ABSTRACT NUMBER: 890

A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib to Placebo and to Adalimumab, in Patients with Active Rheumatoid Arthritis with Inadequate Response to Methotrexate

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Meeting: 2018 ACR/ARHP Annual Meeting

Keywords: Adalimumab, Janus kinase (JAK), radiography and rheumatoid arthritis (RA)

SESSION INFORMATION

Date: Sunday, October 21, 2018

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 assess efficacy, including inhibition of radiographic progression, and safety with upadacitinib (UPA), a JAK1- selective inhibitor, vs placebo (PBO) and active comparator, originator adalimumab (ADA), in patients (pts) with active rheumatoid arthritis (RA) continuing on prior methotrexate (MTX).

Methods: In SELECT–COMPARE, pts with active RA despite MTX were randomized 2:2:1 to once-daily (QD) UPA 15mg, PBO, or ADA 40mg every other week (wk) in a double-blind manner, while continuing stable background MTX. Primary endpoints were ACR20 and the proportion of pts achieving DAS28CRP<2.6 (NRI) at Wk12. Key secondary endpoints included non-inferiority (and superiority) of UPA vs ADA at Wk12 (for ACR50, DAS28CRP≤3.2, change from BL (Δ) in Pain, and ΔHAQ-DI), and radiographic inhibition (ΔmTSS) for UPA vs PBO at Wk26. Pts with <20% improvement in TJC and SJC were rescued between Wks14- 26 (from PBO to UPA, UPA to ADA, or ADA to UPA).

Results:

Of 1629 randomized pts, 91% completed Wk26 (including rescued pts). BL characteristics were similar across arms. All primary and key secondary endpoints were met. At Wk12, significantly more pts on UPA vs PBO achieved ACR20 (70.5% vs 36.4%) and DAS28CRP<2.6 (28.7% vs 6.1%) (**Table 1**). Superiority was met for UPA vs ADA at Wk12 for ACR50 (45.2% vs 29.1%), DAS28CRP≤3.2 (45.0% vs 28.7%), ΔPain (-31.76 vs -25.31) and ΔHAQ-DI (-0.60 vs -0.49). These differences were maintained

through Wk26. At Wk26, pts on UPA vs PBO had significantly less radiographic progression (ΔmTSS, 0.24 vs 0.92), and significantly more pts had no radiographic progression (ΔmTSS ≤0) (83.5% vs. 76.0%). At Wk26, more pts on UPA vs PBO or ADA achieved low disease activity or remission by various criteria (nominal p<.001).

Up to Wk26, the proportion of pts with adverse events (AEs) and serious infections, censored at rescue, was higher for UPA vs PBO but similar vs ADA **(Table 2)**. The proportion of pts with SAEs and AEs leading to discontinuation for UPA was numerically higher vs PBO and lower vs ADA. Herpes Zoster was numerically higher in UPA vs ADA and PBO. Three malignancies, 5 major adverse cardiovascular events, and 4 deaths were reported, none on UPA. Six venous thromboembolic events (VTEs) were reported (1 on PBO, 2 on UPA and 3 on ADA). For pts who were rescued, no deaths, adjudicated MACE, or adjudicated VTE were observed between rescue and Wk26.

Conclusion: UPA 15mg QD showed superiority on improvement in RA signs & symptoms vs PBO and ADA in this MTX-IR population. Radiographic progression was significantly lower with UPA vs PBO. Safety events were consistent with Ph 2 and 3 studies in RA to date.

Table 1. Efficacy Endpoints at Weeks 12 and 26

Endpoint	WEEK 12			WEEK 26		
	PBO N=651	UPA 15MG QD N=651	ADA 40MG EOW N=327	PBO N=651	UPA 15MG QD N=651	ADA 40MG EOW N=327
ACR20, %	36.4	70.5*** #	63.0	35.6	67.4*** ##	57.2
ACR50, %	14.9	45.2*** ###	29.1	20.9	53.9*** ###	41.9
ACR70, %	4.9	24.9*** ###	13.5	9.5	34.7*** ###	22.9
DAS28CRP ≤3.2, %	13.8	45.0*** ###	28.7	18.0	54.7*** ###	38.5
DAS28CRP <2.6, %	6.1	28.7*** ###	18.0	9.2	40.9*** ###	26.9
CDAI ≤10 (LDA), %	16.3	40.4*** ##	30.0	22.1	52.7*** ###	38.2
CDAI ≤2.8 (CR), %	3.1	13.4*** ##	7.6	5.5	23.0*** ###	13.8
SDAI ≤11.0 (LDA), %	15.2	40.4*** ##	30.0	22.1	53.9*** ###	38.8
SDAI ≤3.3 (CR), %	2.8	12.1*** #	7.3	4.8	24.3*** ###	13.8
Boolean remission, %	2.0	9.8*** ##	4.0	3.8	18.1*** ###	9.8
ΔPain	-15.69	-32.10 *** ###	-25.61	-18.60	-36.75*** ##	-31.86
ΔHAQ-DI	-0.28	-0.60 *** ##	-0.49	-0.33	-0.69*** ##	-0.57
ΔmTSS Wk 26 Δ JE Δ JSN	NA	NA	NA	0.92 0.44 0.58	0.24*** 0.03*** 0.22***	0.10 0.02 0.14
No Radiographic Progression Wk 26, %	NA	NA	NA	76.0	83.5**	86.8

Values are LS mean unless specified. Δ, Change from baseline; QD, once daily; ACR20/50/70, 20/50 or 70% improvement in ACR criteria; CR, Clinical remission; DAS28-CRP, 28-joint disease activity score using C-reactive protein; HAQ-DI, health assessment questionnaire disability index; JE, joint erosion; JSN, joint space narrowing; LDA, low disease activity; mTSS, modified total Sharp score; SF-36 PCS, short form 36- physical component score.
Results are based on following analyses: binary endpoints, NRI; mTSS, ANCOVA with linear extrapolation; other continuous endpoints, ANCOVA with rescue handling via LOCF.
**, *** p< .01 and .001 for UPA vs PBO; #, ##, ### p<.05, .01 and .001 for UPA vs ADA. Black symbols indicate comparisons that were pre-specified for multiplicity control; lighter gray symbols indicate comparisons that were not pre-specified for multiplicity control

Table 2. Adverse Events Summary Through Week 26, n (%) (censored at treatment switch)

	PBO N=652	UPA 15MG QD N=650[#]	ADA 40MG EOW N=327
Any Adverse Event (AE)	347 (53.2)	417 (64.2)	197 (60.2)
Serious AE	19 (2.9)	24 (3.7)	14 (4.3)
AE Leading To Discontinuation Of Study Drug	15 (2.3)	23 (3.5)	20 (6.1)
Deaths*	2 (0.3)	0	2 (0.6)
Infection	154 (23.6)	226 (34.8)	95 (29.1)
-Serious Infection	5 (0.8)	12 (1.8)	5 (1.5)
-Opportunistic Infection	4 (0.6)	4 (0.6)	1 (0.3)
-Herpes Zoster	3 (0.5)	5 (0.8)	1 (0.3)
Hepatic disorder	32 (4.9)	43 (6.6)	12 (3.7)
Gastrointestinal perforation [φ]	0	2 (0.3)	0
Malignancy (including NMSC) [γ]	2 (0.3)	0	1 (0.3)
MACE (adjudicated) [δ]	3 (0.5)	0	2 (0.6)
VTE (adjudicated)	1 (0.2)	2 (0.3)	3 (0.9)
-PE	1 (0.2)	1 (0.2)	3 (0.9)
-DVT	0	1 (0.2)	0

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

[#] One pt randomized to UPA received only PBO injection before discontinuing and is included in PBO group for safety assessments

* Deaths: PBO: 1 cardiovascular (CV) death and 1 death due to Pneumocystis jirovecii pneumonia; ADA: 1 death due to craniocerebral injury and 1 CV death.

[φ] Gastrointestinal perforation (Identified using GI perforation MedDRA SMQ): not spontaneous perforations but 1 peritonitis, and 1anal abscess

[γ] Malignancies: PBO: 1 cervical carcinoma, 1 basal cell carcinoma; ADA: 1 basal cell carcinoma.

[δ] MACE, major adverse cardiovascular events (adjudicated): PBO: 2 non-fatal myocardial infarctions and 1 CV death; ADA: 1 non-fatal stroke and 1 CV death.

Disclosure: R. Fleischmann, AbbVie, Lilly, Pfizer, Gilead, 2,AbbVie, Lilly, Pfizer, Gilead, 5; **A. L. Pangan**, AbbVie Inc., 1,AbbVie Inc., 3; **E. Mysler**, AbbVie, Lilly, Pfizer, Roche, BMS, Sandoz, 2,AbbVie, Lilly, Pfizer, Roche, BMS, Sandoz, 5; **L. Bessette**, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Lilly, Novartis, 2, 5, 8; **C. Peterfy**, Spire Sciences, Inc, 3,Spire Sciences, Inc, 1,Amgen, Bristol-Myers Squibb; consultant: Centrexion, Crescendo Bioscience, Daiichi Sankyo, EMD Serono, Five Prime, Flexion Therapeutics, Genentech, Gilead, GlaxoSmithKline, Pfizer, Plexikkon, Regeneron, Roche, SetPoint., 8; **P. Durez**, BMS, Lilly, Sanofi, Pfizer, 8; **A. Ostor**, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Eli Lilly, Novartis, 2,BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Eli Lilly, Novartis, 5,BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Eli Lilly, Novartis, 8; **Y. Li**, AbbVie Inc., 1,AbbVie Inc., 3; **Y. Zhou**, AbbVie Inc., 1,AbbVie Inc., 3; **A. A. Othman**, AbbVie Inc., 1,AbbVie Inc., 3; **I. H. Song**, AbbVie, Inc., 1,AbbVie, Inc., 3; **M. C. Genovese**, AbbVie, Lilly, Pfizer, Galapagos, Gilead, 5,AbbVie, Lilly, Pfizer, Galapagos, Gilead, 2.