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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=304)	-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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Background: The Janus kinase-1 preferential inhibitor filgotinib (FIL) improved signs and symptoms of rheumatoid arthritis (RA) in the FIL clinical program.¹⁻³

Objectives: To assess FIL safety across regions.

Methods: This was an analysis of patients (pts) meeting 2010 ACR/EULAR RA criteria in pooled phase (P)2 DARWIN 1-2 (D1-2), P3 FINCH 1-3 (F1-3), and long-term extension studies (DARWIN 3, FINCH 4). Data were analyzed by region: North America, South and Central America, Western Europe, Eastern Europe, Asia, South East (SE) Asia, and Other. Week (W)12 placebo (PBO)-controlled analysis included data from pts receiving once-daily FIL 100 mg (FIL100), FIL 200 mg (FIL200), or PBO for ≤ 12 W (D1-2, F1-2); long-term as-treated data included pts from all 7 studies receiving FIL100 or FIL200; data after rerandomization were included and contributed to treatment received. Data presented as exposure-adjusted incidence rates (EAIRs)/100 patient-years of exposure (PYE) of treatment-emergent (TE) adverse events (TEAEs).

Results: Table 1 shows EAIRs of TEAEs in PBO-controlled analysis. EAIRs/100 PYE of all TEAEs in Western Europe, Asia, and Other were higher than in remaining regions and for PBO vs FIL arms; EAIRs for FIL200/FIL100 in North America and SE Asia were higher vs PBO. EAIRs/100 PYE of TE serious AEs were higher in SE Asia for FIL100 and for FIL200/FIL100 in Other, with high PBO EAIRs in Western Europe. EAIRs/100 PYE of TEAEs leading to study discontinuation were higher in FIL arms vs PBO in Western Europe and Other (FIL200); in Asia and SE Asia, EAIRs were higher for PBO vs FIL200/FIL100.

Table 1. EAIR of TEAEs (placebo-controlled)

	North America N = 481	South and Central America N = 350	Western Europe N = 141	Eastern Europe N = 933	Asia N = 236	South East Asia N = 135	Other N = 70
TEAE							
FIL200 ^a	216.9 (162.5, 289.5)	205.6 (155.1, 272.6)	285.0 (188.6, 430.8)	150.3 (119.3, 189.4)	248.9 (180.6, 343.1)	165.1 (104.0, 262.1)	298.4 (150.3, 592.5)
FIL100 ^b	182.2 (136.8, 242.7)	159.2 (117.3, 216.1)	285.7 (183.7, 444.3)	146.4 (115.9, 185.0)	246.9 (180.3, 338.1)	153.7 (94.2, 251.0)	263.5 (113.9, 609.2)
PBO ^c	174.5 (130.3, 233.7)	162.1 (118.8, 221.2)	314.9 (200.7, 493.9)	148.4 (117.6, 187.4)	259.0 (188.0, 356.8)	81.6 (40.8, 163.3)	306.0 (142.8, 655.7)
TE serious AE							
FIL200 ^a	14.3 (6.0, 34.4)	11.4 (3.7, 35.5)	8.3 (1.2, 59.0)	12.2 (5.2, 28.7)	5.5 (0.8, 38.9)	0.0 (0.0, ∞)	49.6 (10.2, 144.9)
FIL100 ^b	10.6 (4.0, 28.3)	7.2 (1.8, 28.7)	19.9 (5.0, 79.7)	15.1 (6.8, 33.7)	16.2 (5.2, 50.2)	28.8 (9.3, 89.4)	20.5 (0.5, 114.0)
PBO ^c	16.1 (7.2, 35.9)	7.5 (1.9, 30.0)	29.6 (9.5, 91.7)	4.6 (1.3, 15.8)	11.4 (2.8, 45.5)	10.2 (1.4, 72.4)	0.0 (0.0, 69.2)
TEAE leading to discontinuation							
FIL200 ^a	8.6 (2.8, 26.6)	3.8 (0.1, 21.2)	16.6 (4.2, 66.5)	12.9 (5.5, 30.5)	0.0 (0.0, 20.2)	9.2 (1.3, 65.1)	16.5 (0.4, 92.1)
FIL100 ^b	10.6 (4.0, 28.3)	7.2 (0.9, 26.0)	19.9 (5.0, 79.7)	1.9 (0.2, 13.8)	5.4 (0.1, 30.1)	9.6 (1.4, 68.2)	0.0 (0.0, 75.5)
PBO ^c	5.4 (1.3, 21.5)	0.0 (0.0, 13.8)	9.9 (1.4, 70.0)	12.9 (5.4, 30.7)	17.1 (3.5, 49.9)	20.4 (5.1, 81.6)	0.0 (0.0, 69.2)

Data presented as EAIR (95% CI)/100 patient-years

^aN = 777, 179.8 PYE ^bN = 788, 181.6 PYE ^cN = 781, 178.4 PYE

A subject may contribute to more than one treatment group if they received more than one treatment of interest.

EAIR and corresponding 95% CI were estimated using Poisson regression model by treatment, including study and treatment with an offset of natural log of exposure time, except when 0 events occurred; Poisson model was not adjusted by study.

AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; PBO, placebo; PYE, patient-years of exposure; TE, treatment-emergent. Figure shows serious infections (SI), venous thromboembolism (VTE) and herpes zoster (HZ) EAIRs.

EAIRs for SI were highest in Other for FIL200 and SE Asia for FIL100. While VTE EAIRs were low, pts in 5/7 regions had VTE. HZ EAIRs were highest in Asia.

Conclusion: Although EAIR of TEAEs varied between regions, no consistent trend was reflected in any particular region.

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POS0658 GEOGRAPHIC VARIATION OF EFFICACY IN THE FILGOTINIB RHEUMATOID ARTHRITIS PROGRAM

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Background: The Janus kinase-1 preferential inhibitor filgotinib (FIL) improved signs and symptoms of rheumatoid arthritis (RA) across the FIL clinical program.¹⁻³

Objectives: To assess FIL efficacy across geographic regions.

Methods: Pooled data from patients (pts) meeting 2010 ACR/EULAR RA criteria randomised to once-daily FIL 200 mg (FIL200), FIL100 mg (FIL100), or placebo (PBO) with background conventional synthetic disease-modifying antirheumatic drugs in DARWIN 1 (P2; up to week [W]12) and FINCH 1-2 (P3; up to W24) studies were evaluated. Data were analysed by region: North America, South and Central America, Western Europe, Eastern Europe, Asia, South East (SE) Asia, and Other. W12 American College of Rheumatology 20% improvement (ACR20) and W24 Disease Activity Score in 28 joints (C-reactive protein) (DAS28[CRP]) <2.6 and ≤ 3.2 response rates were analysed by a logistic regression model. Change from baseline (CFB) in Health Assessment Questionnaire-Disability