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POS0655

LONG-TERM SAFETY AND EFFICACY OF UPADACITINIB IN PATIENTS WITH RHEUMATOID ARTHRITIS: 3-YEAR RESULTS FROM THE SELECT-EARLY STUDY

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Background: Upadacitinib (UPA), an oral Janus kinase inhibitor, demonstrated significant improvements in signs, symptoms, and structural inhibition as monotherapy (mono) vs methotrexate (MTX) in MTX-naïve patients (pts) with rheumatoid arthritis (RA) through 48 weeks (wks).¹

Objectives: To report the efficacy and safety of UPA vs MTX mono up to 156 wks in pts with RA from the ongoing long-term extension (LTE) of the SELECT-EARLY trial.

Methods: During the 48-wk double-blind study period, pts were randomized to UPA 15 or 30 mg once daily (QD) or MTX (titrated to 20 mg/wk by Wk 8). At Wk 26, pts who did not achieve Clinical Disease Activity Index (CDAI) remission (≤ 2.8) and had $<20\%$ improvement from baseline in tender or swollen joint count received blinded rescue therapy (addition of MTX for UPA groups and UPA 15 or 30 mg for MTX group). In the LTE, pts received open-label treatment once the last pt reached Wk 48. Efficacy assessments up to Wk 156 were summarized by randomized group and included American College of Rheumatology (ACR) responses, remission and low disease activity (LDA) measures, and change in modified Total Sharp Score (mTSS; up to 96 wks). Treatment-emergent adverse events (AEs) per 100 pt-years (PY) for pts on continuous mono were summarized through 156 wks. Non-responder imputation was used for binary endpoints for missing data and when pts received rescue therapy or prematurely discontinued the study drug.

Results: Of 945 pts randomized and treated, 775 entered the LTE on study drug (including 57 rescued pts; MTX, 33; UPA 15 mg, 17; UPA 30 mg, 7). Overall, 161 (21%) pts discontinued during the LTE. At Wk 156, higher proportions of pts randomized to UPA achieved a 20/50/70% improvement in ACR response (ACR20/50/70), LDA, and remission vs MTX (Figure 1). Change from baseline in mTSS at Wk 96 favored UPA vs MTX (data not shown). Most AEs were numerically more frequent with UPA 30 mg. The overall rate of serious infection was numerically higher with UPA vs MTX (Table 1). Herpes zoster (HZ), neutropenia, non-melanoma skin cancer (NMSC), and creatine phosphokinase (CPK) elevation were more frequent with UPA vs MTX. Two active tuberculosis (TB) events were reported in each UPA arm; 3 adjudicated gastrointestinal (GI) perforation events were observed in the UPA 30 mg arm. Adjudicated major adverse cardiovascular events (MACEs) or venous thromboembolic events (VTEs) were comparable across treatment arms.

Conclusion: UPA monotherapy showed sustained clinically meaningful responses including remission vs MTX through Wk 156 but higher rates of several AEs, including HZ, neutropenia, and CPK elevations; no new safety risks were observed compared with previous results.^{1,2}

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Table 1. Safety overview

E/100 PY (95% CI)	MTX mono (n=314; PY=601.9)	UPA 15 mg QD mono (n=317; PY=703.4)	UPA 30 mg QD mono (n=314; PY=687.6)
Any AE	240.2 (228.0, 252.9)	268.0 (256.0, 280.4)	292.5 (279.8, 305.5)
Any serious AE	10.8 (8.3, 13.8)	12.2 (9.8, 15.1)	16.3 (13.4, 19.6)
Any AE leading to discontinuation of study drug	6.5 (4.6, 8.9)	7.3 (5.4, 9.5)	7.7 (5.8, 10.1)
Any death ^a	0.7 (0.2, 1.7)	0.9 (0.3, 1.9)	1.0 (0.4, 2.1)
Serious infection	2.5 (1.4, 4.1)	3.3 (2.1, 4.9)	4.4 (2.9, 6.2)
Opportunistic infection excluding TB and HZ	0.2 (0.0, 0.9)	0.1 (0.0, 0.8)	0.3 (0.0, 1.1)
HZ	0.8 (0.3, 1.9)	4.5 (3.1, 6.4)	4.7 (3.2, 6.6)
Active TB	0	0.3 (0.0, 1.0)	0.3 (0.0, 1.1)
NMSC	0	0.4 (0.1, 1.2)	1.0 (0.4, 2.1)
Malignancy other than NMSC	1.0 (0.4, 2.2)	0.6 (0.2, 1.5)	1.2 (0.5, 2.3)
Hepatic disorder	14.1 (11.3, 17.5)	12.5 (10.0, 15.4)	15.0 (12.2, 18.2)
GI perforation ^b	0	0	0.4 (0.1, 1.3)
Neutropenia	2.2 (1.2, 3.7)	4.5 (3.1, 6.4)	5.7 (4.0, 7.8)
CPK elevation	1.8 (0.9, 3.3)	7.7 (5.8, 10.0)	15.4 (12.6, 18.6)
MACE ^b	0.3 (0.0, 1.2)	0.4 (0.1, 1.2)	0.6 (0.2, 1.5)
VTE ^b	0.3 (0.0, 1.2)	0.4 (0.1, 1.2)	0.6 (0.2, 1.5)

Data were censored at the time of MTX or UPA addition for rescued pts

^aIncludes treatment-emergent (≤ 30 days after the last dose of study drug) and non-treatment-emergent deaths. ^bAdjudicated

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POS0656

RELATIONSHIP BETWEEN CHANGES IN LIPID LEVELS AND IMPROVEMENT IN DISEASE ACTIVITY OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING UPADACITINIB TREATMENT: POOLED ANALYSIS OF DATA FROM TWO PHASE 3 STUDIES

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Background: Upadacitinib (UPA) is an oral Janus kinase (JAK) inhibitor engineered to have greater selectivity for JAK1 vs JAK2, JAK3, and tyrosine kinase 2, and is approved for the treatment of RA. Across 2 double-blind, placebo (PBO)-controlled Phase 3 studies of UPA in patients with RA, after an initial increase through Week 8, lipid levels remained stable up to Week 24.^{1,2} Previous studies of JAK or IL-6 receptor inhibitors have reported a negative correlation between changes in lipid levels and RA disease activity.^{3,4}

Objectives: To determine the relationship between changes in lipid levels and disease activity outcomes in patients with RA treated with UPA.

Methods: Patients with RA and an inadequate response to conventional synthetic/biologic DMARDs (cs/bDMARD-IR) from SELECT-NEXT/SELECT-BEYOND, respectively, were randomized to receive UPA 15 mg once daily (QD), UPA 30 mg QD, or PBO for 12 weeks followed by an extension of up to 5 years; patients randomized to PBO switched to UPA 15 or 30 mg after 12 weeks. Spearman correlations of maximum changes from baseline (BL) through Week 12 in fasting-state lipid levels (low- and high-density lipoprotein cholesterol [LDL-C; HDL-C], and total cholesterol [TC]) with clinical disease activity outcomes measured by change from BL in Clinical Disease Activity Index (CDAI), DAS of 28 joints using CRP (DAS28[CRP]), tender/swollen joint count in 28 joints (TJC28/SJC28), and pain by visual analog scale (VAS) at Weeks 12 and 24, were determined. Spearman correlations of maximum changes from BL in lipid levels and CRP through Week 12 were also determined.

Results: Available fasting samples from 1,160 pooled patients (UPA 15 mg, n=386; UPA 30 mg, n=384; PBO, n=390) were included. Modest, but statistically significant, negative correlations were observed between maximum changes from BL in TC through Week 12 and change from BL in CDAI, DAS28[CRP], SJC28, and pain (VAS) at Week 12 with UPA 15 or 30 mg (Figure 1); similar trends were observed at Week 24. Significant correlations between changes in LDL-C and HDL-C and disease activity outcomes were also observed, but were not consistent across UPA doses and time points. No significant correlations were noted between changes in lipid levels and disease activity outcomes in the PBO group. Statistically significant weak negative relationships were observed between maximum changes from BL in lipid levels and CRP levels through Week 12 with UPA 15 mg (HDL-C and TC) or UPA 30 mg (LDL-C and TC) (Table 1).

Conclusion: In this large pooled data set of patients receiving UPA, increases in lipid levels showed modest, but statistically significant, correlations with improvement in clinical disease activity outcomes in patients with cs/bDMARD-IR RA. These results add to evidence suggesting a relationship between systemic inflammation and lipid metabolism in patients with RA, which is modifiable with effective interventions, and reinforce the importance of monitoring for hyperlipidemia in these patients.

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Figure. Spearman correlations of maximum changes from BL in lipid levels through Week 12 with disease activity outcomes at Weeks 12 and 24

	Week 12			Week 24			Key*
	LDL-C	HDL-C	TC	LDL-C	HDL-C	TC	
CDAI	UPA 15 mg QD	-0.117* (n=286)	-0.136* (n=288)	-0.160** (n=284)	-0.124* (n=278)	-0.147* (n=280)	-0.179** (n=280)
	UPA 30 mg QD	-0.116 (n=282)	-0.022 (n=285)	-0.158** (n=285)	-0.147* (n=284)	-0.054 (n=287)	-0.157** (n=287)
	PBO	-0.075 (n=281)	-0.071 (n=281)	-0.076 (n=281)			
DAS28[CRP]	UPA 15 mg QD	-0.125* (n=299)	-0.189** (n=301)	-0.195** (n=302)	-0.151** (n=292)	-0.143* (n=294)	-0.185** (n=294)
	UPA 30 mg QD	-0.191** (n=296)	-0.086 (n=301)	-0.240*** (n=303)	-0.224*** (n=296)	-0.117 (n=298)	-0.264*** (n=298)
	PBO	-0.068 (n=301)	-0.074 (n=301)	-0.11 (n=301)			
TJC28	UPA 15 mg QD	-0.093 (n=305)	-0.066 (n=307)	-0.098 (n=307)	-0.084 (n=295)	-0.062 (n=297)	-0.097 (n=297)
	UPA 30 mg QD	-0.106 (n=305)	-0.01 (n=305)	-0.128* (n=305)	-0.112 (n=277)	-0.009 (n=279)	-0.098 (n=279)
	PBO	-0.06 (n=303)	-0.028 (n=303)	-0.063 (n=303)			
SJC28	UPA 15 mg QD	-0.116* (n=302)	-0.067 (n=307)	-0.140* (n=307)	-0.166** (n=297)	-0.069 (n=297)	-0.195** (n=294)
	UPA 30 mg QD	-0.118* (n=303)	-0.023 (n=305)	-0.161** (n=305)	-0.126* (n=277)	-0.043 (n=279)	-0.132* (n=279)
	PBO	-0.069 (n=303)	-0.067 (n=303)	-0.109 (n=303)			
Pain (VAS)	UPA 15 mg QD	-0.046 (n=302)	-0.184** (n=304)	-0.132* (n=304)	-0.047 (n=292)	-0.192*** (n=294)	-0.095 (n=294)
	UPA 30 mg QD	-0.118* (n=299)	-0.044 (n=301)	-0.169** (n=301)	-0.184** (n=273)	-0.037 (n=275)	-0.208*** (n=273)
	PBO	-0.046 (n=301)	-0.093 (n=301)	-0.043 (n=301)			

*p<0.05, **p<0.01, ***p<0.001.

BL, baseline; CDAI, Clinical Disease Activity Index; DAS28[CRP], DAS of 28 joints using CRP; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PBO, placebo; QD, once daily; SJC28, swollen joint count in 28 joints; TC, total cholesterol; TJC28, total joint count in 28 joints; UPA, upadacitinib; VAS, visual analog scale.

Table 1. Spearman correlation of maximum changes from BL in lipid levels through Week 12 with maximum change from BL in CRP through Week 12

	UPA 15 mg QD	UPA 30 mg QD	PBO
LDL-C	-0.099 (n=303)	-0.174** (n=302)	-0.053 (n=303)
HDL-C	-0.184** (n=305)	-0.087 (n=304)	-0.024 (n=303)
TC	-0.189*** (n=305)	-0.236*** (n=304)	-0.056 (n=303)

p<0.01, *p<0.001.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PBO, placebo; QD, once daily; TC, total cholesterol; UPA, upadacitinib

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POS0657

GEOGRAPHIC VARIATION OF SAFETY IN THE FILGOTINIB RHEUMATOID ARTHRITIS PROGRAM

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