Long-Term Risk of Malignancies with Upadacitinib in Comparison to Adalimumab in Rheumatoid Arthritis Up to 5 Years: Post Hoc Analysis of Six Clinical Trials

POS1231

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Final presented on June 6, 2026; European Alliance of Associations for Rheumatology (EULAR) Congress, June 3-6, 2026, London, UK.

OBJECTIVE

- To assess the long-term risk of malignancies with UPA 15 mg in comparison to ADA 40 mg in patients with moderate-to-severe RA over 5 years of exposure in the overall population and in a population similar to that enrolled in the OS trial.

INTRODUCTION

- Upadacitinib (UPA) is an oral selective JAK-1 inhibitor that has demonstrated its efficacy and safety in patients with moderate-to-severe rheumatoid arthritis (RA) in phase 3 SELECT clinical trials.
- In the ORAL Surveillance (OS) trial,[1] an increased risk of adverse events has been reported with tofacitinib in comparison to TNF inhibitors, including an elevated risk of cancer in patients with RA aged ≥50 years who had ≥1 cardiovascular (CV) risk factor; this risk emerged after 2 years of treatment.
- While these findings have influenced clinical practice, there is still limited evidence on malignancy risks associated with UPA in a population with higher CV risk.

METHODS

- Safety data from six phase 3 UPA clinical trials from the SELECT RA program (NCT02706873, NCT02675426, NCT02629159, NCT02706951, NCT02706847, and NCT03086343) were pooled for this integrated analysis.
- Patients received UPA 15 mg once daily (QD) with or without methotrexate (MTX) or adalimumab (ADA) 40 mg once every other week (EOW) with MTX.
- Malignancies excluding non-melanoma skin cancer (NMSC) were assessed in two populations: (1) overall population and (2) patients with higher CV risk (defined as patients aged ≥50 years with ≥1 CV risk factor [based on the OS[1] inclusion criteria: prior history of a CV event, hypertension, diabetes mellitus, former or current smoker, or lowered HDL-cholesterol]) from SELECT-COMPARE (NCT02629159), allowing a direct comparison of UPA and ADA (both receiving concomitant MTX).
- Exposure-adjusted incidence rates (EAIRs) for malignancies excluding NMSC were analysed in both populations.
- Malignancies excluding NMSC through 5 years were analysed using the Kaplan-Meier method and are presented as time to treatment-emergent malignancies, defined as malignancy with an onset on or after the first dose of study drug and ≤30 days (UPA) or ≤70 days (ADA) after the last dose of study drug. Cumulative probability of malignancy until 5 years in both populations was assessed.
- Patients who switched treatments were censored at their first dose of rescue therapy. Otherwise, patients who did not experience an event were censored on the day of the patient's last assessment or the cutoff date (15 Feb 2022), whichever occurred first.

RESULTS

PATIENTS

Overall Population

- In total, 3788 patients were included in the overall population (UPA 15 mg QD, n = 3209; ADA 40 mg EOW, n = 579) with an exposure of 10,111.9 patient-years (PY) for UPA 15 mg and 1456.7 PY for ADA 40 mg.
- The median durations of exposure were 3.7 years on UPA 15 mg (maximum 6.1) and 2.2 years on ADA 40 mg (maximum 6.1).
- Patients and demographic characteristics were well balanced between groups, with most patients being women with a mean DAS28 (CRP) of 5.8 (**Table 1**).
- More than half of patients of the overall population had a high CV risk (UPA 15 mg, n = 1717 [54%]; ADA, n = 320 [55%]).

Higher CV Risk Population

- The higher CV risk population from the SELECT-COMPARE trial included 649 patients treated with UPA 15 mg QD and 177 patients treated with ADA 40 mg EOW.
- Baseline characteristics were similar to those of patients in the OS trial (**Table 1**).

Table 1. Baseline Demographics and Clinical Characteristics

n (%), unless specified	Overall population		Higher CV risk population from SELECT-COMPARE	
	UPA 15 mg QD ± csDMARD (n = 3209)	ADA 40 mg EOW + MTX (n = 579)	UPA 15 mg QD + MTX (n = 649)	ADA 40 mg EOW + MTX (n = 177)
Sex (female)	2581 (80.4)	470 (81.2)	501 (77.2)	133 (75.1)
Age (years), mean (SD)	54.3 (12.0)	54.2 (11.7)	61.1 (7.2)	60.9 (7.6)
Age ≥65 years	643 (20.0)	106 (18.3)	202 (31.1)	52 (29.4)
Time since diagnosis (years), mean (SD)	8.5 (8.4)[a]	8.2 (8.0)	8.9 (8.4)	8.8 (9.4)
DAS28 (CRP),[b] mean (SD)	5.8 (1.0)	5.9 (1.0)	5.8 (0.9)	5.9 (1.0)
Prior bDMARD use	952 (29.7)	55 (9.5)	54 (8.3)	17 (9.6)
Prior TNFi Therapy	819 (25.5)	37 (6.4)	42 (6.5)	12 (6.8)
Other concomitant treatments (glucocorticoids)	1763 (54.9)	350 (60.4)	379 (58.4)	114 (64.4)
Smoking status[c]				
Never smoked	1986 (61.9)	378 (65.5)	342 (52.7)	78 (44.6)
Ever smoked	1221 (38.1)	199 (34.5)	307 (47.3)	97 (55.4)
History of hypertension	1277 (39.8)	252 (43.5)	429 (66.1)	123 (69.5)
History of diabetes mellitus	383 (11.9)	61 (10.5)	119 (18.3)	27 (15.3)
History of VTE	53 (1.7)	9 (1.6)	14 (2.2)	6 (3.4)
History of CV event	385 (12.0)	63 (10.9)	141 (21.7)	20 (11.3)
HDL-cholesterol <40 mg/dL	354 (11.0)	53 (9.2)	87 (13.4)	19 (10.7)

[a]n = 3208; [b]Overall population: UPA 15 mg QD: n=3192; ADA 40 mg EOW: n=575. Higher CV risk population from SELECT-COMPARE: UPA 15 mg QD, n=646; ADA 40 mg EOW, n=176; [c]Overall population: UPA 15 mg QD: n=3207; ADA 40 mg EOW: n=577. Higher CV risk population from SELECT-COMPARE: UPA 15 mg QD: n=649; ADA 40 mg EOW: n=175.
ADA, adalimumab; CRP, C reactive protein; bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DAS28 (CRP), 28-Joint Disease Activity Score based on C reactive protein; EOW, every other week; HDL, high-density lipoprotein; MTX, methotrexate; QD, once daily; SD, standard deviation; TNFi, tumour necrosis factor inhibitor; UPA, upadacitinib; VTE, venous thromboembolism.

RESULTS

MALIGNANCY

Overall Population

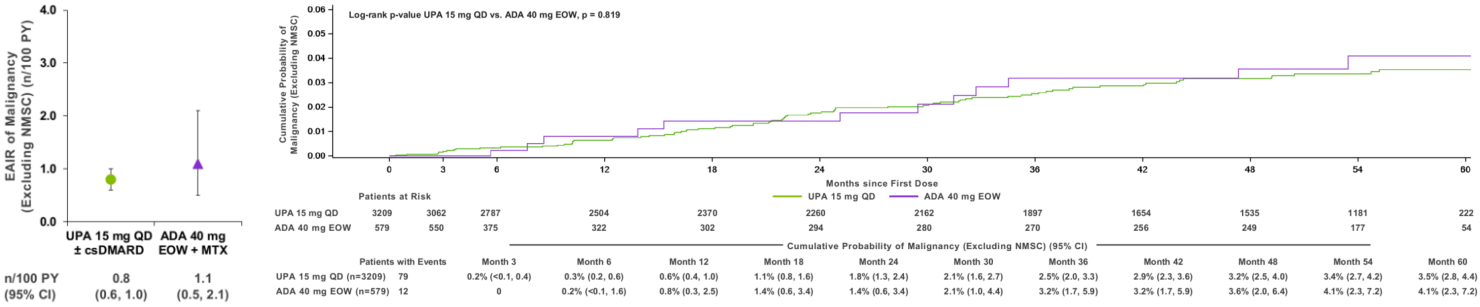
- In the overall population, 79/3209 (2.5%) patients in the UPA 15 mg group and 12/579 (2.1%) patients in the ADA 40 mg group experienced a malignancy (excluding NMSC); with EAIRs of 0.8 n/100 PY (95% CI: 0.6, 1.0) in UPA 15 mg and 1.1 n/100 PY (95% CI: 0.5, 2.1) in ADA 40 mg groups (**Figure 1A**).
- The Kaplan-Meier curves for time to malignancy (excluding NMSC) were similar between UPA and ADA groups, showing no difference at longer exposure up to 5 years with 95% CI of cumulative malignancy probability estimates overlapping across treatment groups (log-rank p-value UPA 15 mg vs. ADA 40 mg, p = 0.819) (**Figure 1A**).

Higher CV Risk Population

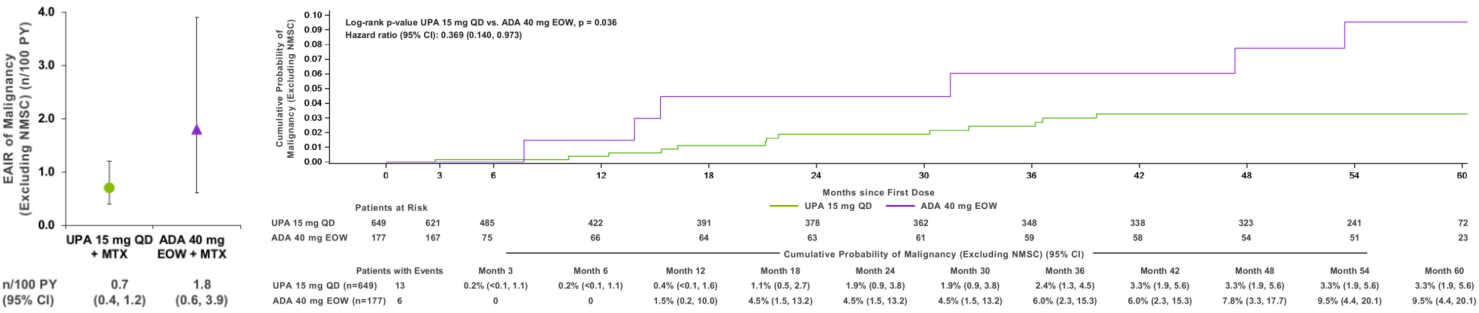
- In the higher CV risk population, malignancies (excluding NMSC) were reported for 13/649 (2.0%) patients treated with UPA 15 mg and for 6/177 (3.4%) patients treated with ADA 40 mg. The EAIRs were 0.7 n/100 PY (95% CI: 0.4, 1.2) in the UPA 15 mg group and 1.8 n/100 PY (95% CI: 0.6, 3.9) in the ADA 40 mg group (**Figure 1B**). No increased risk of malignancy (excluding NMSC) with UPA 15 mg vs. ADA 40 mg was observed using Cox regression analysis (HR 0.37, 95% CI: 0.14, 0.97).
- In this population, patients in the ADA 40 mg group had a shorter time to malignancy compared to patients in the UPA 15 mg group (log-rank p-value UPA 15 mg vs. ADA 40 mg, p = 0.036) (**Figure 1B**).
- These results should be interpreted with caution due to the limited number of malignancy events, the potential for imbalance within the higher risk subpopulation, the post hoc nature of the analysis, and the relatively small ADA sample size.

Figure 1. EAIR of Treatment-Emergent Malignancy (Excluding NMSC) and Kaplan-Meier Plots to Time to Malignancy in (A) Overall Population and (B) Higher CV Risk Population[a]

A – Overall Population



B – Higher CV Risk Population[a]



[a]Patients from SELECT-COMPARE only. ADA, adalimumab; CI, confidence interval; CV, cardiovascular; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EAIR, exposure-adjusted incidence rate; EOW, every other week; MTX, methotrexate; NMSC, non-melanoma skin cancer; PY, patient-years; QD, once daily; UPA, upadacitinib.

CONCLUSIONS

- Whilst this represents a post hoc subgroup analysis with limited patient numbers, especially those exposed to ADA, long-term outcomes did not identify any difference in cumulative probability of malignancy between UPA 15 mg and ADA 40 mg through 5 years of exposure. These findings also applied to patients representative of those evaluated in the OS trial.
- Results are consistent with the previously reported safety profile of UPA across RA studies.[2,3]

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ACKNOWLEDGMENTS

AbbVie and the authors thank the patients, study sites, and investigators who participated in these clinical trials (NCT02706873, NCT02675426, NCT02629159, NCT02706951, NCT02706847, and NCT03086343). AbbVie funded these studies and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Eva Mateu, PhD of TFS HealthScience.

DISCLOSURES

The financial relationships disclosed by the authors with companies whose products may be related to this report are provided as declared by the authors: J. Avouac has received honoraria from Alfasigma, Lilly, Pfizer, AbbVie, Bristol-Myers Squibb, Sanofi, Roche-Chugai, Nordic Pharma, Medac, Novartis, Biogen, Fresenius Kabi, Janssen, Celltrion, and MSD, and has received research grants from Bristol-Myers Squibb, Pfizer (Passerelle), Novartis (Dreamer), Fresenius Kabi, Alfasigma, and Nordic Pharma; C. Richez has received grant support from Biogen, Nordic Pharma and Lilly, and has been consultant for AbbVie, Alpha Sigma, Astra Zeneca, Boehringer Ingelheim, GSK, Novartis, Pfizer, and Zenas Bio; A. Garrison and C. Facon are employees of AbbVie and may hold stock or stock options; C. Charles-Schoeman has received grant support from Alexion, Priovant, CSL Behring, and Janssen, has been consultant for Boehringer Ingelheim, Recludix, and Galapagos, and has received grant support and has been consultant for Octapharma, Pfizer, AbbVie, and Bristol-Myers Squibb.