Long-Term Safety of Upadacitinib Across Rheumatoid Arthritis, Psoriatic Arthritis, and Axial Spondyloarthritis Encompassing ~17,000 Patient-Years of Clinical Trial Data

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OBJECTIVE

- To evaluate the long-term integrated safety profile of upadacitinib (UPA) 15 mg across rheumatological indications, in the context of active comparators, from the SELECT clinical program

INTRODUCTION

- The efficacy and safety of UPA, an oral JAK inhibitor, have been demonstrated in the SELECT clinical trials for several rheumatic diseases, including RA, PsA, AS (also referred to as r-axSpA), and nr-axSpA
- This analysis provides further characterization of the long-term safety profile of UPA across diverse patient populations and in the context of active comparators, such as adalimumab (ADA) and MTX

METHODS

- Safety data (cutoff date: 15 August 2024) from 11 phase 3 UPA trials were compiled for RA (6 trials), PsA (2 trials), AS (2 trials, one of which is a phase 2/3), and nr-axSpA (1 trial) for this integrated analysis[1,2]
- Treatment-emergent adverse events (TEAEs), defined as adverse events (AEs) with an onset on or after the first dose of study drug and ≤ 30 days (UPA 15 mg and MTX) or ≤ 70 days (ADA) after last dose of study drug, were coded using MedDRA version 27.0
- TEAEs are reported for RA (pooled UPA 15 mg, ADA [1 study only], and MTX [1 study only]), PsA (pooled UPA 15 mg and ADA [1 study only]), AS (pooled UPA 15 mg), nr-axSpA (UPA 15 mg), and pooled axSpA (pooled UPA 15 mg from the AS and nr-axSpA studies)
- TEAEs are presented as exposure-adjusted event rates (EAERs; events/100 patient-years [E/100 PY]) with 95% CIs; a subset of TEAEs of special interest are also presented as exposure-adjusted incidence rates (EAIRs; n/100 PY) with 95% CIs
- For EAERs, total patient exposure was used which could include multiple events in the same patient; for EAIRs, patients were censored and further exposure to study drug after the first event was not counted
- Deaths (including COVID-19), MACE, VTE, and gastrointestinal perforations were adjudicated by blinded, independent committees using pre-specified definitions
- Country-age-gender adjusted standardized mortality ratios (SMRs) using the World Health Organization 2019 data were calculated

RESULTS

PATIENTS

- In total, 4998 patients received ≥ 1 dose of UPA 15 mg in the SELECT trials, totaling 16,683.5 PYs of exposure, with the majority of exposure from the RA studies **(Table 1)**
- Baseline demographics and clinical characteristics are representative of the patient populations; most patients (range: 73.9%–83.6%) had ≥ 1 cardiovascular (CV) risk factor

Table 1. Baseline Demographics and Clinical Characteristics

	RA			PsA		AS	nr-axSpA
	UPA 15 mg QD n = 3209 PY = 12315.8	ADA 40 mg EOW n = 579 PY = 1978.0	MTX n = 314 PY = 860.1	UPA 15 mg QD n = 907 PY = 2971.7	ADA 40 mg EOW n = 429 PY = 1520.0	UPA 15 mg QD n = 596 PY = 1015.3	UPA 15 mg QD n = 286 PY = 380.7
Age (years), mean (SD)	54.3 (12.0)	54.2 (11.7)	53.3 (12.9)	51.5 (12.1)	51.4 (12.0)	43.3 (12.3)	42.2 (12.2)
Sex (female), n (%)	2581 (80.4)	470 (81.2)	240 (76.4)	478 (52.7)	222 (51.7)	162 (27.2)	167 (58.4)
Time since diagnosis (years), mean (SD)	8.5 (8.4)	8.2 (8.0)	2.6 (5.1)	7.2 (7.8)	5.9 (7.1)	7.4 (7.9)	5.0 (5.8)
Concomitant therapies, n (%)							
csDMARD	2548 (79.4)	579 (100.0)	0	652 (71.9)	346 (80.7)	159 (26.7)	88 (30.8)
Glucocorticoid	1756 (54.7)	350 (60.4)	164 (52.2)	133 (14.7)	70 (16.3)	59 (9.9)	31 (10.8)
NSAID	2032 (63.3)	364 (62.9)	223 (71.0)	566 (62.4)	281 (65.5)	471 (79.0)	213 (74.5)
Statin	321 (10.0)	42 (7.3)	26 (8.3)	82 (9.0)	28 (6.5)	17 (2.9)	8 (2.8)
≥ 1 CV risk factor,[a] n (%)	2472 (77.0)	446 (77.0)	232 (73.9)	758 (83.6)	339 (79.0)	454 (76.2)	234 (81.8)

ADA, adalimumab; csDMARD, conventional synthetic DMARD; CV, cardiovascular; EOW, every other week; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PY, patient-years; QD, once daily; UPA, upadacitinib.

[a]CV risk factors include: prior CV event, hypertension, diabetes mellitus, current and former tobacco/nicotine use, elevated LDL-C (≥ 3.36 mmol/L), and lowered HDL-C (≤ 1.034 mmol/L).

OVERVIEW OF TEAEs AND DEATHS

- Rates of serious AEs were generally similar across treatment groups and indications, although higher with UPA 15 mg and ADA in RA **(Table 2)**
- Rates of AEs leading to discontinuation of study drug were also generally similar
  - The most frequently reported AEs leading to discontinuation of UPA 15 mg varied by indication; RA: pneumonia (n = 22/575; 0.2 E/100 PY), PsA: COVID-19 (n = 7/151; 0.2 E/100 PY), AS: headache (n = 3/42; 0.3 E/100 PY), nr-axSpA: worsening axial spondyloarthritis, pulmonary embolism, and nasal polyps (each n = 2/20; 0.5 E/100 PY), and pooled axSpA: headache and pulmonary embolism (each n = 4/62; 0.3 E/100 PY)
- Rates of treatment-emergent deaths were numerically higher with UPA 15 mg vs comparators in RA and PsA; rates of treatment-emergent COVID-19–related deaths ranged from 0.0 to 0.2 E/100 PY and CV deaths ranged from 0.0 to 0.1 E/100 PY
  - COVID-19/COVID-19 pneumonia was the most common cause of death across all rheumatological indications in the SELECT clinical program
- SMR (95% CI) for treatment-emergent deaths with UPA 15 mg was 0.63 (0.49, 0.80) in RA and 0.66 (0.38, 1.06) in PsA; SMRs were not calculated for AS or nr-axSpA (low events)

Table 2. TEAEs in Patients Treated With UPA, ADA, or MTX Across RA, PsA, AS, nr-axSpA, and Pooled axSpA[a]

	RA			PsA		AS	nr-axSpA	Pooled axSpA
	UPA 15 mg QD n = 3209	ADA 40 mg EOW n = 579	MTX n = 314	UPA 15 mg QD n = 907	ADA 40 mg EOW n = 429	UPA 15 mg QD n = 596	UPA 15 mg QD n = 286	UPA 15 mg QD n = 882
Exposure								
Total, PY	12,315.8	1978.0	860.1	2971.7	1520.0	1015.3	380.7	1396.0
Mean (SD), weeks	200.3 (125.8)	178.3 (162.7)	143.0 (105.3)	171.0 (90.4)	184.9 (95.4)	88.9 (28.5)	69.5 (33.1)	82.6 (31.4)
Median (min, max), weeks	216.3 (0.3, 441.0)	114.3 (0.1, 446.6)	134.1 (1.0, 263.1)	190.1 (0.1, 332.9)	259.7 (2.0, 294.4)	91.0 (0.1, 198.0)	53.8 (0.1, 119.6)	90.6 (0.1, 198.0)
TEAEs, E/100 PY (95% CI)								
Any AE	201.4 (198.9, 203.9)	181.1 (175.2, 187.1)	205.4 (196.0, 215.2)	229.4 (224.0, 234.9)	198.4 (191.4, 205.6)	189.9 (181.5, 198.6)	211.7 (197.4, 226.9)	195.8 (188.6, 203.3)
Any serious AE	12.7 (12.1, 13.3)	12.7 (11.2, 14.4)	9.1 (7.2, 11.3)	10.6 (9.5, 11.8)	8.2 (6.8, 9.7)	7.8 (6.2, 9.7)	8.7 (6.0, 12.2)	8.0 (6.6, 9.7)
Any AE leading to discontinuation of study drug	4.7 (4.3, 5.1)	5.0 (4.0, 6.0)	5.8 (4.3, 7.7)	5.1 (4.3, 6.0)	4.1 (3.2, 5.3)	4.1 (3.0, 5.6)	5.3 (3.2, 8.1)	4.4 (3.4, 5.7)
All deaths[b]	0.8 (0.6, 1.0)	0.9 (0.5, 1.4)	0.9 (0.4, 1.8)	0.8 (0.5, 1.2)	0.3 (0.1, 0.8)	< 0.1 (0.0, 0.5)	0.0 (0.0, 1.0)	< 0.1 (0.0, 0.4)
Treatment-emergent deaths[c]	0.6 (0.4, 0.7)	0.5 (0.2, 0.9)	0.1 (0.0, 0.6)	0.6 (0.3, 0.9)	0.2 (0.0, 0.6)	< 0.1 (0.0, 0.5)	0.0 (0.0, 1.0)	< 0.1 (0.0, 0.4)
Nontreatment-emergent deaths[d]	0.2 (0.2, 0.3)	0.4 (0.1, 0.7)	0.8 (0.3, 1.7)	0.3 (0.1, 0.5)	0.1 (0.0, 0.5)	0.0 (0.0, 0.4)	0.0 (0.0, 1.0)	0.0 (0.0, 0.3)

ADA, adalimumab; AE, adverse event; E, event; EOW, every other week; PY, patient-years; QD, once daily; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

[a]Due to the completion of several SELECT studies, slight variations in the reported data may be noted compared with previous publications.

[b]With UPA 15 mg treatment, there were a total of 98 deaths in RA, 25 in PsA, 1 in AS, and 0 in nr-axSpA.

[c]Treatment-emergent deaths were defined as on or after the first dose of study drug and ≤ 30 days after the last dose of study drug for UPA 15 mg and MTX or ≤ 70 days for ADA.

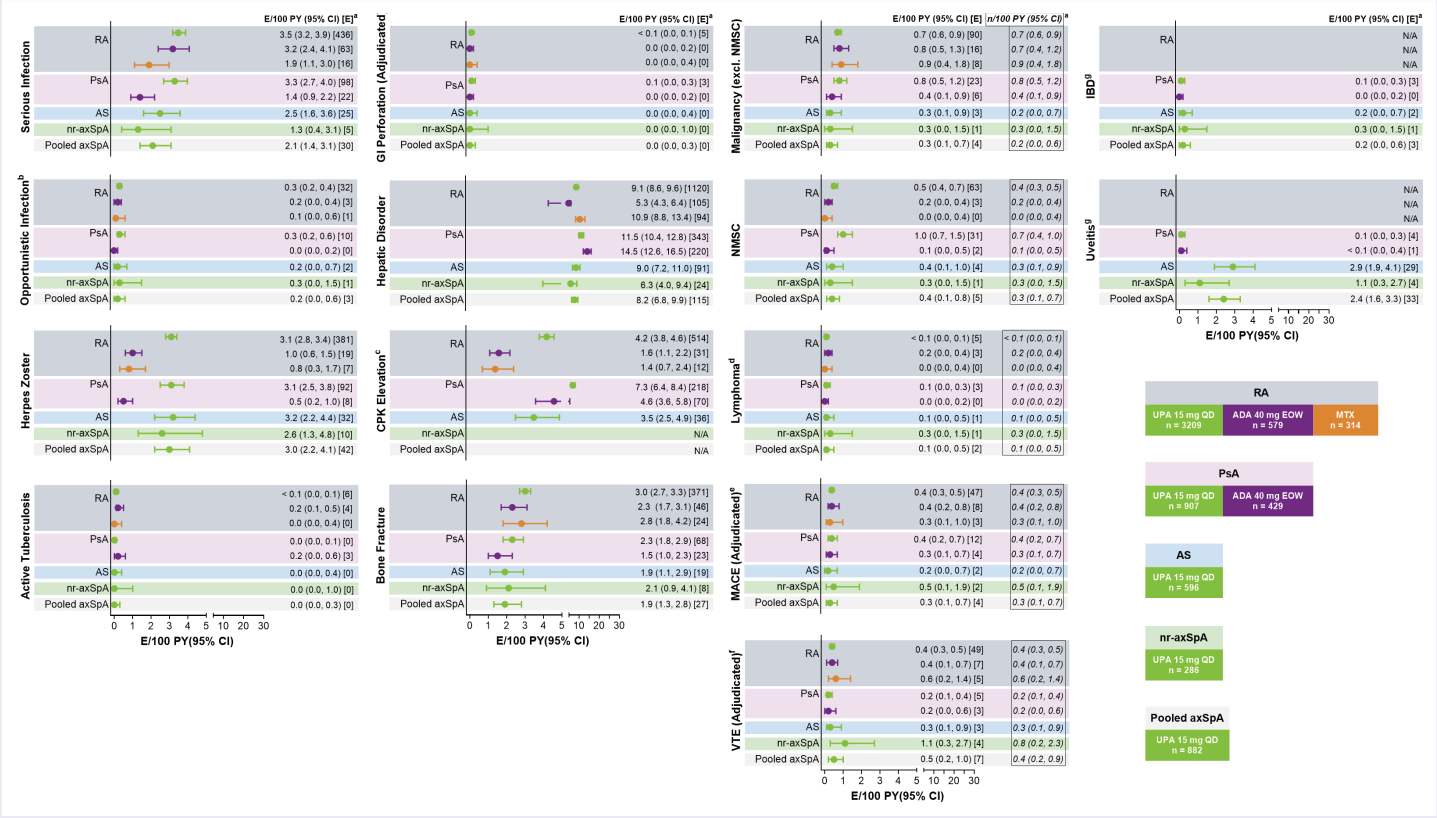
[d]Nontreatment-emergent deaths were defined as > 30 days after the last dose of study drug for UPA 15 mg and MTX or > 70 days for ADA.

RESULTS (CONTINUED)

TEAEs OF SPECIAL INTEREST (AESI)

- Rates of serious infection and opportunistic infection were generally similar across treatment groups and indications, with the exception of serious infection in PsA (predominately COVID-19/COVID-19 pneumonia), which was higher with UPA 15 mg vs ADA (**Figure**)
  - The most common serious infection and serious AE with UPA 15 mg across all indications was COVID-19 pneumonia
- Rates of herpes zoster (HZ) and elevated creatinine phosphokinase (CPK), which are known risks for JAK inhibitors, were higher with UPA 15 mg vs active comparators in RA and PsA, while rates of HZ with UPA 15 mg were similar across indications
  - Most treatment-emergent events of HZ with UPA 15 mg were nonserious (RA: 95.8%; PsA: 96.7%; AS: 96.9%; nr-axSpA: 100.0%) and involved a single dermatome (RA: 75.4%; PsA: 76.5%; AS: 81.5%; nr-axSpA: 80.0%); few patients had a history of HZ vaccination (range: 1.8%–3.9%)
- Rates of malignancy excluding nonmelanoma skin cancer (NMSC) were generally low and similar across treatment groups and indications; rates of NMSC were also generally low and were higher with UPA 15 mg vs active comparators in RA and PsA
  - Basal cell carcinoma was the most common type of malignancy reported with UPA 15 mg treatment in RA (29 events) and PsA (14 events), with few events reported in AS (3) and nr-axSpA (1)
- Rates of MACE and VTE were generally low and were similar across treatment groups and indications; most events occurred in patients with ≥ 1 baseline CV risk factor
- Rates of extra-musculoskeletal manifestations, including inflammatory bowel disease and uveitis, were generally low across spondyloarthritis conditions; however, rates of uveitis were higher in AS, nr-axSpA, and pooled axSpA vs PsA

Figure. TEAEs of Special Interest in Patients Treated With UPA Across RA, PsA, AS, nr-axSpA, and Pooled axSpA



ADA, adalimumab; CPK, creatine phosphokinase; E, event; EAER, exposure-adjusted event rate; EAIR, exposure-adjusted incidence rate; EOW, every other week; GI, gastrointestinal; IBD, inflammatory bowel disease; NMSC, nonmelanoma skin cancer; PY, patient-years; QD, once daily; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

[a]UPA sample sizes include patients who switched from placebo and received ≥ 1 dose of UPA; data are presented as EAERs (defined as E/100 PY [95% CI]) [number of E] or as EAIRs (defined as n/100 PY [95% CI]; shown in box). For EAERs, total patient exposure was used with multiple events in the same patient included. For EAIRs, patients were censored at the time of the first event.

[b]Excluding tuberculosis and herpes zoster.

[c]Per the protocol, CPK elevation was not measured in the nr-axSpA study.

[d]Cases of abnormal lymphocyte morphology are included (UPA 15 mg: RA [1], PsA [3], AS [1], and nr-axSpA [1]), as this preferred term is included in the Malignant Lymphoma Standardized MedDRA Queries but were not confirmed to be true lymphomas.

[e]Defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death.

[f]Includes deep vein thrombosis and pulmonary embolism (fatal and nonfatal).

[g]IBD includes inflammatory bowel disease, colitis ulcerative, ulcerative colitis, Crohn's disease, ulcerative proctitis, and proctitis; uveitis includes uveitis, iritis, and iridocyclitis; neither IBD or uveitis data were captured for RA.

CONCLUSIONS

- As reported previously,[1,3,4] across RA, PsA, AS, nr-axSpA, and pooled axSpA, UPA 15 mg demonstrated a consistent overall safety profile, with no new safety risks identified with long-term treatment in the SELECT clinical trials
- Except for serious infection (in PsA, predominantly COVID-19/COVID-19 pneumonia), HZ, elevated creatine phosphokinase, and NMSC, the rates of TEAEs were generally similar between UPA 15 mg treatment and active comparators (ADA and MTX) in RA and PsA
- Real-world data, especially for indications with more limited clinical trial exposure (ie, AS and nr-axSpA), are needed to further contextualize and confirm the findings reported here

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