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OP0034

LONG-TERM EFFECTIVENESS OF THE COBRA SLIM REMISSION INDUCTION AND TREAT TO TARGET STRATEGY IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS LACKING CLASSICAL MARKERS OF POOR PROGNOSIS: 2 YEAR RESULTS OF THE CARERA TRIAL

V. Stouten¹, J. Joly², S. Pazmino¹, K. Van der Elst^{1,2}, D. De Cock¹, R. Westhovens^{1,2}, P. Verschuere^{1,2}, on behalf of the CareRA study group.

¹Skeletal Biology and Engineering Research Centre, KU Leuven; ²Rheumatology, University Hospitals Leuven, Belgium

Background: EULAR guidelines recommend to treat all patients with early Rheumatoid Arthritis (eRA) with a combination of methotrexate (MTX) and a short-term course of Glucocorticoids (GC). The COBRA Slim strategy with MTX and a moderately dosed tapering down scheme of GC was effective, also in patients without classical markers of poor prognosis during the first year.

Objectives: To compare the outcomes of MTX with or without initial step-down GC in Low-Risk patients during the second year of the CareRA trial, in terms of disease control, safety and DMARD use.

Methods: CareRA is a two-year prospective investigator-initiated pragmatic multicentre RCT. DMARD naïve eRA patients were stratified into a High- or Low-Risk group based on classical prognostic markers (presence of erosions, RF, anti-CCP and DAS28-CRP). Low-Risk patients (n=90) were randomised to either Tight-Step Up (TSU) with MTX 15 mg weekly without GC or to COBRA Slim, a combination of MTX 15 mg weekly and prednisone tapering down scheme starting at 30 mg, tapered to 5 mg daily from w6 and stopped at w34. A treat-to-target approach was applied until year 1 and afterwards treatment was at the discretion of the rheumatologist. Proportions of DAS28-CRP remission at year 2 was a co-primary CareRA endpoint. Secondary outcomes were efficacy according to other remission criteria, EULAR/ACR response rates and functionality measured by HAQ (ITT analysis, last observation carried forward). Adverse events (AEs) and concomitant medication were registered.

Results: At year 2, 67.4% of Slim and 70.2% of TSU patients were in remission according to DAS28CRP (p=0.777). Out of patients in DAS28CRP remission at year 1, 80.0% (24/30) in the Slim group, versus 69.0% (20/29) in the TSU group remained in remission at every three-monthly evaluation until year 2. Remission rates defined by Boolean criteria were higher in patients of the Slim (39.5%) versus TSU group (19.1%) (p=0.033). Functionality measured by mean area under the HAQ curve over 2 years was better in Slim patients (38.3±47.2) than in TSU patients (56.4±48.7) (p=0.025). Other secondary efficacy outcomes did not differ

Abstract OP0034 – Table 1 Clinical outcomes during the second year per treatment arm

	COBRA slim (n=43)	TSU (n=47)	p-value
Remission DAS28-CRP year 2	29 (67.4%)	33 (70.2%)	0.777
DAS28-CRP change BL-year 2	2.2±1.8	2.2±2.0	0.929
DAS28-CRP change year 1-year 2	0.1±0.8	0.0±0.9	0.486
Mean AUC of DAS28CRP	248.9±110.8	266.1±82.3	0.119
Good EULAR response at year 2	55.8%	61.7%	0.571
ACR50 improvement at year 2	25 (58.1%)	23 (48.9%)	0.382
ACR70 improvement at year 2	19 (44.2%)	15 (31.9%)	0.230
Remission CDAI year 2	20 (46.5%)	15 (31.9%)	0.156
Remission SDAI year 2	20 (46.5%)	15 (31.9%)	0.156
Remission Boolean year 2	17 (39.5%)	9 (19.1%)	0.033
Mean AUC of HAQ	38.3±47.2	56.4±48.7	0.025
Clinically meaningful HAQ change at year 2	53.5%	59.6%	0.561
HAQ = 0 at year 2	48.8%	36.2%	0.224

DAS28-CRP= 28 Joint disease activity score calculated with C-reactive protein; good EULAR response = low disease activity with a DAS28-CRP change (BL-year 2) >1.2; AUC = Area Under the Curve (BL-year 2); HAQ= health assessment questionnaire; clinically meaningful HAQ change (BL-year2) = HAQ change >0.22.

between the treatment arms. The total numbers of AEs reported as related to study therapy, were 69 in 34 TSU patients and 63 in 28 Slim patients. Biologicals were started in 14 Low-Risk patients (15.6%), more specifically in 8 Slim and 6 TSU patients during the CareRA trial. At the year 2 visit 62.5% of Slim patients were on MTX monotherapy and 12.5% on a combination of csDMARDs. In the TSU group 58.5% was taking MTX as only DMARD, and 19.5% took a combination of csDMARDs. Out of all Low-Risk patients 11.0% (8/73) was taking oral GC at the year 2 visit, 5 patients in the TSU group and 3 patients in Slim group, all at a low dosages.

Conclusions: In eRA patients lacking classical markers of poor prognosis COBRA Slim showed persistently high remission rates and good disease control 2 years after initiating therapy in a treat to target setting. COBRA slim seems to be slightly more effective than TSU according to the year 2 Boolean remission criteria and the 2 year functionality AUC but the CareRA study was not powered for this analysis.

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OP0035

UPADACITINIB AS MONOTHERAPY: A PHASE 3 RANDOMISED CONTROLLED DOUBLE-BLIND STUDY IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE

J. Smolen¹, S. Cohen², P. Emery³, W. Rigby⁴, Y. Tanaka⁵, Y. Zhang⁶, A. Friedman⁶, A. Othman⁶, H. Camp⁶, A. Pangan⁶. ¹Med Univ of Vienna, Vienna, Austria; ²Metrex Clin Res Ctr, Dallas, USA; ³Leeds Inst of Rheum and Musculoskeletal Med, Leeds NIHR BRC, UK, Leeds, UK; ⁴Dartmouth Coll, Hanover, USA; ⁵Univ of Occ and Env Health, Kitakyushu, Japan; ⁶AbbVie, N Chicago, USA

Background: 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}

Objectives: Safety and efficacy of switching to UPA 15 mg or 30 mg 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 randomised 1:1:1 in a double-blind manner to once-daily (QD) UPA 15 mg or 30 mg 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 randomised, 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<0.001); at Wk 14, a significantly greater proportion of pts receiving UPA monotherapy (15 mg and 30 mg) 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 1). 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 1). 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 1). 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 oestrogen therapy). One death (haemorrhagic 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.

Abstract OP0035 – Table 1

EFFICACY ENDPOINTS AT WEEK 14 ^a			
	cMTX, N=216	UPA 15, N=217	UPA 30, 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% ***
CDAI10 (%)	24.5%	34.6%*	46.5%***
ΔDAS28-CRP (LSM)	-1.20	-2.29 ***	-2.61 ***
ΔHAQ-DI (LSM)	-0.32	-0.65 ***	-0.78 ***
ΔSF-36 PCS (LSM)	4.32	8.28 ***	10.19 ***
ΔMorning Stiffness Duration (min.) (LSM)	-53.0	-94.6 **	-102.3 ***
ADVERSE EVENT SUMMARY, n (%)			
	cMTX, N=216	UPA 15, N=217	UPA 30, 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 Study Drug D/C	6 (2.8)	8 (3.7)	6 (2.8)
Infection	57 (26.4)	42 (19.4)	54 (25.1)
-Serious Infection ^f	1 (0.5)	1 (0.5)	0
-Opportunistic Infection ^g	1 (0.5)	0	3 (1.4)
-Herpes Zoster	1 (0.5)	3 (1.4)	6 (2.8)
Hepatic disorder ^h	4 (1.9)	4 (1.8)	5 (2.3)
Any Malignancy (including NMSC) ⁱ	1 (0.5)	2 (0.9)	0
-NMSC	1 (0.5)	0	0
MACE (adjudicated) ^j	0	1 (0.5)	2 (0.9)
Venous Thromboembolism (adjudicated)	0	1 (0.5) ^k	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)

^aResults 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 < 0.05, < 0.01 and < 0.001 respectively

^fSerious infection events: cMTX: urosepsis; UPA 15: abscess limb

^gOpportunistic infection events: cMTX: fungal oesophagitis; UPA 30: 2 oral candidiasis, 1 oropharyngeal candidiasis

^hHepatic disorders: Except for 1 case of mild hepatic cyst, all due to liver enzyme elevation

ⁱMalignancies: cMTX: basal cell carcinoma; UPA 15: 1 non-Hodgkins' lymphoma, 1 breast cancer

^jMACE (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

^kVTE: Pulmonary embolism (BMI 35, estrogen hormone therapy); investigator deemed as unrelated to study drug

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

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OP0036

A PHASE 3 RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF UPADACITINIB (ABT-494), A SELECTIVE JAK-1 INHIBITOR, IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS WITH INADEQUATE RESPONSE TO CONVENTIONAL SYNTHETIC DMARDS

G. Burmester¹, J. Kremer², F. van den Bosch³, Y. Li⁴, Y. Zhou⁴, A. Othman⁴, A. Pangan⁴, H. Camp⁴, ¹Charité – Universitätsmedizin, Berlin, Germany; ²Albany Medical College, Albany, USA; ³Ghent University Hospital, Ghent, Belgium; ⁴AbbVie Inc., North Chicago, USA

Background: Upadacitinib (UPA) is an oral, selective JAK-1 inhibitor in development for the treatment of patients (pts) with moderate to severe rheumatoid arthritis (RA) and other immune-mediated diseases.

Methods: This Phase 3 study in pts with inadequate response (IR) to csDMARDs included a double-blind placebo (PBO)-controlled period (Period 1, reported here), during which pts were randomised 1:1:1 to receive once-daily (QD) extended-release formulation of UPA at 15 mg or 30 mg, or PBO for 12 weeks (wks). The primary efficacy endpoints were the proportion of pts who achieved an ACR20 response and the proportion who achieved DAS28-CRP low disease activity (LDA, ≤3.2) at Wk 12, using non-responder imputation (NRI).

Results: Of 661 pts who were randomised, all received study drug, and 618 (93.5%) completed Period 1. At baseline, demographics and disease characteristics were similar across arms. The study met all primary and key secondary endpoints with p values < 0.001 for both doses. At Wk 12, significantly more pts receiving UPA 15 mg and 30 mg QD vs PBO achieved an ACR20 response (63.8% and 66.2% vs 35.7%, p < 0.001), and DAS28-CRP LDA (48.4% and 47.9% vs 17.2%, p < 0.001) (table 1). Onset of action was rapid with significantly more pts in both UPA arms achieving ACR20 at Wk 1 vs PBO. At Wk 12, significantly more pts met ACR50 and ACR70 in the UPA 15 mg (38% and 20.8%) and 30 mg QD arms (43.4% and 26.5%) vs PBO (14.9% and 5.9%). Significantly more patients receiving UPA 15 mg and 30 mg QD vs PBO achieved DAS28-CRP < 2.6 (30.8% and 28.3% vs 10%, p < 0.001) and CDAI-LDA (40.3% and 42% vs 19%, p < 0.001), and pts receiving UPA at both doses experienced significantly greater improvements in DAS28-CRP, HAQ-DI, morning stiffness and FACIT-F vs PBO (p < 0.001).

Adverse events (AEs) and serious AEs were numerically higher with UPA than PBO (table 1). The overall incidence of infection was higher for UPA 15 mg and 30 mg QD vs PBO, but few were serious infections. There were 4 cases of herpes zoster/Varicella Zoster Virus infection (1 on PBO). Asymptomatic CPK elevations were only reported for patients on UPA. Two malignancies and 3 adjudicated cardiovascular events were reported. No PE/DVT were reported. There were no deaths, cases of TB or GI perforations. Types and frequency of laboratory abnormalities were similar to findings in Phase 2 studies with UPA.

Abstract OP0036 – Table 1

Efficacy Endpoints ^a			
	PLACEBO N=221	UPADACITINIB 15 MG QD N=221	UPADACITINIB 30 MG QD N=219
Primary Endpoints			
ACR20 (%)	35.7	63.8 ***	66.2 ***
DAS28-CRP LDA (%)	17.2	48.4 ***	47.9 ***
Key Secondary Endpoints			
ACR20 at Week 1 (%)	8.6	22.2 ***	28.3 ***
ACR50 (%)	14.9	38.0 ***	43.4 ***
ACR70 (%)	5.9	20.8 ***	26.5 ***
DAS28-CRP < 2.6 (%)	10.0	30.8 ***	28.3 ***
CDAI LDA (%)	19.0	40.3 ***	42.0 ***
Δ DAS28-CRP	-1.02	-2.20 ***	-2.34 ***
Δ HAQ-DI	-0.25	-0.59 ***	-0.54 ***
Δ SF-36 PCS	3.03	7.56 ***	8.01 ***
Δ Morning Stiffness Duration (min.)	-34.27	-58.28 ***	-65.13 ***
Δ FACIT-F	2.96	7.91 ***	7.74 ***
Summary of Adverse Events, n (%)			
Any Adverse Event (AE)	108 (48.9)	125 (56.6)	118 (53.9)
Serious AE	5 (2.3)	9 (4.1)	6 (2.7)
AE Leading To Discontinuation Of Study Drug	7 (3.2)	7 (3.2)	13 (5.9)
Severe AE	5 (2.3)	8 (3.6)	7 (3.2)
AE of Special Interest			
Infection	47 (21.3)	64 (29.0)	69 (31.5)
Serious Infection ^b	1 (0.5)	1 (0.5)	3 (1.4)
Opportunistic Infection ^c	1 (0.5)	0	3 (1.4)
Anemia	3 (1.4)	0	3 (1.4)
Neutropenia	1 (0.5)	4 (1.8)	8 (3.7)
Herpes Zoster	1 (0.5)	1 (0.5)	2 (0.9) ^d
Hepatic disorder	5 (2.3)	4 (1.8)	6 (2.7)
CPK elevation ^e	0	5 (2.3)	6 (2.7)
Malignancy (including NMSC) ^f	0	0	2 (0.9)
Cardiovascular event (adjudicated) ^g	0	2 (0.9)	1 (0.5)
MACE	0	0	1 (0.5)
Other adjudicated CEs	0	2 (0.9)	0

Δ, Change from baseline; ***p < 0.001.

^aResults for binary endpoints are based on NRI analysis. Results for continuous endpoints based Multiple Imputation or Mixed Effect Model Repeat Measurement analysis.

^bSerious infection events: PBO: pneumonia; UPA 15 mg: enterococci infection; UPA 30 mg: 1 varicella zoster, 1 viral upper respiratory tract infection, 1 staphylococcal wound infection

^cOpportunistic infection events: PBO: oral candidiasis; UPA 30 mg: 2 oral candidiasis, 1 varicella zoster pneumonia

^d1 patient on UPA 30 mg was exposed to chicken pox and had primary varicella infection.

^eAll asymptomatic

^fMalignancies: UPA 30 mg: 1 case of basal cell carcinoma in patient with history of skin cancer, 1 case of chronic lymphocytic leukemia/lymphoid lymphoma. Both were deemed unrelated to study drug by the investigator.

^gCardiovascular events (adjudicated): MACE: ischemic stroke in patient with history of hypertension (upadacitinib 30 mg). Other adjudicated CEs: 1 congestive cardiac failure (upadacitinib 15 mg), 1 silent placed in patient with prior history of angina, coronary artery disease and transient ischemic attack (upadacitinib 15 mg).

Abbreviations: CPK, creatine phosphokinase; NMSC, non-melanoma skin cancer

Conclusions: The efficacy of UPA at 15 mg and 30 mg QD vs PBO was demonstrated in this csDMARD-IR study population. The most notable responses were observed in the more stringent endpoints of LDA (by either DAS28-CRP or CDAI)