Safety Profile of Upadacitinib up to 6.5 Years of Exposure in Patients With Rheumatoid Arthritis

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OBJECTIVE

- To describe the long-term integrated safety profile of upadacitinib (UPA) relative to active comparators in patients with rheumatoid arthritis from the SELECT clinical program through the cutoff date of 15 August 2022

INTRODUCTION

- UPA is an oral JAK inhibitor that has demonstrated safety and efficacy in patients with moderate-to-severe RA in the phase 3 SELECT clinical program[2–7]
- Assessing the long-term safety of RA treatments is important for understanding benefits and risks and informing patient care

METHODS

STUDY DESIGN AND ANALYSIS

- Pooled safety data were analyzed from 6 randomized controlled trials evaluating UPA in RA[2–7] up to the data cut-off of August 15, 2022 **(Figure 1)**
- Treatment-emergent adverse events (TEAEs) and AEs of special interest were summarized for 3 groups: pooled UPA 15 mg once daily (QD; 6 trials), adalimumab (ADA) 40 mg every other week (EOW; 1 trial), and MTX (1 trial)
- Patients who switched from placebo, ADA, or MTX to UPA were included in the UPA group from the start of UPA treatment; those who switched from UPA to ADA were included in the ADA group from the start of ADA treatment and censored at the time of switch; MTX monotherapy data was censored at the time of rescue to combination therapy (addition of UPA)

METHODS (CONTINUED)

Figure 1. Integrated Safety Dataset From the SELECT Program

ADA, adalimumab; bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; EOW, every other week; IR, inadequate response; QD, once daily; UPA, upadacitinib.

- TEAEs were defined as AEs with an onset after the first dose and ≤30 days (UPA and MTX) or ≤70 days (ADA) after the last dose of study drug
- Blinded independent committees adjudicated deaths, cardiovascular events, VTEs, and gastrointestinal (GI) perforations using pre-specified definitions
- TEAEs were reported as exposure-adjusted event rates (EAERs; events per 100 patient-years [E/100 PY])
- Standardized mortality ratio (SMR) was estimated for the general population using World Health Organization country-age-gender specific mortality rates through 2016; age- and gender-adjusted standardized incidence ratio (SIR) for malignancy excluding non-melanoma skin cancer (NMSC) was estimated using maglinancy data from the Surveillance, Epidemiology, and End Results (SEER) database (2000–2018) for the general population

RESULTS

PATIENTS

- A total of 3209 patients received ≥1 dose of UPA 15 mg
- Baseline characteristics were generally similar across groups **(Table 1)**

Table 1. Patient Baseline Characteristics

	UPA 15 mg QD (n = 3209)	ADA 40 mg EOW (n = 579)	MTX monotherapy (n = 314)
Age (years), mean (SD)	54.3 (12.0)	54.2 (11.7)	53.3 (12.9)
Age ≥65 years, n (%)	643 (20.0)	106 (18.3)	58 (18.5)
Sex (female), n (%)	2581 (80.4)	470 (81.2)	240 (76.4)
BMI (kg/m^2), mean (SD)	29.1 (6.7)	29.4 (7.1)	28.0 (6.3)
BMI ≥30, n (%)	1201 (37.4)	227 (39.2)	97 (30.9)
Time since diagnosis (years), mean (SD)	8.6 (8.4)	8.3 (8.0)	2.6 (5.1)
Statin use (yes), n (%)	368 (11.5)	55 (9.5)	26 (8.3)
Patient history of, n (%)			
VTE	53 (1.7)	9 (1.6)	3 (1.0)
Prior CV event[a]	385 (12.0)	63 (10.9)	27 (8.6)
Hypertension	1302 (40.6)	252 (43.5)	112 (35.7)
Diabetes mellitus	383 (11.9)	61 (10.5)	31 (9.9)
Tobacco/nicotine use (current + former)	1222 (38.1)	199 (34.4)	120 (38.2)
Elevated LDL-C (≥3.36 mmol/L)	867 (27.2)	169 (29.2)	86 (27.5)
Lowered HDL-C (<1.034 mmol/L)	354 (11.0)	53 (9.2)	39 (12.4)

ADA, adalimumab; BMI, body mass index; CV, cardiovascular; EOW, every other week; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; QD, once daily; SD, standard deviation; UPA, upadacitinib.
[a]Prior CV events included any patient with a medical history term coded to the system organ class of cardiac disorders.

EXPOSURE AND TEAEs

- Overall exposure to UPA 15 mg treatment was 10 782.7 PY **(Table 2)**
- EAERs of AEs, serious AEs (SAEs), and AEs leading to discontinuation on UPA 15 mg were comparable to ADA and MTX
  - The most common AEs (≥5 E/100 PY) reported with UPA 15 mg were urinary tract infection, upper respiratory tract infection, and nasopharyngitis
  - COVID-19 pneumonia was the most common SAE with UPA 15 mg (0.7 E/100 PY); rates of SAEs of COVID-19 pneumonia were similar between ADA (0.2 E/100 PY) and MTX (0.1 E/100 PY)
- Rates of death were similar across the treatment groups
  - SMR analysis indicated that the mortality rate among patients with RA treated with UPA 15 mg was not higher than what would be expected among the general population (SMR [95% CI]: 0.67 [0.52, 0.86] including COVID-19 deaths; 0.41 [0.29, 0.56] excluding COVID-19 deaths)

Table 2. TEAEs in Patients Treated With UPA, ADA, and MTX

	UPA 15 mg QD (n = 3209)	ADA 40 mg EOW (n = 579)	MTX monotherapy (n = 314)
Exposure			
Total PY	10 782.7	1573.2	865.1
Mean (SD), years	3.4 (1.9)	2.7 (2.3)	2.8 (2.0)
Median (range), years	4.0 (0.0, 6.6)	2.2 (0.0, 6.6)	2.6 (0.0, 5.4)
TEAEs, E/100 PY (95% CI)			
Any AE	206.1 (203.4, 208.8)	195.5 (188.6, 202.5)	203.2 (193.8, 212.9)
Any SAE	12.8 (12.2, 13.5)	13.5 (11.7, 15.4)	9.0 (7.1, 11.3)
Any AE leading to study drug discontinuation	4.8 (4.4, 5.2)	5.5 (4.4, 6.8)	5.5 (4.1, 7.4)
Any COVID-19-related AE	4.6 (4.2, 5.0)	4.7 (3.7, 5.9)	2.4 (1.5, 3.7)
Deaths[a]	0.8 (0.7, 1.0)	1.0 (0.5, 1.6)	0.9 (0.4, 1.8)

ADA, adalimumab; CI, confidence interval; E/100 PY; events per 100 patient-years; EOW, every other week; PY, patient-years; QD, once daily; SAE, serious AE; SD, standard deviation; TEAEs, treatment-emergent AEs; UPA, upadacitinib.
[a]Includes treatment-emergent, non-treatment-emergent, and COVID-related deaths.

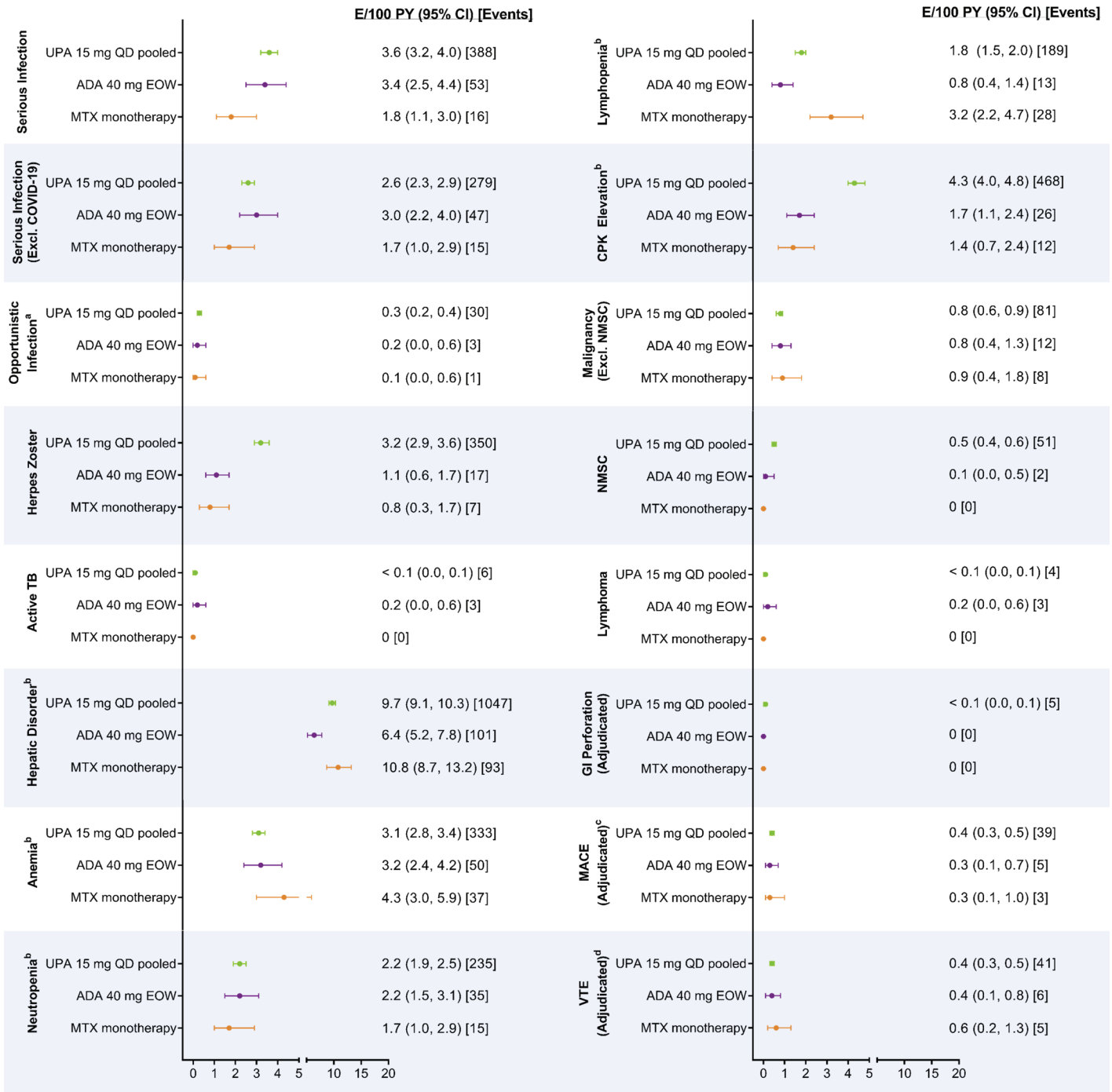
AEs OF SPECIAL INTEREST

- Rates of serious infections and opportunistic infections were similar between UPA 15 mg and ADA but higher compared with MTX **(Figure 2)**
  - Pneumonia was the most common serious infection reported with UPA 15 mg (0.5 E/100 PY)
- Herpes zoster (HZ) rates were higher with UPA 15 mg vs ADA and MTX
  - Most HZ cases with UPA 15 mg were non-serious (95%) and affected a single (75%) or unilateral multiple (16%) dermatomes; 8% of HZ cases were disseminated and none involved the central nervous system
- Similar rates of adjudicated MACE, adjudicated VTE, and malignancy (excluding NMSC) were seen across groups
  - The rate of NMSC was numerically higher with UPA 15 mg vs ADA; no cases occurred with MTX
  - SIR analysis indicated that the malignancy risk among patients with RA treated with UPA 15 mg was not higher than what would be expected among the general population (SIR [95% CI]: 0.98 [0.79, 1.20])
- Creatine phosphokinase elevations were transient and more common with UPA 15 mg than ADA or MTX
- Most anemia, neutropenia, and lymphopenia events with UPA 15 mg were non-serious and rarely led to treatment discontinuation (≤0.1 E/100 PY)
  - Higher rates of lymphopenia were seen with MTX vs UPA 15 mg and ADA

RESULTS (CONTINUED)

- Rates of hepatic disorders were similar between UPA 15 mg and MTX but higher compared with ADA
  - Most hepatic disorders were mild or moderate transaminase elevations; no cases of drug-induced livery injury attributed to UPA were identified
- Most cases of COVID-19 infection were mild or moderate in severity (UPA 15 mg, 82%; ADA, 94%; MTX, 95%), and the study drug was interrupted (UPA 15 mg, 67%; ADA, 57%; MTX, 50%) but rarely withdrawn (UPA 15 mg, 5%; ADA, 1%; MTX, 0%)

Figure 2. TEAEs of Special Interest in Patients Treated With UPA, ADA, and MTX



ADA, adalimumab; CI, confidence interval; CPK, creatine phosphokinase; E/100 PY; events per 100 patient-years; EOW, every other week; GI, gastrointestinal; NMSC, non-melanoma skin cancer; QD, once daily; TB, tuberculosis; TEAEs, treatment-emergent AEs; UPA, upadacitinib.

MTX: n = 314, PY = 865.1; ADA 40 mg EOW: n = 579, PY = 1573.2; UPA 15 mg QD pooled: n = 3209, PY = 10782.7.

[a]Opportunistic infections excluding TB and herpes zoster.

[b]Laboratory-related TEAEs of special interest were defined according to investigator-reported AEs as opposed to objective laboratory measures.

[c]MACE was defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

[d]VTE was defined as deep vein thrombosis and pulmonary embolism.

CONCLUSIONS

- The integrated safety profile of UPA in patients with RA remained consistent with previous findings,[1] with no new safety risks identified up to 6.5 years of exposure
- Similar rates of AEs of special interest were observed for UPA 15 mg and ADA, except for higher rates of HZ, hepatic disorder, creatine phosphokinase elevation, and NMSC with UPA

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