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A Phase 3, Randomized, Controlled Trial Comparing Upadacitinib Monotherapy to MTX Monotherapy in MTX-Naïve Patients with Active Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: 3S087 ACR Abstract: RA–Treatments I: JAK Inhibitors (886–891)

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: To compare the clinical efficacy, including inhibition of structural damage, and safety of upadacitinib (UPA), a JAK1-selective inhibitor, as monotherapy, vs methotrexate (MTX) monotherapy, in MTX-naïve patients (pts) with moderate to severely active rheumatoid arthritis (RA).

Methods: In SELECT–EARLY, MTX-naïve pts with active RA who were positive for both RF and ACPA and/or had ≥1 joint erosion were randomized 1:1:1 to once-daily (QD) UPA at 15mg or 30mg, or weekly MTX (titrated by Wk8). Separate primary endpoints were ACR50 at Wk12 (FDA), or the proportion of pts achieving DAS28CRP<2.6 at Wk24 (EMA). Secondary endpoints included mean changes from baseline (Δ BL) in modified Total Sharp Score (mTSS) and proportion of pts with no radiographic progression (mTSS≤0) at Wk24.

Results:

Of 947 randomized pts, 945 received study drug; 840 (88.7%) completed Wk24. ~50% had an RA diagnosis of <6 months and RA symptoms <2 years; Of the 945 pts, 874 (92.5%) had no prior MTX exposure; 706 (74.7%) had no prior csDMARD exposure. Both primary endpoints were met. Significantly more patients receiving UPA 15 and 30mg vs MTX achieved ACR50 responses at Wk12 (52.1% and 56.4% vs 28.3%) and DAS28CRP<2.6 at Wk24 (48.3% and 50.0% vs 18.5%) (**Table 1)**. All ranked secondary endpoints were met: ACR50 at Wk24, improvements in DAS28CRP, HAQ-DI, SF36-PCS, and the proportion of pts achieving DAS28CRP≤3.2 at Wks12 and 24. At Wk24, mean ΔmTSS

were 0.14 and 0.07 vs 0.67; significantly more pts had no radiographic progression on UPA 15 and 30mg vs MTX. LDA and remission by various criteria at Wks12 and 24 were achieved in more pts on UPA vs MTX (nominal p<.001 for all).

Up to Wk24, treatment-emergent adverse events (AEs) and serious AEs were similar in the UPA 15mg and MTX arms, and slightly higher in the UPA 30mg arm **(Table 2)**. AEs leading to discontinuation were similar across arms. A numerically higher proportion of pts on UPA 30mg reported serious infections vs MTX and UPA 15mg, and there were more cases of herpes zoster in the UPA vs MTX arms. Four malignancies, 4 major adverse cardiovascular events (MACE), and 6 deaths were reported **(Table 2)**. Two venous thromboembolic events were reported (1 pulmonary embolism on MTX, 1 deep vein thrombosis on UPA 30mg, none on UPA 15mg). Laboratory abnormalities were consistent with other Phase 2 and 3 studies with UPA.

Conclusion: In MTX-naïve pts, UPA 15 and 30mg QD demonstrated significant and clinically meaningful improvements in RA signs & symptoms vs MTX. Radiographic progression was significantly less with UPA vs MTX. Safety events were consistent with Phase 2 and 3 studies with UPA in RA to date.

Table 1. Efficacy at Weeks 12 and 24

	WEEK 12			WEEK 24		
	MTX N=314	UPA 15 MG QD N= 317	UPA 30 MG QD N=314	MTX N=314	UPA 15 MG QD N= 317	UPA 30 MG QD N=314
ACR20, %	54.1	75.7***	77.1***	58.6	78.9***	78.0***
ACR50, %	28.3	52.1***	56.4***	33.4	60.3***	65.6***
ACR70, %	14.0	32.5***	36.9***	18.5	44.5***	49.7***
DAS28CRP<2.6, %	13.7	35.6***	40.8***	18.5	48.3***	50.0***
DAS28CRP≤3.2, %	28.3	53.3***	54.8***	32.2	59.9***	65.0***
ΔDAS28CRP	-1.85	-2.73***	-2.85***	-2.15	-3.07***	-3.34***
ΔHAQ-DI	-0.49	-0.83***	-0.86***	-0.60	-0.87***	-0.91***
ΔSF-36 PCS	5.74	9.99***	10.08***	6.97	10.70***	11.39***
ΔmTSS	NA	NA	NA	0.67	0.14**	0.07***
No radiographic progression, %	NA	NA	NA	77.7	87.5**	89.3***
CDAI≤10 (LDA), %	29.6	46.4***	49.0***	38.2	56.2***	60.5***
CDAI≤2.8 (REM), %	6.4	16.1***	21.3***	10.5	28.4***	29.3***
Boolean REM, %	6.4	12.9**	15.3***	7.0	24.3***	24.8***

Values are LS mean unless otherwise specified. Δ, Change from baseline; QD, once daily; ACR20/50/70, 20/50 or 70% improvement in ACR criteria; CDAI, clinical disease activity index; DAS28CRP, 28-joint disease activity score using C-reactive protein; HAQ-DI, health assessment questionnaire disability index; LDA, low disease activity; mTSS, modified total Sharp score; SF-36 PCS, short form 36- physical component score; REM, remission.
Results are based on following analyses: binary endpoints, NRI; DAS28CRP and HAQ-DI, ANCOVA with Multiple Imputation; mTSS, ANCOVA with linear extrapolation.
,* p<.01, p<.001 for UPA vs MTX

Table 2. Treatment-Emergent Adverse Events Summary Through Week 24, n (%)			
	MTX N=314	UPA 15 MG QD N= 317	UPA 30 MG QD N=314
Any Adverse Event (AE)	205 (65.3)	203 (64.0)	224 (71.3)
Serious AE	13 (4.1)	15 (4.7)	20 (6.4)
AE Leading To Discontinuation Of Study Drug	16 (5.1)	14 (4.4)	12 (3.8)
Deaths*	1 (0.3)	2 (0.6)	3 (1.0)
Infection	103 (32.8)	104 (32.8)	115 (36.6)
-Serious Infection	4 (1.3)	5 (1.6)	8 (2.5)
-Opportunistic Infection	0	1 (0.3)	1 (0.3)
-Herpes Zoster ¥	1 (0.3)	7 (2.2)	7 (2.2)
Hepatic disorder	17 (5.4)	19 (6.0)	14 (4.5)
Gastrointestinal perforation φ	0	0	2 (0.6)
Malignancy (including NMSC) γ	1 (0.3)	3 (0.9)	0
MACE (adjudicated) δ	1 (0.3)	1 (0.3)	2 (0.6)
VTE (adjudicated)	1 (0.3)	0	1 (0.3)
-PE	1 (0.3)	0	0
-DVT	0	0	1 (0.3)

AE, adverse event; NMSC, non-melanoma skin cancer; VTE, venous thromboembolic events; PE, pulmonary embolism. DVT, deep vein thrombosis.

*Deaths: MTX: 1 sudden cardiovascular (CV) death; UPA 15, 1 CV death, 1 death due to metastatic malignant melanoma; UPA 30, 1 CV death, 1 death due to pneumonia and sepsis, 1 death due to peritonitis (also counted under GI perforation)

¥Herpes zoster: All non-serious, 12 were single dermatome

φ Gastrointestinal perforation UPA 30, 1 pt with large intestinal perforation, 1 pt with peritonitis

γ Malignancies: MTX: 1 case of ovarian cancer; UPA 15: 1 metastatic malignant melanoma, 1 squamous cell carcinoma of the lung, 1 uterine carcinoma in situ

δ MACE, major adverse cardiovascular events (adjudicated): MTX, 1 CV death; UPA 15, 1 non-fatal myocardial infarction (MI), CV death due to other CV causes; UPA30, 1 non-fatal MI and 1 CV death (sudden).

Disclosure: R. van Vollenhoven, AbbVie, Arthrogen, BMS, GSK, Lilly, Pfizer, UCB, 2,AbbVie, AstraZeneca, Biotest, BMS, Celgene, GSK, Janssen, Lilly, Medac, Merck, Novartis, Pfizer, Roche, UCB, 9; **T. Takeuchi**, Mitsubishi-Tanabe Pharma Corporation, Janssen Pharmaceutical KK, Chugai Pharmaceutical Co Ltd, Astellas Pharma Inc., AbbVie GK, Eisai Co., Ltd, Bristol-Myers Squibb Company, Daiichi Sankyo Company Ltd, Eli Lilly Japan KK, Pfizer Japan Inc;, 9,Astellas Pharma Inc., 9,Chugai Pharmaceutical Co Ltd, Mitsubishi-Tanabe Pharma Corporation; Grants; Pfizer Japan Inc., Eisai Co., Ltd, Astellas Pharma Inc., AbbVie GK, Asahi Kasei Pharma Corporation, Nippon Kayaku Co., Ltd, Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmace, 9,Astellas Pharma Inc., AbbVie GK, Eisai Co., Mitsubishi-Tanabe Pharma Corporation, Chugai Pharmaceutical Co Ltd, Bristol-Myers Squibb Company, UCB Japan Co., Ltd, 9; **A. L. Pangan**, AbbVie Inc., 1,AbbVie Inc., 3; **A. Friedman**, AbbVie Inc., 1,AbbVie Inc., 3; **M. E. Mohamed**, AbbVie Inc., 1,AbbVie Inc., 3; **S. Chen**, AbbVie Inc., 1,AbbVie Inc., 3; **M. Rischmueller**, Abbvie, Bristol-Meyer-Squibb, Celgene, Glaxo Smith Kline, Hospira, Janssen Cilag, MSD, Novartis, Pfizer, Roche, Sanofi, UCB, 5; **R. Blanco**, AbbVie, MSD, and Roche, 2,AbbVie, Pfizer, Roche, Bristol-Myers, Janssen, and MSD, 2, 8; **R. M. Xavier**, Abbvie, Pfizer, Novartis,

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