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 BILOGIC DMARDS

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Background: Upadacitinib (UPA), an oral, JAK1-selective inhibitor, demonstrated efficacy through 12 and 24 weeks (wk) 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 ≥50% improvement in ACR components. Among ACR50 responders, the proportions of pts achieving ≥50% improvement in all 7 components of the ACR response criteria [Tender Joint Count (TJC68), Swollen Joint Count (SJc66), Pt and Physician Global Assessment (PtGA, PhysGA), CDAI, DAS28-CRP] 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 12.2 yrs, CDAI of 38.2 and 40.9, in csDMARD- and bDMARD-IR pts, respectively; 53% of bDMARD-IR pts received UPA 15 mg or 30 mg or PBO for 12 wks (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 ≥50% improvement in all 7 ACR components. While there were no differences in 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.

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.

REFERENCES:

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


Background: Glucocorticoids (GC) are highly effective in the treatment of inflammatory diseases but chronic treatment is limited by severe adverse effects including hyperglycaemia 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 (TNFα) 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 TNFα release. Efficacy was evaluated in an adjuvant-induced arthritis model in a human single ascending dose study the effect of AZD9567 on TNFα 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 TNFα 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 tmax 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. TNFα 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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