1 in bDMARD-IR.

		SELECT-NEXT			SELECT-BEYOND		
		(csDMARD-IR)			(bDMARD-IR)		
		N	n (%)	Δ from	N	n (%)	Δ from
TJC $\geq 50\%$ Improvement	PBO	207	95 (45.9)	-	147	68 (46.3)	-
	UPA 15	210	140 (66.7)***	20.8***	157	116 (73.9)***	27.6***
	UPA 30	201	143 (71.1)***	25.2***	149	105 (70.5)***	24.2***
SJC $\geq 50\%$ Improvement	PBO	207	114 (55.1)	-	147	81 (55.1)	-
	UPA 15	210	153 (72.9)***	17.8***	157	123 (78.3)***	23.3***
	UPA 30	201	158 (78.6)***	23.5***	149	109 (73.2)***	18.1***
Pain $\geq 50\%$ Improvement	PBO	206	42 (20.4)	-	145	34 (23.4)	-
	UPA 15	207	112 (54.1)***	33.7***	156	67 (42.9)***	19.5***
	UPA 30	200	111 (55.5)***	35.1***	146	70 (47.9)***	24.5***
PtGA $\geq 50\%$ Improvement	PBO	206	49 (23.8)	-	145	33 (22.8)	-
	UPA 15	207	108 (52.2)***	28.4***	156	73 (46.8)***	24.0***
	UPA 30	200	109 (54.5)***	30.7***	147	74 (50.3)***	27.5***
PhGA $\geq 50\%$ Improvement	PBO	192	74 (38.5)	-	137	56 (40.9)	-
	UPA 15	193	129 (66.8)***	28.3***	150	97 (64.7)***	23.6***
	UPA 30	187	140 (74.9)***	36.4***	137	94 (68.6)***	27.7***
HAQ-DI $\geq 50\%$ Improvement	PBO	206	48 (23.3)	-	145	22 (15.2)	-
	UPA 15	206	91 (44.2)***	20.9***	156	41 (26.3)*	11.1*
	UPA 30	200	83 (41.5)***	18.2***	146	41 (28.1)**	12.9**
hsCRP $\geq 50\%$ Improvement	PBO	207	38 (18.4)	-	146	39 (26.7)	-
	UPA 15	209	159 (76.1)***	57.7***	155	114 (73.5)***	46.6***
	UPA 30	201	145 (72.1)***	53.7***	146	100 (68.5)***	41.6***
$\geq 50\%$ Improvement in all 7 ACR	PBO	32	2 (6.3)	-	20	2 (10)	-
	UPA 15	84	38 (45.2)***	38.9***	56	19 (33.9)	23.9
	UPA 30	94	39 (41.5)***	35.2***	58	19 (32.8)	22.6

*, **, *** $p < .05$, .01 and .001 respectively for comparisons of UPA vs PBO; delta (Δ) = difference

Conclusions: In pts with an insufficient response to either csDMARDs or bDMARDs, treatment responses at 12 wks were observed in significantly higher proportions with UPA vs PBO. Favorable effects with UPA were seen in the composite scores and the individual parameters, including PROs and acute-phase reactants.

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SAT0245

AZD9567: A NOVEL ORAL SELECTIVE GLUCOCORTICOID RECEPTOR MODULATOR, DEMONSTRATED TO HAVE AN IMPROVED THERAPEUTIC RATIO COMPARED TO PREDNISOLONE IN PRE-CLINICAL STUDIES, IS SAFE AND WELL TOLERATED IN FIRST CLINICAL STUDY.

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Background: Glucocorticoids (GC) are highly effective in the treatment of inflammatory diseases but chronic treatment is limited by severe adverse effects including hyperglycemia and bone re-modelling. AZD9567 is a novel, orally delivered, non-steroidal Selective Glucocorticoid Receptor Modulator (SGRM) with the potential to demonstrate an improved therapeutic ratio (TR) compared to steroidal GC such as prednisolone.

Objectives: To investigate the effects of AZD9567 and prednisolone on biomarkers of inflammation, glucose metabolism and bone re-modelling in pre-clinical models. To confirm the inhibition of inflammatory biomarker production and to evaluate safety and pharmacokinetics (PK) of AZD9567 in a first clinical study.

Methods: The effects on biomarkers of gluconeogenesis (tyrosine aminotransferase, TAT mRNA), bone re-modelling (osteoprotegerin, OPG mRNA) and anti-inflammatory activity (TNF α) were evaluated *in vitro* using human hepatocytes, an osteoblast cell line and whole blood, respectively. *In vivo*, effects on plasma insulin and osteocalcin levels were compared with inhibition of whole blood TNF α release in rats. Efficacy was evaluated in an adjuvant-induced rat arthritis model. In a human single ascending dose study the effect of AZD9567 on TNF α inhibition was investigated, together with assessment of safety profile and PK.

Results: Potent *in vitro* anti-inflammatory activity (IC₅₀, 6.2 nM, 7-fold more potent than prednisolone) was observed, whilst no effect on TAT mRNA expression in human hepatocytes was detected for AZD9567 (prednisolone EC₅₀ 92 nM). This resulted in a substantially better TR compared to prednisolone. Furthermore, AZD9567 showed a 7-fold superior TR compared to prednisolone based on OPG mRNA expression in human osteoblasts. An improved profile for AZD9567 was also demonstrated *in vivo* in the rat (TR of 7.5 for osteocalcin and 3.6 for insulin). Efficacy was demonstrated in the rat arthritis model where an inhibition of joint inflammation was observed (ED₅₀ 0.1 mg/kg). In human, AZD9567 was safe and well tolerated after single doses (2–155 mg). The PK properties showed a fast absorption with a median t_{max} of 0.50 to 1.25 hour and a dose-dependent increase in exposure, with a mean terminal half-life of 3.9 to 6.4 hours, suitable for a once daily dosing regimen. TNF α release was inhibited in a concentration-dependent manner (IC₅₀, 5.2 nM), consistent with pre-clinical findings.

Conclusions: In pre-clinical models, AZD9567 demonstrated anti-inflammatory activity with a reduced effect on gluconeogenesis and biomarkers of bone re-modelling compared to prednisolone. Single oral dosing of AZD9567 was well tolerated and showed good PK properties in healthy subjects. These results support that AZD9567 has the potential to improve the treatment of several inflammatory diseases with a better TR compared to prednisolone. AZD9567 is currently in clinical evaluation in rheumatoid arthritis.

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