Figure: Changes in ABCA1-dependent cholesterol efflux are significantly elevated in UPA-treated patients at Week 12

Abstract THU0166 – Figure 1

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THU0167

SAFETY PROFILE OF UPADACITINIB IN RHEUMATOID ARTHRITIS: INTEGRATED ANALYSIS FROM THE SELECT PHASE 3 CLINICAL PROGRAM

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Background: Upadacitinib (UPA), a JAK1-selective inhibitor, significantly improved clinical signs and symptoms of rheumatoid arthritis (RA) in patients (pts) naïve to methotrexate (MTX) and with an inadequate response to conventional synthetic DMARDs (csDMARD-IR) or biologic DMARDs (bDMARD-IR)^{1,2,3}.

Objectives: Assess the safety of UPA as monotherapy (mono) and as combination therapy with background csDMARDs in pts with moderately to severely active RA from the safety database of the Phase 3 clinical program.

Methods: Treatment-emergent adverse events (TEAEs) from 5 pivotal, randomized, double-blind, controlled Phase 3 trials of UPA 15 mg [included in all 5 trials] or 30 mg QD [included in 4 trials] in RA pts were analyzed using integrated short-term (ST, 12/14 week, placebo [PBO]-controlled; n [%]), individual studies with long-term [LT] active comparator (UPA mono vs MTX; UPA 15 mg with background MTX vs originator adalimumab, ADA, events/100 patient-years [E/100PY]) and integrated LT (all Phase 3 exposure; E/100PY) analyses sets.

Results: Across the Phase 3 trials, 3834 pts received ≥1 dose of UPA 15 mg (n=2630) or 30 mg QD (n=1204) =4020.1 PY of UPA exposure with no option to switch doses. The ST frequencies of overall SAEs and AEs leading to discontinuation were low, but higher on both UPA doses vs PBO. LT event rates were similar on UPA 15 mg vs ADA and slightly higher on UPA vs MTX mono. Deaths occurred in all treatment groups. Serious infection (SIEs) frequencies were higher on both UPA doses vs PBO. SIE rates on both UPA doses were higher vs MTX, but similar on UPA 15 mg vs ADA. Herpes zoster (HZ) frequencies and

rates were higher on both UPA doses vs PBO, and vs MTX, ADA, respectively. The rates of SIE and HZ were higher on UPA 30 vs 15 mg. Adjudicated MACE were reported in all treatment groups including PBO. LT MACE rates were similar on UPA 15 mg and ADA and on UPA 15 mg and MTX mono, but higher on UPA 30 mg mono (low number of events, 2-4 per set). Adjudicated VTEs occurred at comparable frequencies on UPA vs PBO and at comparable rates on UPA vs active comparators. Malignancy (excluding non-melanoma skin cancer [NMSC]) rates were similar on UPA vs MTX, UPA 15 mg vs ADA, and 15 vs 30 mg. The NMSC rates on UPA 15 mg and ADA were similar; the rate on 30 mg was higher than 15 mg, but both UPA NMSC rates were in the range reported for RA patients treated with DMARDs⁴. The standardized incidence ratio (95% CI) for malignancy (15 mg: 0.98 [0.61, 1.49], 30 mg: 1.49 [0.85, 2.42]) was not elevated vs the general population.

Conclusion: Treatment with UPA increased the risk of SIE and HZ, but not those of VTE, MACE, and malignancy vs comparators. These data support that UPA has an acceptable safety profile in the treatment of moderately to severely active RA.

Abstract THU0167 – Table 1.

Table: Overall TEAEs and AEs in pts treated with UPA compared to PBO and active control

	PBO-Controlled Short-term Exposure			Long-term MTX-controlled Analysis			Long-term Adalimumab-Controlled Analysis ¹			All Phase 3 Long-term	
	UPA 15 mg QD (N=1035)	PBO (N=1042)	UPA 30 mg QD (N=384)	UPA 15 mg QD Mono (N=317)	UPA 30 mg QD Mono (N=314)	MTX Mono (N=319)	Any UPA 15 mg QD (N=1417)	Any ADA 40 mg QD (N=579)	Any ADA 40 mg QD (N=579)	Any UPA 15 mg QD (N=1417)	Any UPA 30 mg QD (N=1044)
Any AE	56.0	48.4	59.9	34.4	38.2	30.1	26.4	29.8	29.7	26.7	36.7
Any SAE	3.4	1.8	4.9	14.3	15.4	11.9	12.9	15.6	15.0	21.3	21.3
Any AE leading to discontinuation	2.8	2.0	7.3	11.4	10.7	8.9	7.4	11.1	8.4	13.3	13.3
Deaths ²	0	0.2	0.3	1.2	1.8	0.3	0.4	0.9	0.5	1.0	1.0
AEs											
Serious Infections	1.2	0.6	1.8	4.1	5.0	2.9	4.1	4.3	3.8	6.2	6.2
Herpes Zoster	0.7	0.3	1.6	6.4	4.8	1.3	3.1	1.3	3.7	7.0	7.0
MACE (adjudicated)	<0.1	0.3	0.3	0.9	1.2	0.6	0.4	0.4	0.6	1.0	1.0
VTE (adjudicated)	0.2	<0.1	0	0	0.3	0.6	0.3	1.1	0.6	0.3	0.3
Any non-melanoma skin cancer (NMSC)	0	<0.1	0.5	0.3	0.3	0	0.2	0.2	0.3	1.1	1.1
Any malignancy other than NMSC	<0.1	<0.1	0.8	1.2	0.6	1.0	0.4	0.6	0.9	1.4	1.4

ADA, adalimumab; AE, adverse event; CV, cardiovascular; E, events; MACE, major adverse cardiovascular events; MI, myocardial infarction; Mono, monotherapy; MTX, methotrexate; PBO, placebo; PY, patient-years; QD, once-daily; RTI, respiratory tract infection; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolism.

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