ABSTRACT NUMBER: 889

Upadacitinib As Monotherapy: A Phase 3 Randomized Controlled Double-Blind Study in Patients with Active Rheumatoid Arthritis and Inadequate Response to Methotrexate

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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: Upadacitinib (UPA), an oral JAK inhibitor, showed efficacy in rheumatoid arthritis (RA) patients (pts) with an inadequate response to csDMARDs or bDMARDs on continuing stable csDMARD(s)[1,2]. We assessed the safety and efficacy of switching to UPA 15 or 30mg monotherapy vs continuing methotrexate (MTX) as a blinded study drug was evaluated in pts with inadequate response to MTX (MTX-IR).

Methods: Pts with active RA (TJC≥6, SJC≥6, hsCRP≥3 mg/L) on stable MTX were enrolled and randomized 1:1:1 in a double-blind manner to once-daily (QD) UPA 15mg or 30mg monotherapy or to continue MTX (cMTX) at their prior stable dose. At BL, all pts discontinued prior MTX without washout and received PBO (for pts on UPA) or MTX at prior dose (cMTX) as blinded study drug. The primary endpoints at Week (Wk) 14 were the proportion of pts achieving ACR20, and the proportion achieving DAS28-CRP ≤3.2 (NRI).

Results: 648 pts were randomized, all received study drug; 598 (92.3%) completed 14 wks. BL demographics and disease characteristics were generally similar across arms. Both primary endpoints were met (p<.001); at Wk 14, a significantly greater proportion of pts receiving UPA monotherapy (15mg and 30mg) vs cMTX achieved ACR20 (67.7% and 71.2% vs 41.2%), and DAS28-CRP≤3.2 (44.7% and 53.0% vs 19.4%) (**Table)**. All key secondary endpoints also showed UPA 15 and UPA 30 monotherapy to be superior to cMTX, including ACR50 (41.9% and 52.1% vs 15.3%), ACR70 (22.6% and 33.0% vs 2.8%), DAS28-CRP<2.6 (28.1% and 40.5% vs 8.3%), ΔHAQ-DI (-0.65 and -0.73 vs -0.32). ΔSF-36 PCS and ΔMorning Stiffness data are also shown **(Table)**. The proportion of pts achieving CDAI≤10 was significantly greater with UPA 15 and 30 vs cMTX (34.6% and 46.5% vs 24.5%).

Adverse events (AEs) were reported at similar frequencies across arms; serious AEs were numerically higher in UPA 15 but similar between cMTX and UPA 30 **(Table)**. Numerically more infections were reported in cMTX and UPA 30 vs UPA 15. One serious infection each was reported in UPA 15 and cMTX, and none in UPA 30. Herpes zoster was more frequent in UPA 30 vs UPA 15 or cMTX. 3 malignancies (1 in cMTX and 2 in UPA 15) and 3 adjudicated MACE (1 in UPA 15 and 2 in UPA 30) were reported. One adjudicated pulmonary embolism was reported (UPA 15) in a pt with known risk factors (BMI 36; on estrogen therapy). One death (hemorrhagic stroke due to ruptured aneurysm) was reported in UPA 15. No TB, renal dysfunction or GI perforation was reported. Rates and types of laboratory abnormalities were consistent with prior UPA RA studies to date.

Conclusion: In this MTX-IR study population, switching to UPA as monotherapy at 15mg and 30mg QD showed significant improvements in RA signs and symptoms vs continuing MTX. Numerically higher responses were observed for UPA 30mg vs 15mg, particularly for more stringent efficacy criteria. Safety observations were similar to those in prior UPA studies.

EFFICACY ENDPOINTS AT WEEK 14#			
	cMTX N=216	UPA 15 MG N=217	UPA 30 MG N=215
ACR20 (%)	**41.2%**	**67.7% *****	**71.2% *****
DAS28-CRP≤3.2 (%)	**19.4%**	**44.7% *****	**53.0% *****
ACR50 (%)	15.3%	41.9% ***	52.1% ***
ACR70 (%)	2.8%	22.6%***	33.0% ***
DAS28-CRP<2.6 (%)	8.3%	28.1% ***	40.5% ***
CDAI≤10 (%)	24.5%	34.6%*	46.5%***
ΔDAS28-CRP (LSM)	-1.20	-2.29 ***	-2.61 ***
ΔHAQ-DI (LSM)	-0.32	-0.65 ***	-0.73 ***
ΔSF-36 PCS (LSM)	4.32	8.28 ***	10.19 ***
ΔMorning (AM) Stiffness Duration (min.) (LSM)	-53.0	-94.6 **	-102.3 ***
ADVERSE EVENT SUMMARY			
n (%)	cMTX N=216	UPA 15 MG N=217	UPA 30 MG N=215
Any Adverse Event (AE)	102 (47.2)	103 (47.5)	105 (48.8)
Serious AE	6 (2.8)	11 (5.1)	6 (2.8)
AE Leading To Discontinuation Of Study Drug	6 (2.8)	8 (3.7)	6 (2.8)
Infection	57 (26.4)	42 (19.4)	54 (25.1)
-Serious Infection[†]	1 (0.5)	1 (0.5)	0
-Opportunistic Infection[*]	1 (0.5)	0	3 (1.4)
-Herpes Zoster	1 (0.5)	3 (1.4)	6 (2.8)
Hepatic disorder[¶]	4 (1.9)	4 (1.8)	5 (2.3)
Any Malignancy (including NMSC)[ᵞ]	1 (0.5)	2 (0.9)	0
-NMSC	1 (0.5)	0	0
MACE (adjudicated)[ᵟ]	0	1 (0.5)	2 (0.9)
Venous Thromboembolism (adjudicated)	0	1 (0.5)[ᵡ]	0
Death	0	1 (0.5)	0

cMTX, Continuing MTX as a blinded study drug. LSM, least square means; Δ, Change from baseline; CPK, creatine phosphokinase; NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular event (cardiovascular death, non-fatal MI, non-fatal stroke)

#Results for binary endpoints are based on NRI. Results for DAS28-CRP and HAQ-DI are based on Multiple Imputation. Results for other endpoints are based on Mixed Effect Model Repeat Measurement.

*, **,*** p <.05, < .01 and .001 respectively

[†]Serious Infection events: cMTX: urosepsis; UPA 15: abscess limb

[*]Opportunistic infection events: cMTX: fungal oesophagitis; UPA 30: 2 oral candidiasis, 1 oropharyngeal candidiasis

[¶]Hepatic disorders: Except for 1 case of mild hepatic cyst, all due to liver enzyme elevation

[ᵞ]Malignancies: cMTX: basal cell carcinoma; UPA 15: 1 non-Hodgkins' lymphoma, 1 breast cancer

[ᵟ]MACE (adjudicated): UPA 15: 1 hemorrhagic stroke due to ruptured aneurysm (fatal), investigator deemed as unrelated to study drug; UPA 30: 1 myocardial infarction, 1 stroke; investigators reported both events as unrelated to study drug

[ᵡ]VTE: Pulmonary embolism (BMI 36, estrogen hormone therapy); investigator deemed as unrelated to study drug

References:

1. Burmester et al; 2017, Arth Rheum;69 S10
2. Genovese et al; 2017, Arth Rheum;69 S10

Disclosure: J. S. Smolen, AbbVie Inc., 2, 5; **S. Cohen**, Abbvie, Gilead, Eli Lilly, Pfizer, 2, 5; **P. Emery**, Pfizer, MSD, AbbVie, Bristol-Myers Squibb, UCB, Roche, Novartis, Samsung, Sandoz and Lilly, 2, 5; **W. F. C. Rigby**, None; **Y. Tanaka**, Daiichi Sankyo Ltd, Astellas Pharma Inc,, Pfizer Japan Inc., Mitsubishi-Tanabe, BMS, Chugai Ltd, YL Biologics, Eli Lilly Japan KK, Sanofi KK, Janssen KK, UCB Japan, Ltd, 8,Astellas, Takeda, BMS, Kowa Ltd, Daiichi Sankyo Ltd, YL Biologics, Chugai Ltd, Sanofi KK, Celgene, 9; **Y. Zhang**, AbbVie Inc., 1, 3; **A. Friedman**, AbbVie Inc., 1, 3; **A. A. Othman**, AbbVie Inc., 1, 3; **H. S. Camp**, AbbVie Inc., 1, 3; **A. L. Pangan**, AbbVie Inc., 1, 3.

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