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 NEXT[1] and SELECT BEYOND[2] 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 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 ≥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 ≥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.

Proportions of Patients Achieving 50% Improvements in Core Components of the ACR Score at Week 12

		SELECT-NEXT (csDMARD-IR)			SELECT-BEYOND (bDMARD-IR)		
		N	n (%)	Δ from	N	n (%)	Δ from
TJC ≥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 ≥50% Improvement	PBO	207	114 (55.1)	-	147	81 (55.1)	-
	UPA 15	210	153 (72.9)***	17.8***	157	123 (78.3)***	23.2***
	UPA 30	201	158 (78.6)***	23.5***	149	109 (73.2)***	18.1***
Pain ≥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 ≥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 ≥50% Improvement	PBO	192	74 (38.5)	-	137	56 (40.9)	-
	UPA 15	193	129 (66.8)***	28.3***	150	97 (64.7)***	23.8***
	UPA 30	187	140 (74.9)***	36.4***	137	94 (68.6)***	27.7***
HAQ-DI ≥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 ≥50% Improvement	PBO	207	38 (18.4)	-	146	39 (26.7)	-
	UPA 15	209	159 (76.1)***	57.7***	155	114 (73.5)***	46.8***
	UPA 30	201	145 (72.1)***	53.7***	146	100 (68.5)***	41.8***
≥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)	22.8

*, **, *** 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 (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 in rats. Efficacy was evaluated in an adjuvant-induced rat 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 ($IC_{50,u}$6.2 nM, 7-fold more potent than prednisolone) was observed, whilst no effect on TAT mRNA expression in human hepatocytes was detected for AZD9567 (prednisolone EC_{50}92 nM). This resulted in a substantially better TR compared to prednisolone. Furthermore, AZD9567 showed a 7-fold superior TR compared to prednisolone based on OPG mRNA expression in human osteoblasts. An improved profile for AZD9567 was also demonstrated *in vivo* in the rat (TR of 7.5 for osteocalcin and 3.6 for insulin). Efficacy was demonstrated in the rat arthritis model where an inhibition of joint inflammation was observed (ED_{50}0.1 mg/kg). In human, AZD9567 was safe and well tolerated after single doses (2–155 mg). The PK properties showed a fast absorption with a median t_{max} of 0.50 to 1.25 hour and a dose-dependent increase in exposure, with a mean terminal half-life of 3.9 to 6.4 hours, suitable for a once daily dosing regimen. TNFa release was inhibited in a concentration-dependent manner ($IC_{50,u}$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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SAT0246 AT WHICH POINT AND FOR WHICH REASONS ARE ORAL MTX FORMULATIONS SWITCHED TO INJECTABLE ONES IN RA PATIENTS? COMBINED RESULTS FROM 3 INDEPENDENT OBSERVATIONAL AND CLINICAL TRIALS

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Background: MTX is considered as a cornerstone in RA treatment since the 1990s and its injectable forms have proven their enhanced clinical and pharmacological efficacy and safety in case of insufficient response or poor tolerance of oral formulations. Few data are available considering the timepoint at which the route of administration is changed in current practice.

Objectives: The objective of this work was to investigate across 3 independent trials if there was a consistency in patterns of MTX oral ->injectable switches in terms of RA characteristics, MTX dosages (before and after the switch) and reasons of passage.

Methods: Three trials were considered for this work: 1/STRATEGE (observational study designed to investigate the therapeutic strategies used in current practice in RA patients insufficiently responding to initial MTX monotherapy), 2/APRiM (observational study aimed to investigate the treatment adherence of RA patients switching from oral to injectable MTX or between two different MTX prefilled syringes) and 3/SELFi (phase III randomized trial aiming to compare a new MTX autoinjector to the historical MTX prefilled syringe in terms of treatment adherence and functional capacity in RA patients at 6 months). In all three studies we selected baseline data concerning patients switching from oral to injectable MTX at the inclusion visit.

Results:

	STRATEGE N = 151	APRiM N = 270	SELFi N = 98
RA duration, years (mean±SD) (median (min;max))	4.9±6.1 2.8 (0.0; 29.0)	6.6±8.1 3.0 (0.0; 40.0)	4.5±5.9 2.0 (0.2; 30.5)
MTX treatment duration, years (mean±SD) (median (min;max))	3.6±4.5 1.9 (0.0; 24.3)	3.3±4.2 1.4 (0.0; 23.6)	2.5±2.8 1.4 (0.1; 15.4)
DAS28 (mean±SD)	4.4±0.9	3.9±0.9	3.5±1.2
MTX oral dosage at V0, mg/wk (mean±SD)	15.3±3.7	15.0±4.1	14.8±3.8
MTX injectable dosage at the end of V0, mg/wk (mean±SD)	17.0±4.0	16.3±3.8	17.0±4.0
Distribution MTX dosage unchanged/raised/ reduced	50%/45%/ 5%	62%/34%/ 4%	51%/42%/ 7%

Consistent data were observed across the three considered trials concerning the oral/injectable MTX switch. It occurs after about 3 years of treatment, at a DAS28 of 4 and at an average dose of 15 mg/wk (which is consistent with bioavailability data shown before). In most situations, MTX dosage is unchanged or very slightly raised at the switch timepoint. The main switch reasons were "non-achievement of treatment target" and "RA worsening", the safety reasons were mentioned only in 5% of cases.

Conclusions: Our work showed a consistent pattern across 3 independent trials concerning the oral/injectable MTX switch. It generally occurs at 15 mg/wk, the new injectable dosage being either unchanged or very slightly raised as compared to the last oral one. Surprisingly, the MTX route of administration seems to be modified mostly for efficacy reasons, safety issues being anecdotal.

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SAT0247 IMPACT OF GLUCOCORTICOIDS ON EFFICACY AND SAFETY OF TOFACITINIB WITH AND WITHOUT METHOTREXATE AND ADALIMUMAB WITH METHOTREXATE FOR RHEUMATOID ARTHRITIS: RESULTS FROM A PHASE 3B/4 RANDOMISED TRIAL

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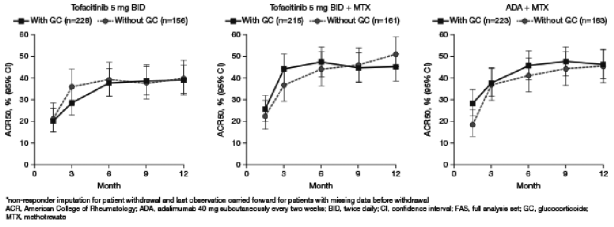
Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Glucocorticoids (GC) are an established therapy in RA that are often used to rapidly reduce pain and inflammation while awaiting the effects of disease-modifying antirheumatic drugs.

Objectives: A post hoc analysis to describe the impact of background GC on the efficacy and safety of tofacitinib with and without methotrexate (MTX) and adalimumab (ADA) with MTX in ORAL Strategy.

Methods: ORAL Strategy (NCT02187055) was a 1-year, double-blind, Phase 3b/4, head-to-head, non-inferiority randomised controlled trial in adult patients (pts) with active RA despite MTX therapy. Pts were randomised 1:1:1 to receive tofacitinib 5 mg twice daily (BID; tofa mono), tofacitinib 5 mg BID + MTX (tofa +MTX) or subcutaneous ADA 40 mg every other week + MTX (ADA+MTX). Pts receiving low-dose GC (≤10 mg/day prednisone or equivalent) before enrolment maintained a stable dose throughout the study period. The following efficacy endpoints were assessed through Month 12 for pts receiving tofa mono, tofa+MTX and ADA+MTX with/without GC: ACR20, ACR50 and ACR70 response rates, proportions of patients achieving low disease activity (LDA; DAS28–4[ESR]≤3.2) and remission (DAS28–4[ESR]<2.6) and change from baseline (BL) in HAQ-DI (ΔHAQ-DI). Safety endpoints were evaluated throughout the study and included adverse events (AEs), serious AEs (SAEs), discontinuations due to AEs and serious infection events (SIEs).

Results: 1146 patients were randomised and treated; low-dose BL GC were received by 228/384 (59.4%) pts receiving tofa mono (mean [SD] BL GC dose: 7.5 [13.7] mg/day), 215/376 (57.2%) pts receiving tofa+MTX (mean [SD] BL GC dose: 6.5 [2.5] mg/day) and 223/386 (57.8%) pts receiving ADA+MTX (mean [SD] BL GC dose: 6.4 [2.6] mg/day). BL demographics and disease characteristics were generally similar across treatment groups, regardless of BL GC use. Efficacy endpoints (ACR50 response rate, LDA and remission rates, ΔHAQ-DI) were generally similar for each treatment group when stratified by GC use (figure 1, table 1; similar results were seen for ACR20/70 response rates – data not shown). GC use did not appear to be associated with higher rates of AEs, discontinuations due to AEs, SIEs and SAEs; some AE rates were higher with MTX than without MTX (table 2). SIEs in pts using GC included herpes zoster (HZ; tofa mono, n=2) and tuberculous meningitis (tofa+MTX, n=1); in pts not using GC, there was 1 event each of cytomegalovirus chorioretinitis (tofa+MTX), pulmonary TB (tofa+MTX), HZ (ADA +MTX) and varicella (ADA+MTX).



*Non-responder imputation for patient withdrawal and last observation carried forward for patients with missing data before withdrawal
ACR, American College of Rheumatology; ADA, adalimumab 40 mg subcutaneously every two weeks; BID, twice daily; CI, confidence interval; FAS, full analysis set; GC, glucocorticoids; MTX, methotrexate

Figure 1. Proportion of patients achieving ACR50 response according to treatment group and GC use (FAS, with imputation*)