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.

REFERENCES:

- [1] Burmester, et al. *Arth Rheum* 2017;69:S10.
- [2] Genovese, et al. *Arth Rheum* 2017;69:S10.

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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

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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	-59.28 ***	-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/lymphocytic 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 stent 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)

and ACR70. The safety and tolerability profile was consistent with observations in the Phase 2 studies with UPA.

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OP0037

EFFICACY OF TOFACITINIB AFTER TEMPORARY DISCONTINUATION IN PATIENTS WITH RHEUMATOID ARTHRITIS: ANALYSIS OF DATA FROM OPEN-LABEL LONG-TERM EXTENSION STUDIES

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Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Given the chronic nature of RA, there may be situations when therapy is temporarily discontinued. It is important to understand loss of response during temporary discontinuation and the ability to regain disease control following treatment reinitiation. Re-establishment of tofacitinib efficacy following temporary discontinuation/reinitiation has been previously demonstrated in patients (pts) with RA participating in the vaccine sub-study of the long-term extension (LTE) study ORAL Sequel.¹

Objectives: To further assess tofacitinib efficacy and safety after temporary discontinuation and reinitiation in pts with RA in LTE studies.

Methods: Data were pooled from two open-label LTE studies (NCT00413699 [database lock: March 2017] and NCT00661661) of pts with RA who had completed qualifying Phase 1/2/3 index studies. Pts received tofacitinib 5 or 10 mg twice daily as monotherapy or with conventional synthetic disease-modifying antirheumatic drugs. Pts who received continuous tofacitinib for ≥4 months, temporarily discontinued tofacitinib for 14–30 days and then resumed treatment were included in the analysis. Efficacy outcomes were analysed at the pre-interruption visit (≤90 days before discontinuation) and at the post-interruption visit (within 14–42 days of resuming treatment); data from the interruption period were not analysed. Efficacy outcomes included: ACR20/50/70 response rates, mean tender and swollen joint counts, mean C-reactive protein levels and mean DAS28–4 (ESR), CDAI, HAQ-DI, Patient Global Assessment of arthritis, Pain and Physician Global Assessment of arthritis scores. Safety was analysed from Day 1 of temporary discontinuation to the post-interruption visit and included adverse events (AEs), serious AEs (SAEs) and discontinuations due to AEs that occurred within the time range.

Results: 261 pts met the criteria for temporary discontinuation. Median (range) duration of temporary discontinuation was 19^{14–30} days. Pt demographics are shown in table 1. Efficacy outcomes were generally similar at pre- and post-interruption visits (table 2). From Day 1 of discontinuation to the post-interruption visit, AEs, SAEs and discontinuations due to AEs occurred in 142 (54.4%), 29 (11.1%) and 4 (1.5%) pts, respectively.

Abstract OP0037 – Table 1 Patients demographics and baseline disease characteristics¹

	All tofacitinib (N=261)
Age (years), mean (SD)	53.7 (11.3)
Sex, n (%)	
Female	224 (85.8)
Race, n (%)	
White	173 (66.3)
Black	7 (2.7)
Asian	63 (24.1)
Other	18 (6.9)
BMI (kg/m ²), mean (SD)	26.8 (6.4)
Duration of disease (years), mean (SD)	9.4 (8.2)
TJC, mean (SD)	25.1 (15.2)
SJC, mean (SD)	15.4 (8.6)
CRP (mg/L), mean (SD)	20.6 (23.9)
DAS28-4(ESR), mean (SD)	6.4 (1.0)
CDAI, mean (SD)	36.6 (12.1)
HAQ-DI, mean (SD)	1.5 (0.7)
PtGA, mean (SD)	60.4 (22.1)
Pain-VAS, mean (SD)	58.8 (23.3)
PGA, mean (SD)	61.1 (16.9)
Background csDMARD use, n (%) ^b	181 (69.3)

^aBaseline values were those of the index study if patients began LTE study treatment ≤14 days from the last tofacitinib dose in the index study. Otherwise, LTE baseline values were used; ^bAt LTE baseline

BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LTE, long-term extension; PGA, Physician Global Assessment of arthritis; PtGA, Patient Global Assessment of arthritis; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale

Abstract OP0037 – Table 2 Efficacy endpoints at the pre-interruption visit (≤90 days before temporary discontinuation) and post-interruption visit (within 14–42 days of resuming treatment)

	All tofacitinib (N=261)	
	Pre-interruption visit	Post-interruption visit
ACR20, % (95% CI)	75.5 (69.8, 80.6)	74.3 (68.6, 79.5)
ACR50, % (95% CI)	54.4 (48.2, 60.6)	51.0 (44.7, 57.2)
ACR70, % (95% CI)	31.8 (26.2, 37.8)	31.4 (25.8, 37.4)
TJC, mean (95% CI)	6.1 (4.9, 7.2)	8.0 (6.4, 9.6)
SJC, mean (95% CI)	3.4 (2.8, 4.1)	5.0 (3.9, 6.2)
CRP (mg/L), mean (95% CI)	0.48 (0.38, 0.58)	0.46 (0.37, 0.56)
DAS28-4(ESR), mean (95% CI)	3.6 (3.4, 3.7)	3.9 (3.7, 4.0)
CDAI, mean (95% CI)	10.0 (8.9, 11.1)	11.8 (10.3, 13.2)
HAQ-DI, mean (95% CI)	0.94 (0.85, 1.03)	0.98 (0.88, 1.07)
PtGA, mean (95% CI)	28.4 (25.8, 31.0)	29.3 (26.6, 32.1)
Pain (VAS), mean (95% CI)	28.1 (25.4, 30.8)	28.8 (26.0, 31.7)
PGA, mean (95% CI)	17.1 (15.3, 18.9)	18.0 (16.0, 19.9)

Median (range) time from the pre-interruption visit to Day 1 of temporary discontinuation was 43 (0–90) days and the median (range) time from resuming treatment to the post-interruption visit was 28 (14–42) days

N is the total number of patients in the analysis; the number of patients evaluable for each endpoint may be fewer than N

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; PGA, Physician Global Assessment of arthritis; PtGA, Patient Global Assessment of arthritis; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale

Conclusions: In pts with RA who temporarily discontinued tofacitinib, similar efficacy responses were observed at pre- and post-interruption visits, suggesting that there is no loss of efficacy after temporary withdrawal and reinitiation of tofacitinib. The safety profile was consistent with previous tofacitinib reports in LTE studies over 9 years.²