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ORIGINAL RESEARCH

Benefit–risk analysis of upadacitinib versus adalimumab in patients with rheumatoid arthritis and higher or lower risk of cardiovascular disease

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ABSTRACT

Objectives Evaluate the risks and benefits of upadacitinib 15 mg vs adalimumab in rheumatoid arthritis (RA) patients with an inadequate response to methotrexate based on cardiovascular (CV) risk.

Methods In SELECT-COMPARE, patients received upadacitinib 15 mg, placebo or adalimumab 40 mg every other week, with background methotrexate. This post hoc analysis assessed patients with lower (age <65 years; no CV risk factors) and higher CV risk (age ≥65 years and/or ≥1 CV risk factor). Safety and efficacy outcomes were compared between upadacitinib and adalimumab over the short term (~6 months) and long term (5 years) based on CV risk.

Results The study included 211 lower-risk patients (upadacitinib, n=129; adalimumab, n=82) and 767 higher-risk patients (upadacitinib, n=522; adalimumab, n=245). Rates of malignancy excluding nonmelanoma skin cancer (NMSC), major adverse cardiovascular event and venous thromboembolism were comparable between upadacitinib and adalimumab in both risk groups but numerically higher in the higher-risk group. Upadacitinib showed higher rates of herpes zoster versus adalimumab in both risk groups and numerically higher rates of serious infection and NMSC in the higher-risk group. Upadacitinib demonstrated consistently better efficacy outcomes, including 28-joint Disease Activity Score (C reactive protein) <2.6, Clinical Disease Activity Index remission and Boolean remission at 6 months, which were generally maintained through 5 years.

Conclusions Regardless of baseline CV risk, upadacitinib demonstrated comparable safety to adalimumab, except for higher rates of herpes zoster in both CV risk groups and NMSC and serious infections in the higher-risk group. Upadacitinib consistently showed better clinical and functional outcomes than adalimumab. The benefit–risk profile of upadacitinib in RA patients was favourable, independent of CV risk category, in both short and long term.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous analyses from the SELECT phase 3 rheumatoid arthritis programme, including a head-to-head study of upadacitinib versus adalimumab (SELECT-COMPARE), demonstrated a favourable benefit–risk profile for upadacitinib 15 mg across the overall trial population.

WHAT THIS STUDY ADDS

⇒ This post hoc analysis evaluated the benefit–risk profiles of upadacitinib 15 mg and adalimumab in patients with lower or higher cardiovascular (CV) risk over the short term (~6 months) and long term (~5 years).

⇒ Regardless of baseline CV risk, upadacitinib 15 mg showed similar rates of adverse events versus adalimumab, except for higher rates of herpes zoster in both CV risk groups and higher rates of nonmelanoma skin cancer and serious infections for upadacitinib-treated patients in the higher CV risk group.

⇒ Upadacitinib 15 mg showed consistently better clinical and functional outcomes than adalimumab in both CV risk groups over the short term and long term.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study provide insights into the benefit–risk profiles of upadacitinib and adalimumab in patients with varying CV risks, suggesting that upadacitinib may offer efficacy advantages over adalimumab irrespective of baseline CV risk, with generally similar rates of adverse events.

INTRODUCTION

Active rheumatoid arthritis (RA) is associated with accelerated atherosclerosis, underscoring the increased susceptibility of RA patients to cardiovascular (CV) disease, with a prevalence nearly two times greater than that of the general population.[1 2] In ORAL Surveillance, a head-to-head randomised, open-label, postmarketing study with tofacitinib (a Janus kinase (JAK) inhibitor), differential safety risks were reported for tofacitinib

relative to tumour necrosis factor (TNF) inhibitor therapy in a population aged ≥50 years enriched for patients with CV risk factors.[3] Numerically higher risk of malignancies and major adverse cardiovascular events (MACE) was identified in patients receiving tofacitinib versus TNF inhibitors, leading global regulatory authorities to re-evaluate the labelling of JAK inhibitor medications.[4–7] A post hoc analysis of ORAL Surveillance data revealed a higher risk of MACE with tofacitinib versus TNF inhibitors in patients with a history of atherosclerotic CV disease but not in those without prior history,[8] highlighting the influence of varying CV risks on safety outcomes in RA. Of note, however, real-world evidence assessments have yielded conflicting results regarding the potential differences in the rates of these adverse events between JAK and TNF inhibitors in patients at higher CV risk.[9–11]

The JAK inhibitor upadacitinib has demonstrated efficacy and safety in the SELECT RA clinical trial programme and has been approved for use in patients with moderately to severely active RA after inadequate response or intolerance to methotrexate (MTX-IR).[12–17] An integrated benefit–risk profile analysis of the SELECT RA phase 3 programme, which included a head-to-head study of upadacitinib versus adalimumab (SELECT-COMPARE), showed that upadacitinib 15 mg has a favourable benefit–risk profile.[18] A subsequent analysis in SELECT-COMPARE evaluated the number needed to treat and the number needed to harm, demonstrating that upadacitinib provided greater benefits in RA control compared with adalimumab over 3 years, while maintaining a generally similar risk profile.[19]

To better understand the benefits and risks of RA treatments in patients with different background CV risk, we here assessed the short-term and long-term benefit–risk profiles of upadacitinib and adalimumab in patients enrolled in SELECT-COMPARE. The evaluation was done separately for patients at lower or higher risk of CV disease, focusing on risk definitions from the European Medicines Agency (EMA; further detailed in the Methods section).

METHODS

Patients and study design

This post hoc analysis was performed using data collected from the SELECT-COMPARE phase 3 trial (NCT02629159). Study eligibility and baseline characteristics of patients enrolled in SELECT-COMPARE were described previously.[14] In brief, patients enrolled in the study were ≥18 years old and had active RA according to the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria.[20] Patients received MTX treatment for ≥3 months before baseline and had achieved a stable dose of 15–25 mg/week for ≥4 weeks before receiving the study drug (or ≥10 mg/week MTX if intolerant of ≥12.5 mg/week). All patients were naïve to JAK inhibitors and adalimumab. Patients who had an inadequate response to prior biological disease-modifying antirheumatic drugs (bDMARD) therapy were also excluded from the study.

The SELECT-COMPARE trial consisted of a 26-week placebo-controlled period during which patients were randomly assigned to upadacitinib 15 mg orally once daily, adalimumab 40 mg every other week or placebo, with all patients on background MTX treatment. This was followed by a 48-week double-blind, active comparator-controlled period. Patients who did not achieve a sufficient clinical response were blindly switched from placebo to upadacitinib, upadacitinib to adalimumab or adalimumab to upadacitinib within the first 26 weeks. Rescue occurred at weeks 14, 18 and 22 for patients who did not achieve at least 20% improvement in both tender and swollen joint counts or at week 26 for those who did not meet LDA criteria, as defined by Clinical Disease Activity Index (CDAI) >10. All patients still receiving placebo at week 26 were switched to upadacitinib. Modifications in background RA medications were allowed starting at week 26, and changes in conventional synthetic DMARDs (csDMARDs) were allowed starting at week 48. Patients who completed the 48-week period could continue receiving the same treatment in an open-label manner thereafter in the ongoing long-term extension for up to an overall trial length of 10 years. The present analysis includes results through week 264 (~5 years).

Patient populations and CV risk definitions

Two patient populations were assessed: those with a lower risk (<65 years of age and no CV risk factors) and those with higher risk (≥65 years of age and/or ≥1 CV risk factor) of CV disease, focusing on risk definitions from the EMA.[5 6] CV risk factors used to identify high-risk patients in our analysis included prior history of a CV event (defined by system organ class of 'cardiac disorders' per Medical Dictionary for Regulatory Activities (V.25.0), hypertension (based on medical history), diabetes mellitus, current or former smoker, age ≥65 years, elevated baseline low-density lipoprotein cholesterol (LDL-C; ≥3.36 mmol/L) and lowered baseline high-density lipoprotein cholesterol (HDL-C; <1.034 mmol/L). Additional CV risk factors identified by the EMA that were not evaluated in the present analysis include obesity, a history of malignancy, inherited blood clotting or a history of blood clots and treatment with hormonal contraceptives or hormone replacement therapy. Many of those risk factors were excluded due to the original trial design of SELECT-COMPARE, which excluded patients with previous malignancies (except successfully treated nonmelanoma skin cancer (NMSC) or localised carcinoma in situ of the cervix) and patients with moderate to severe congestive heart failure, uncontrolled hypertension or recent (ie, within the past 6 months) myocardial infarction (MI), stroke or some other CV conditions (detailed in online supplemental text). Patients receiving hormone replacement therapy

were excluded from SELECT-COMPARE given their increased risk for thrombosis.

Safety assessments

Safety data were evaluated in all patients who received at least one dose of upadacitinib or adalimumab. Treatment-emergent adverse events (TEAEs) included serious TEAEs, serious infections, herpes zoster (HZ), malignancies excluding NMSC, NMSC, MACE and venous thromboembolism (VTE). TEAEs were identified as any adverse event that began on or after the initiation of the study drug and up to 30 days (upadacitinib) or 70 days (adalimumab) after the last dose of study drug for patients who discontinued treatment prematurely. Mortality assessments included both treatment-emergent and non-treatment-emergent deaths.

The adjudication of MACE and VTE was carried out by a blinded independent CV adjudication committee. MACE included CV deaths, non-fatal MI and non-fatal strokes. VTE was defined as deep vein thrombosis (DVT) and pulmonary embolism (PE). Reports of malignancy were submitted by study investigators and underwent further medical review by AbbVie study physicians.

Efficacy measures

Efficacy assessments included the proportions of patients achieving 28-joint Disease Activity Score-C reactive protein (DAS28(CRP)) <2.6 and ≤3.2, clinical remission (based on CDAI ≤2.8,[21] Simplified Disease Activity Index (SDAI) ≤3.3, and the 2010 ACR/EULAR definition of Boolean remission[20]), LDA (defined as CDAI ≤10 and SDAI≤11) and ACR20/50/70 responses.[22] Additional efficacy endpoints included the proportions of patients attaining minimal clinically important differences (MCID) in change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) of ≤−0.22, as well as ≥30% and ≥50% change from baseline in patient's global assessment of pain.

Statistical analyses

Baseline characteristics, safety and efficacy were evaluated separately in the lower and higher CV risk groups. Safety data were assessed through week 26 (~6 months) and through week 264 (~5 years). Safety analyses included adverse events of interest from any upadacitinib 15 mg (including patients who started and remained on upadacitinib as well as the upadacitinib exposure from those rescued from placebo or adalimumab) and those receiving any adalimumab (including patients who started and remained on adalimumab as well as the adalimumab exposure from those rescued from upadacitinib). Assignment of TEAEs was based on drug exposure at the time of the event. Safety outcomes are reported as exposure-adjusted event rates (EAERs) per 100 patient-years (PY); 95% CIs were calculated using the exact method for the Poisson mean. Absolute differences in EAERs between upadacitinib versus adalimumab are also presented and account for varying exposure lengths due to treatment switch and different discontinuation rates between the study drugs. The standardised mortality ratio (SMR) was calculated separately by CV risk subgroup for patients receiving upadacitinib using country-specific, age-specific and sex-specific mortality estimates from the WHO through 2016; 95% CIs were calculated using Byar's approximation.

Efficacy data at week 26 (~6 months) and week 264 (~5 years) were analysed by original treatment group for patients randomised to upadacitinib or adalimumab at baseline. Non-responder imputation (NRI) was used for binary endpoints to account for rescue treatments, missing data at a visit and data from all visits after rescue or premature discontinuation of study drug. Treatment comparisons between upadacitinib and adalimumab were based on the Cochran-Mantel-Haenszel test, adjusting for the stratification factor of prior bDMARD use. Additional efficacy analyses were performed for the subset of patients who were in DAS28(CRP) <2.6 or clinical remission at week 26. Kaplan-Meier analysis was performed to estimate the time from the week 26 visit to loss of response, defined as the earliest date at which response was lost (ie, higher disease activity than the DAS28(CRP) <2.6 or remission) at two consecutive visits or discontinuation of the study drug due to lack of efficacy.

RESULTS

Patients

The lower CV risk group included 211 patients (upadacitinib 15 mg, n=129; adalimumab, n=82), and the higher CV risk group included 767 patients (upadacitinib 15 mg, n=522; adalimumab, n=245). Among the higher CV risk group, 187 (24%) patients were aged ≥65 years. Demographics and baseline disease characteristics were generally comparable between the upadacitinib 15 mg and adalimumab treatment groups, within each CV risk group (table 1). Across treatment and risk groups, the mean disease duration ranged from 7.6 to 8.4 years, and the mean CDAI score at baseline ranged from 38.5 to 40.2. Nearly all patients received concomitant csDMARD treatment with MTX alone at baseline. Patients were an average of 13 years older in the higher-risk group versus the lower-risk group (mean age: 57 years vs 44 years). In the higher-risk group, the most common comorbidities were history of hypertension (~54%), followed by elevated LDL-C (~35%) and lowered HDL-C (~11%). The overall exposure time to upadacitinib 15 mg was higher than to adalimumab in both the lower-risk group (6 months: 88.1 PY vs 38.3 PY; 5 years: 1127.9 PY vs 279.3 PY) and the higher-risk group (6 months: 321.2 PY vs 135.5 PY; 5 years: 3368.5 PY vs 1191.6 PY).

Within each risk category, a numerically higher percentage of patients randomised to upadacitinib remained on study drug for at least 264 weeks compared with those randomised to adalimumab (online supplemental table 1). Among those randomised to upadacitinib, a numerically higher percentage of patients

Table 1 Baseline demographics and disease characteristics of patients at lower and higher cardiovascular risk

n (%), unless specified	Lower-risk group*		Higher-risk group†	
	UPA 15 mg QD+MTX (n=129)	ADA 40 mg EOW+MTX (n=82)	UPA 15 mg QD+MTX (n=522)	ADA 40 mg EOW+MTX (n=245)
Female	114 (88.4)	76 (92.7)	407 (78.0)	183 (74.7)
Age, mean (SD), years	44.3 (11.2)	44.2 (9.4)	56.6 (11.0)	57.0 (10.6)
Age, years				
Age <50	82 (63.6)	56 (68.3)	123 (23.6)	48 (19.6)
Age ≥50 to <65 years	47 (36.4)	26 (31.7)	268 (51.3)	141 (57.6)
Age ≥65 years	0	0	131 (25.1)	56 (22.9)
BMI, mean (SD), kg/m^2	26.2 (5.7)	26.8 (6.8)	30.0 (7.1)	29.2 (6.4)
BMI ≥30 kg/m^2	27 (20.9)	22 (26.8)	223 (42.7)	91 (37.1)
Race				
Asian	10 (7.8)	6 (7.3)	21 (4.0)	9 (3.7)
Black or African American	3 (2.3)	2 (2.4)	30 (5.7)	15 (6.1)
White	116 (89.9)	73 (89.0)	460 (88.1)	219 (89.4)
All other races	0	1 (1.2)	11 (2.1)	2 (0.8)
Geographic region				
North America	14 (10.9)	11 (13.4)	108 (20.7)	49 (20.0)
Rest of the world	115 (89.1)	71 (86.6)	414 (79.3)	196 (80.0)
Time since diagnosis, mean (SD), years	7.6 (7.5)	8.0 (7.4)	8.2 (7.8)	8.4 (8.7)
CDAI‡, mean (SD)	38.7 (14.6)	38.5 (12.2)	40.0 (12.5)	40.2 (13.5)
DAS28(CRP)§, mean (SD)	5.7 (1.1)	5.8 (1.0)	5.8 (0.9)	5.9 (1.0)
RF positive	101 (78.3)	68 (82.9)	420 (80.5)	197 (80.4)
ACPA positive	107 (82.9)	67 (81.7)	418 (80.1)	197 (80.4)
Prior bDMARD use	12 (9.3)	7 (8.5)	37 (7.1)	27 (11.0)
Prior TNFi therapy	8 (6.2)	5 (6.1)	27 (5.2)	16 (6.5)
Other bDMARD therapy	5 (3.9)	2 (2.4)	11 (2.1)	12 (4.9)
Concomitant csDMARD use	129 (100)	82 (100)	522 (100)	245 (100)
MTX alone	129 (100)	82 (100)	521 (99.8)	245 (100)
MTX and other csDMARD	0	0	1 (0.2)	0
csDMARDs other than MTX	0	0	0	0
None	0	0	0	0
Other concomitant treatments				
Glucocorticoid	89 (69.0)	50 (61.0)	302 (57.9)	155 (63.3)
Aspirin	1 (0.8)	0	42 (8.0)	18 (7.3)
Statin	0	2 (2.4)	73 (14.0)	19 (7.8)
Anti-thrombotic agent	1 (0.8)	0	48 (9.2)	21 (8.6)
History of tobacco use/nicotine use				
Current	0	0	114 (21.8)	73 (29.8)
Former	0	0	111 (21.3)	45 (18.4)
Never	129 (100)	81 (98.9)	297 (56.9)	126 (51.4)
Unknown	0	1 (1.2)	0	1 (0.4)
CV risk factors				
Hypertension	0	0	277 (53.1)	136 (55.5)
Diabetes mellitus	0	0	53 (10.2)	19 (7.8)

Continued

Table 1 Continued

n (%), unless specified	Lower-risk group*		Higher-risk group†	
	UPA 15 mg QD+MTX (n=129)	ADA 40 mg EOW+MTX (n=82)	UPA 15 mg QD+MTX (n=522)	ADA 40 mg EOW+MTX (n=245)
History of VTE	0	0	7 (1.3)	6 (2.4)
History of CV event	0	0	82 (15.7)	26 (10.6)
LDL-C ≥3.36 mmol/L	0	0	178 (34.2)	91 (37.1)
HDL-C<1.034 mmol/L	0	0	61 (11.7)	29 (11.8)
Elevated LDL-C and lowered HDL-C	0	0	15 (2.9)	8 (3.3)

Baseline demographics and disease characteristics were analysed by original treatment group for patients randomised to upadacitinib or adalimumab.
*Patients in the lower-risk group were <65 years of age and had no CV risk factors.
†Patients in the higher-risk group were ≥65 years of age and/or ≥1 CV risk factor.
‡Lower-risk group: UPA 15 mg: n=124; ADA: n=73. Higher-risk group: UPA 15 mg: n=492; ADA: n=232.
§Lower-risk group: UPA 15 mg: n=128; ADA: n=82. Higher-risk group: UPA 15 mg: n=519; ADA: n=243.
ACPA, anti-cyclic citrullinated peptide antibody; ADA, adalimumab; bDMARD, biologic disease-modifying anirheumatic drug; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; CV, cardiovascular; DAS28, 28-joint Disease Activity Score; EOW, every other week; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MTX, methotrexate; QD, once daily; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitor; UPA, upadacitinib; VTE, venous thromboembolism.

remained on their original treatment in the lower-risk group versus the higher-risk group (45% vs 33%) through at least 264 weeks. For patients randomised to adalimumab, similar proportions of patients remained on their original treatment in both risk groups (23% and 25% in the lower-risk and higher-risk groups, respectively) through at least 264 weeks.

Risks

The rates of any TEAE, serious TEAEs and adverse events leading to discontinuation of study drug were comparable between upadacitinib 15 mg and adalimumab in both CV risk groups in the short-term (6 months) and long-term (5 years) treatment analysis (table 2). As expected, rates of most adverse events were greater in the higher-risk group compared with the lower-risk group, although rates were generally similar between upadacitinib and adalimumab across risk categories (table 2 and figure 1).

The rates of serious infections in the short-term treatment analysis were numerically lower for patients receiving upadacitinib compared with adalimumab (rate difference (95% CI): −1.5 E/100 PY (−7.1, 4.1)) in the lower-risk group and similar with both treatments (rate difference (95% CI): 0.4 E/100 PY (−4.2, 5.1)) in the higher-risk group (figure 1). The rates of serious infections in the long-term treatment analysis were numerically higher with upadacitinib versus adalimumab in the higher-risk group (rate difference (95% CI): 1.1 E/100 PY (−0.2, 2.3)) but were numerically lower with upadacitinib than with adalimumab in the lower-risk group (−1.8 E/100 PY (95% CI: −4.2, 0.5)). In the short-term analysis, there was no discernible pattern in the types of serious infections, with no more than 1 event reported for any infection type, except gastroenteritis (two events occurring with upadacitinib in the higher-risk group) (online supplemental table 2). Over the 5-year period, the rates of serious infections by type remained low and were generally comparable between upadacitinib and adalimumab, except for COVID-19 pneumonia, which was higher with UPA in the higher-risk group (1.0 E/100 PY with UPA vs 0.1 E/100 PY with ADA) (online supplemental table 3).

Consistent with previous reports,[19 23–25] higher rates of HZ were observed with upadacitinib than adalimumab (figure 1). More specifically, rates of HZ were higher with upadacitinib versus adalimumab through 6 months in the higher-risk group (rate difference: 1.0 E/100 PY (95% CI −1.7, 3.7)); no HZ events were reported in the lower-risk group during this period. Over 5 years, rates of HZ were greater with upadacitinib than adalimumab in both CV risk groups (rate difference: lower-risk group, 0.6 E/100 PY (95% CI −1.0, 2.2); higher-risk group, 2.0 E/100 PY (95% CI 1.2, 2.8)). Most HZ infections were non-serious, involved one dermatome, and were non-disseminated. In the higher-risk group, there were three events of ophthalmic herpes zoster, with similar rates observed between upadacitinib and adalimumab through 5 years (rate difference (95% CI): 0.0 E/100 PY (−0.2, 0.2)). No cases of ophthalmic herpes zoster were reported in the lower-risk group. Rates of opportunistic infections (excluding tuberculosis and herpes zoster) were generally similar between patients receiving upadacitinib and adalimumab in both risk groups through 5 years (rate difference (95% CI): lower-risk group, 0.2 (−0.1, 0.4); higher-risk group, 0.2 (−0.1, 0.5)).

Most malignancy events occurred in the higher-risk group and developed over time. Specifically, in the lower-risk group, there were two events of malignancy (excluding NMSC) with upadacitinib through 5 years (rate: 0.2 E/100 PY), whereas no events occurred with

Table 2 Overview of adverse events in patients at lower and higher cardiovascular risk receiving UPA 15 mg or ADA

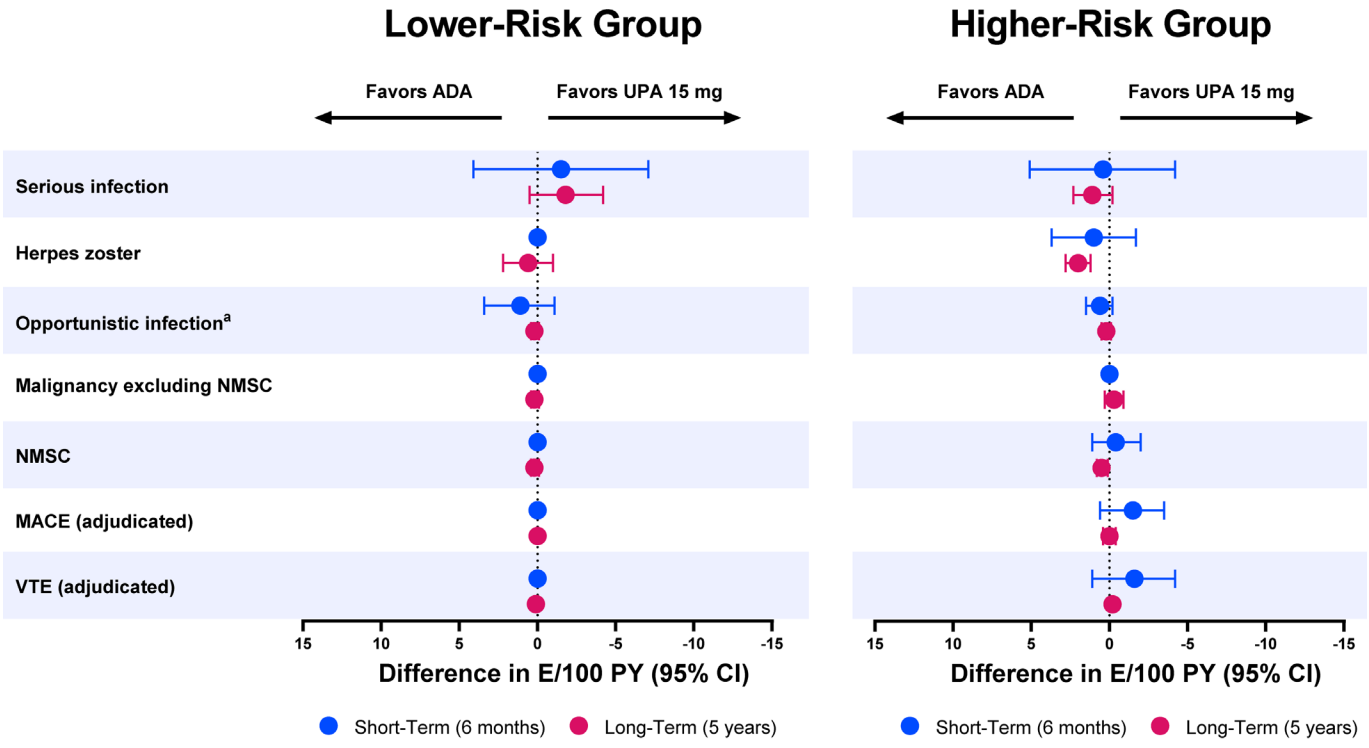
	Lower-risk group			
	Short-term (6 months)		Long-term (5 years)	
E/100 PY (95% CI) (E)	UPA 15 mg QD+MTX (n=310; PY=88.1)	ADA 40 mg EOW+MTX (n=121; PY=38.3)	UPA 15 mg QD+MTX (n=310; PY=1127.9)	ADA 40 mg EOW+MTX (n=121; PY=279.3)
Any TEAE	358.7 (320.2, 400.5) (316)	368.1 (309.9, 434.2) (141)	161.9 (154.6, 169.5)(1826)	194.1 (178.1, 211.1) (542)
Serious TEAE	5.7 (1.8, 13.2) (5)	5.2 (0.6, 18.9) (2)	6.3 (4.9, 7.9) (71)	7.9 (4.9, 11.9) (22)
Adverse event leading to discontinuation of study drug	5.7 (1.8, 13.2) (5)	18.3 (7.3, 37.7) (7)	1.7 (1.0, 2.6) (19)	5.4 (3.0, 8.9) (15)
Deaths*	0 (0, 4.2) (0)	2.6 (0.1, 14.5) (1)	0.2 (0, 0.6) (2)	0.7 (0.1, 2.6) (2)
	Higher-risk group			
	Short-term (6 months)		Long-term (5 years)	
E/100 PY (95% CI) (E)	UPA 15 mg QD+MTX (n=1106; PY=321.2)	ADA 40 mg EOW+MTX (n=458; PY=135.5)	UPA 15 mg QD+MTX (n=1107; PY=3368.5)	ADA 40 mg EOW+MTX (n=458; PY=1191.6)
Any TEAE	400.1 (378.5, 422.5) (1285)	425.1 (391.1, 461.3) (576)	195.7 (191.0, 200.5)(6593)	204.4 (196.4, 212.7) (2436)
Serious TEAE	13.4 (9.7, 18.0) (43)	19.9 (13.1, 29.0) (27)	13.2 (12.0, 14.5) (446)	14.6 (12.5, 16.9) (174)
Adverse event leading to discontinuation of study drug	12.8 (9.2, 17.3) (41)	22.1 (14.9, 31.6) (30)	5.2 (4.5, 6.1) (176)	5.5 (4.3, 7.0) (66)
Deaths*	0.3 (0, 1.7) (1)	0.7 (0, 4.1) (1)	1.2 (0.8, 1.6) (39)	1.0 (0.5, 1.8) (12)

MTX-IR patients received UPA or ADA, each in combination with background MTX, and were stratified into lower CV risk (<65 years of age and no CV risk factors) or higher CV risk (≥65 years of age and/or ≥1 CV risk factor) groups. The safety analysis was performed for adverse events from any UPA 15 mg exposure vs adverse events from any ADA 40 mg exposure.
*Includes treatment-emergent deaths (≤30 days after last dose of UPA or ≤70 days after last dose of ADA) and non-treatment-emergent deaths (>30 days after last dose of UPA or >70 days after last dose of ADA). Through week 26, one death was reported with UPA in the higher-risk group and two deaths with ADA (one each in the lower-risk and higher-risk groups). Over 5 years, 41 deaths were reported with UPA (two in the lower-risk and 39 in the higher-risk groups), while 14 were reported with ADA (two in the lower-risk and 12 in the higher-risk groups).
ADA, adalimumab; CV, cardiovascular; E, event; EOW, every other week; IR, inadequate response or intolerance; MTX, methotrexate; PY, patient-years; QD, once daily; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

adalimumab (figure 1). In the higher-risk group, rates of malignancy (excluding NMSC) were similar between upadacitinib and adalimumab (rate difference (95% CI): −0.3 E/100 PY (−0.9, 0.3)). No predominant type of malignancy occurred among patients (malignancy subtype data were further described by Rubbert-Roth *et al*[26]). Over 5 years, rates of NMSC were numerically greater in higher-risk patients treated with upadacitinib than those treated with adalimumab (rate difference: 0.5 E/100 PY (0.1, 0.8)). In the lower-risk group, rates of NMSC through 5 years were 0.2 E/100 PY (2 events) with upadacitinib, whereas no events were reported with adalimumab.

MACE and VTE were uncommon, and rates were generally comparable between upadacitinib and adalimumab through 5 years in both CV risk groups (figure 1). No events of MACE were reported with either upadacitinib or adalimumab in the lower-risk group, and rates were similar between both treatments in the higher-risk group (rate difference (95% CI): 0 E/100 PY (−0.4, 0.4)). Across treatment groups, most instances of MACE were non-fatal. In the higher-risk group, 5 fatal MACE (0.1 E/100 PY) and 7 non-fatal MACE (0.2 E/100 PY), including 4 non-fatal MI and 3 non-fatal strokes, were reported with upadacitinib; 1 fatal MACE (<0.1 E/100 PY) and 3 non-fatal MACE (0.3 E/100 PY), all of which were non-fatal strokes, occurred with adalimumab. In the lower-risk group, 1 VTE event (<0.1 E/100 PY) occurred in the upadacitinib group, and no VTE was reported in the adalimumab group. In the higher-risk group, rates of VTE were similar between patients receiving either upadacitinib or adalimumab (rate difference: −0.2 E/100 PY (95% CI: −0.6, 0.3)). In the lower-risk group, one non-fatal DVT was reported in the upadacitinib group. In the higher-risk group, 1 fatal PE (<0.1 E/100 PY) and 10 non-fatal VTEs (0.3 E/100 PY), including 4 non-fatal PE, 3 non-fatal DVT and 3 concurrent PE and DVT, were reported in the upadacitinib group; no fatal VTE events and 6 events of non-fatal VTE (0.5 E/100 PY), including 4 non-fatal PE and 2 non-fatal DVT, were reported in the adalimumab group.

Through 5 years, a total of 55 deaths (41 of which were treatment-emergent) occurred in patients receiving upadacitinib and adalimumab. The rate of death was similar between patients treated with upadacitinib or adalimumab in either CV risk group (rate difference (95% CI): lower-risk group, −0.5 E/100 (−1.6, 0.5) PY; higher-risk group, 0.2 E/100 PY (−0.5, 0.8)) (table 2). An SMR analysis indicated that the mortality rate among patients treated with upadacitinib was generally similar to the expected rate in an age, sex and country-matched general population. In the lower-risk group, SMR (95% CI) results were 0.44 (0.01, 2.44), regardless of whether COVID-19-related deaths were included or not. In the higher-risk group, the respective results were 1.11 (0.69, 1.70) when including COVID-19-related deaths and 0.85 (0.50, 1.36) when



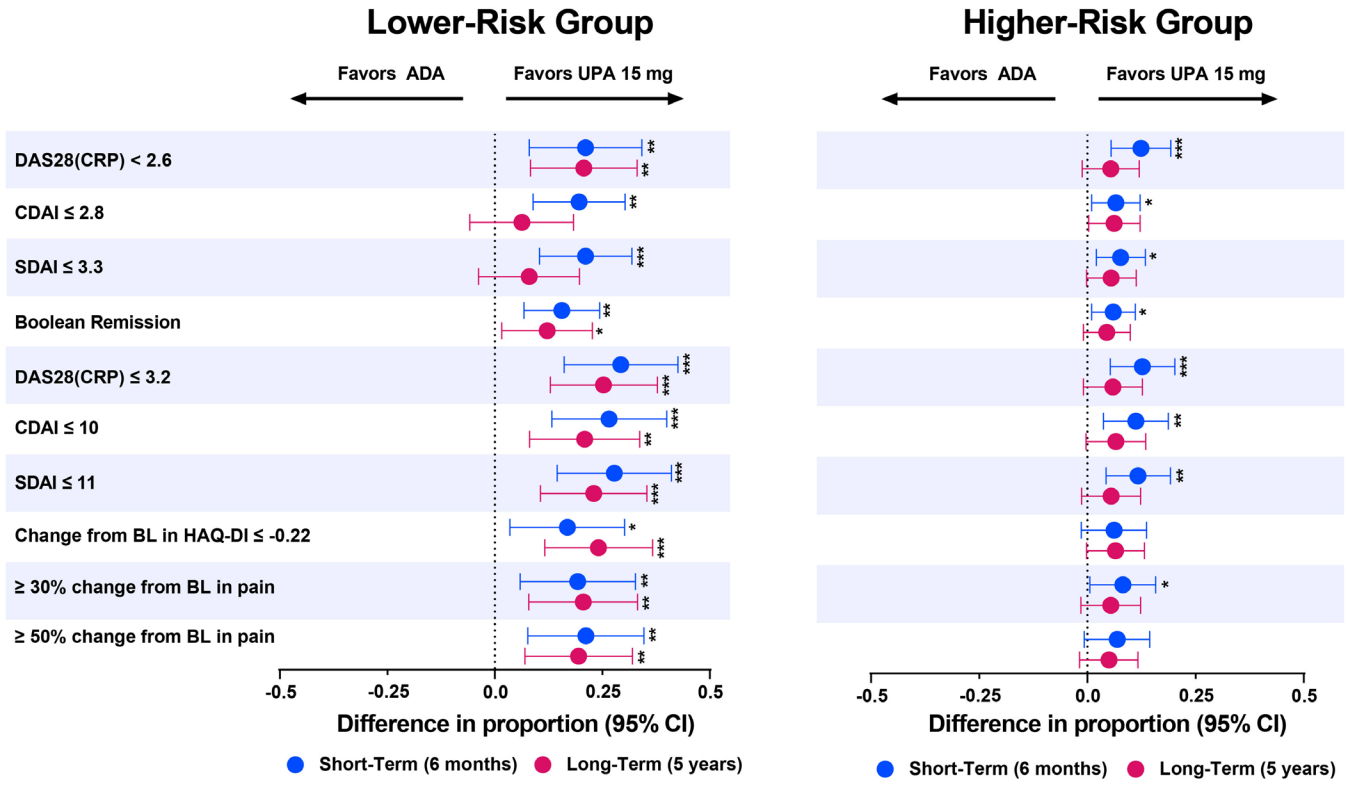
E/100 PY (95% CI)	Lower-Risk Group				Higher-Risk Group			
	Short-Term (6 months)		Long-Term (5 years)		Short-Term (6 months)		Long-Term (5 years)	
	UPA 15 mg + MTX (n = 310; PY = 88.1)	ADA + MTX (n = 121; PY = 38.3)	UPA 15 mg + MTX (n = 310; PY = 1127.9)	ADA + MTX (n = 121; PY = 279.3)	UPA 15 mg + MTX (n = 1106; PY = 321.2)	ADA + MTX (n = 458; PY = 135.5)	UPA 15 mg + MTX (n = 1107; PY = 3368.5)	ADA + MTX (n = 458; PY = 1191.6)
Serious infection	1.1 (0, 6.3)	2.6 (0.1, 14.5)	1.8 (1.1, 2.7)	3.6 (1.7, 6.6)	5.6 (3.3, 8.9)	5.2 (2.1, 10.6)	4.4 (3.7, 5.1)	3.3 (2.3, 4.5)
Herpes zoster	0 (0, 4.2)	0 (0, 9.6)	2.0 (1.3, 3.1)	1.4 (0.4, 3.7)	2.5 (1.1, 4.9)	1.5 (0.2, 5.3)	3.1 (2.5, 3.7)	1.1 (0.6, 1.9)
Opportunistic infection[a]	1.1 (0, 6.3)	0 (0, 9.6)	0.2 (0, 0.6)	0 (0, 1.3)	0.6 (0.1, 2.2)	0 (0, 2.7)	0.3 (0.2, 0.6)	0.2 (0, 0.6)
Malignancy excluding NMSC	0 (0, 4.2)	0 (0, 9.6)	0.2 (0, 0.6)	0 (0, 1.3)	0 (0, 1.1)	0 (0, 2.7)	0.7 (0.5, 1.1)	1.0 (0.5, 1.8)
NMSC	0 (0, 4.2)	0 (0, 9.6)	0.2 (0, 0.6)	0 (0, 1.3)	0.3 (0, 1.7)	0.7 (0, 4.1)	0.7 (0.4, 1.0)	0.2 (0, 0.6)
MACE (adjudicated)	0 (0, 4.2)	0 (0, 9.6)	0 (0, 0.3)	0 (0, 1.3)	0 (0, 1.1)	1.5 (0.2, 5.3)	0.4 (0.2, 0.6)	0.3 (0.1, 0.9)
VTE (adjudicated)	0 (0, 4.2)	0 (0, 9.6)	< 0.1 (0, 0.5)	0 (0, 1.3)	0.6 (0.1, 2.2)	2.2 (0.5, 6.5)	0.3 (0.2, 0.6)	0.5 (0.2, 1.1)

Figure 1 Risks of UPA 15 mg vs ADA in patients at lower and higher cardiovascular risk. MTX-IR patients received UPA or ADA, each in combination with background MTX, and were stratified into lower CV risk (<65 years of age and no CV risk factors) or higher CV risk (≥65 years of age and/or ≥1 CV risk factor) groups. The safety analysis was performed for adverse events from any UPA 15 mg exposure vs adverse events from any ADA 40 mg exposure. The exposure-adjusted event rate was used for comparison, accounting for different exposure lengths due to treatment switch and different discontinuation rates between the study drugs. A negative value indicates more favourable safety with UPA than ADA. A positive value indicates more favourable safety with ADA than UPA. The table presents the corresponding exposure-adjusted event rates of each adverse event. [a]Excludes herpes zoster and tuberculosis. ADA, adalimumab; CV, cardiovascular; E, event; IR, inadequate response or intolerance; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, nonmelanoma skin cancer; PY, patient-years; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolism.

excluding COVID-19-related deaths. Mortality rates for patients receiving adalimumab were also generally similar to the rate expected in an age, sex, and country-matched general population. SMR (95% CI) results for adalimumab, including COVID-19 deaths, were 1.99 (0.22, 7.18) for the lower-risk group and 0.98 (0.45, 1.86) for the higher-risk group; the respective results excluding COVID-19 deaths were 1.99 (0.22, 7.18) and 0.65 (0.24, 1.42).

Benefits

Across all examined efficacy endpoints, patients receiving upadacitinib showed consistently better outcomes compared with those receiving adalimumab in both the short-term and long-term results as analysed by NRI (figure 2). At 6 months, DAS28(CRP)<2.6 was attained by 21% and 12% more patients (absolute percent difference) randomised to upadacitinib than those randomised to adalimumab in the lower-risk and higher-risk groups, respectively (nominal p=0.003 and p<0.001). At 5 years, 21% and 5% more patients achieved



Response Rate (95% CI)	Lower-Risk Group				Higher-Risk Group			
	Short-Term (6 months)		Long-Term (5 years)		Short-Term (6 months)		Long-Term (5 years)	
	UPA 15 mg + MTX (n = 129)	ADA + MTX (n = 82)	UPA 15 mg + MTX (n = 129)	ADA + MTX (n = 82)	UPA 15 mg + MTX (n = 522)	ADA + MTX (n = 245)	UPA 15 mg + MTX (n = 522)	ADA + MTX (n = 245)
DAS28(CRP) < 2.6	50.4 (41.8, 59.0)	29.3 (19.4, 39.1)	42.6 (34.1, 51.2)	22.0 (13.0, 30.9)	38.5 (34.3, 42.7)	26.1 (20.6, 31.6)	29.1 (25.2, 33.0)	23.7 (18.4, 29.0)
CDAI ≤ 2.8	31.8 (23.7, 39.8)	12.2 (5.1, 19.3)	29.5 (21.6, 37.3)	23.2 (14.0, 32.3)	20.9 (17.4, 24.4)	14.3 (9.9, 18.7)	23.4 (19.7, 27.0)	17.1 (12.4, 21.9)
SDAI ≤ 3.3	33.3 (25.2, 41.5)	12.2 (5.1, 19.3)	28.7 (20.9, 36.5)	20.7 (12.0, 29.5)	22.0 (18.5, 25.6)	14.3 (9.9, 18.7)	21.5 (17.9, 25.0)	15.9 (11.3, 20.5)
Boolean Remission	21.7 (14.6, 28.8)	6.1 (0.9, 11.3)	25.6 (18.1, 33.1)	13.4 (6.0, 20.8)	17.0 (13.8, 20.3)	11.0 (7.1, 14.9)	18.0 (14.7, 21.3)	13.5 (9.2, 17.7)
DAS28(CRP) ≤ 3.2	65.9 (57.7, 74.1)	36.6 (26.2, 47.0)	47.3 (38.7, 55.9)	22.0 (13.0, 30.9)	51.9 (47.6, 56.2)	39.2 (33.1, 45.3)	31.6 (27.6, 35.6)	25.7 (20.2, 31.2)
CDAI ≤ 10	62.0 (53.6, 70.4)	35.4 (25.0, 45.7)	46.5 (37.9, 55.1)	25.6 (16.2, 35.1)	50.4 (46.1, 54.7)	39.2 (33.1, 45.3)	33.9 (29.8, 38.0)	27.3 (21.8, 32.9)
SDAI ≤ 11	64.3 (56.1, 72.6)	36.6 (26.2, 47.0)	45.0 (36.4, 53.5)	22.0 (13.0, 30.9)	51.3 (47.1, 55.6)	39.6 (33.5, 45.7)	31.2 (27.3, 35.2)	25.7 (20.2, 31.2)
Change from BL in HAQ-DI ≤ -0.22	70.5 (62.7, 78.4)	53.7 (42.9, 64.5)	47.3 (38.7, 55.9)	23.2 (14.0, 32.3)	58.8 (54.6, 63.0)	52.7 (46.4, 58.9)	31.4 (27.4, 35.4)	24.9 (19.5, 30.3)
≥ 30% change from BL in pain	70.5 (62.7, 78.4)	51.2 (40.4, 62.0)	45.0 (36.4, 53.5)	24.4 (15.1, 33.7)	58.8 (54.6, 63.0)	50.6 (44.4, 56.9)	32.8 (28.7, 36.8)	27.3 (21.8, 32.9)
≥ 50% change from BL in pain	65.1 (56.9, 73.3)	43.9 (33.2, 54.6)	42.6 (34.1, 51.2)	23.2 (14.0, 32.3)	51.0 (46.7, 55.2)	44.1 (37.9, 50.3)	30.3 (26.3, 34.2)	25.3 (19.9, 30.8)

Figure 2 Benefits of UPA 15 mg vs ADA in patients at lower and higher cardiovascular risk. MTX-IR patients randomised to UPA or ADA, each in combination with background MTX, were stratified into lower CV risk (<65 years of age and no CV risk factors) or higher CV risk (≥65 years of age and/or CV risk factors) groups. Efficacy was analysed by randomised group, and non-responder imputation was applied for missing data. A negative value indicates more favourable efficacy with ADA than UPA. Comparisons between UPA and ADA were based on the Cochran-Mantel-Haenszel test, adjusting for the stratification factor of prior biologic DMARD use. Nominal *p<0.05, **p<0.01, ***p<0.001. The table presents the corresponding response rate comparisons between UPA and ADA. ADA, adalimumab; BL, baseline; CDAI, Clinical Disease Activity Index; CV, cardiovascular; DAS28(CRP), 28-joint Disease Activity Score based on C reactive protein; HAQ-DI, Health Activity Questionnaire-Disability Index; IR, inadequate response or intolerance; LDA, low disease activity; MTX, methotrexate; SDAI, Simplified Disease Activity Index; UPA, upadacitinib.

DAS28(CRP)<2.6 with upadacitinib relative to adalimumab in the lower-risk and higher-risk groups, respectively (p=0.002 and p=0.127). Additionally, 20% and 7% more patients achieved CDAI remission at 6 months with upadacitinib than adalimumab in the lower-risk and higher-risk groups, respectively (nominal p=0.001; p=0.031); numerically higher proportions also attained CDAI remission in each risk group with upadacitinib vs

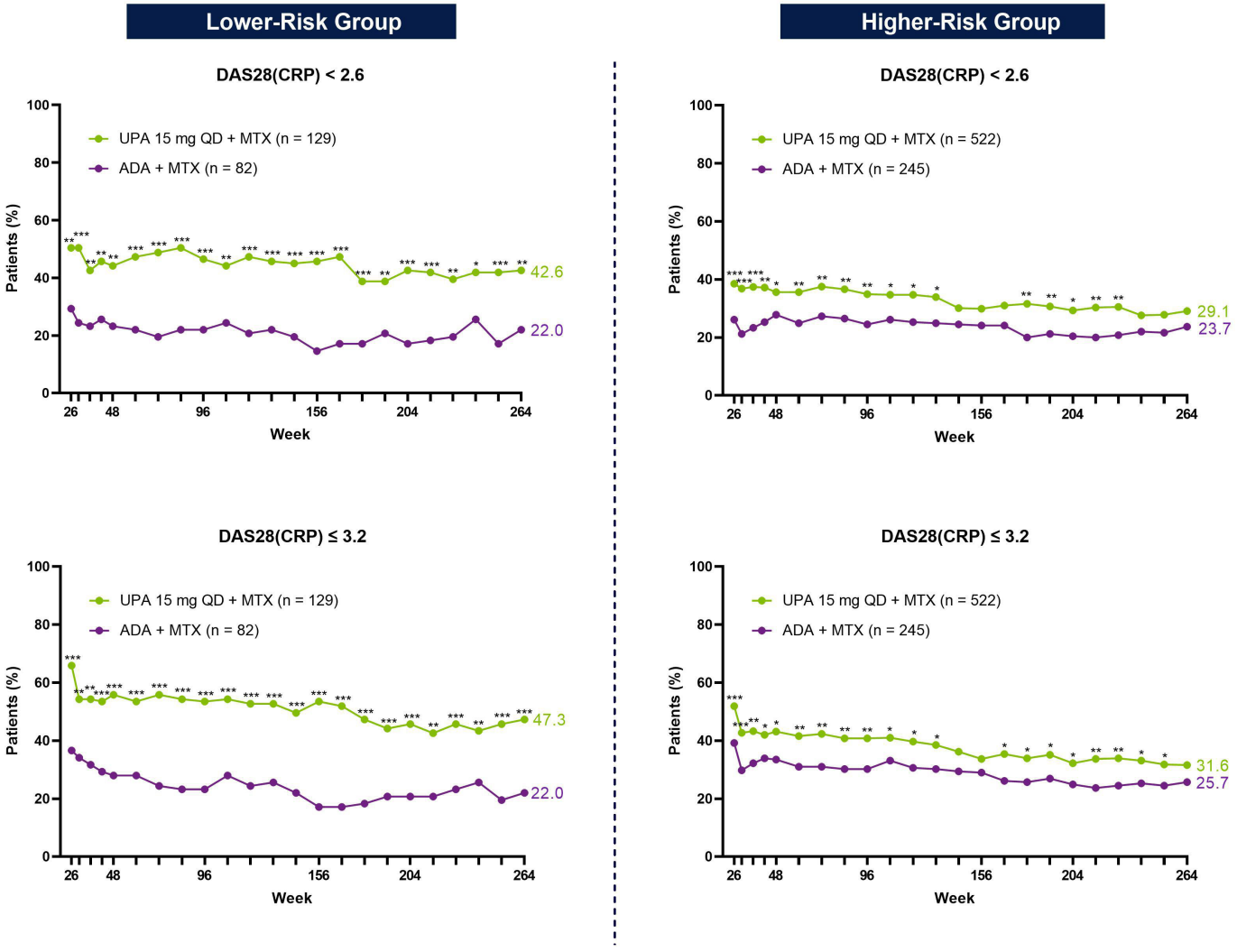


Figure 3 Proportions of patients at lower and higher CV risk achieving DAS28(CRP) response through 5 years. MTX-IR patients randomised to UPA or ADA, each in combination with background MTX, were stratified into lower CV risk (<65 years of age and no CV risk factors) or higher CV risk (≥65 years of age and/or CV risk factors) groups. Efficacy was analysed by randomised group, and non-responder imputation was applied for missing data. Comparisons between UPA and ADA were based on the Cochran-Mantel-Haenszel test, adjusting for the stratification factor of prior biologic DMARD use. Nominal *p<0.05, **p<0.01, ***p<0.001. ADA, adalimumab; CV, cardiovascular; DAS28(CRP), 28-joint disease activity score based on C reactive protein; DMARD, disease-modifying antirheumatic drug; IR, inadequate response or intolerance; MTX, methotrexate; QD, once daily; UPA, upadacitinib.

adalimumab at 5 years. Regarding achievement of the stringent ACR/EULAR Boolean remission criteria, 16% and 6% more patients achieved Boolean remission with upadacitinib than adalimumab in the lower-risk and higher-risk group at 6 months, respectively (nominal p=0.002 and p=0.029), while attainment was 12% and 5% higher in the respective groups at 5 years (nominal p=0.034 and p=0.131). Similar patterns were observed for LDA targets and SDAI response. Additionally, higher proportions of patients showed improvements in patient-reported outcomes, such as MCID in HAQ-DI and ≥30%/≥50% improvement from baseline in pain with upadacitinib versus adalimumab in both CV risk groups. Figures 3 and 4 and online supplemental figures 1–4 show the proportions of patients achieving the above efficacy responses at each time point from week 26 to week 264. Notably, patients receiving upadacitinib had numerically better responses than those receiving adalimumab for all evaluated endpoints at all visits through 5 years.

For time to loss of response analyses, early responders randomised to upadacitinib maintained their target response numerically longer than those randomised to adalimumab for both CV risk groups. At 5 years, maintenance of DAS28(CRP) <2.6 was 15% higher with upadacitinib versus adalimumab in the lower-risk group and 10% higher in the higher CV risk group (figure 5). Maintenance of CDAI remission was 4% and 5% higher with upadacitinib than adalimumab in the lower-risk and higher-risk groups, respectively (figure 6). Results were consistent for SDAI remission (online supplemental figure 5).

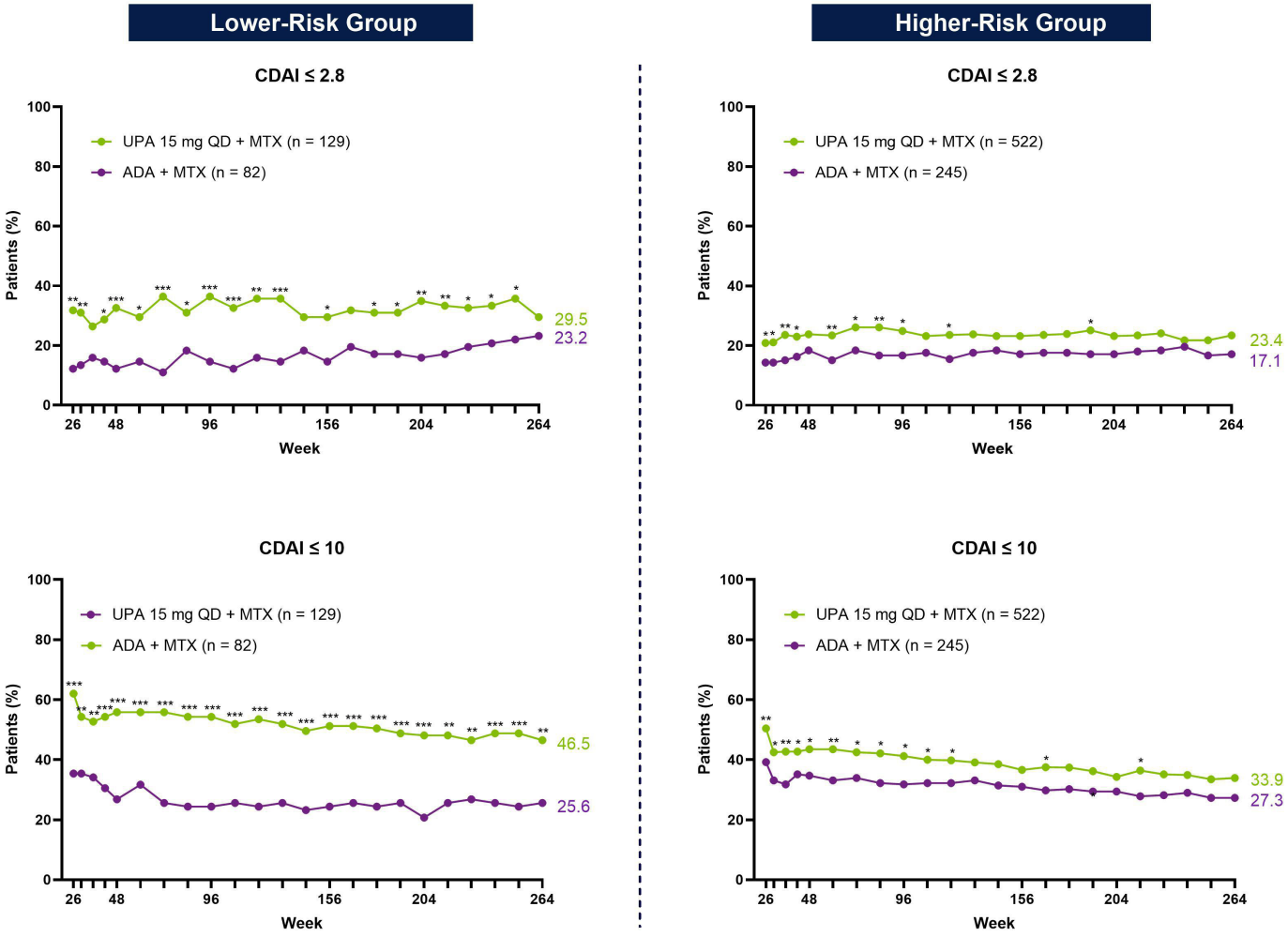
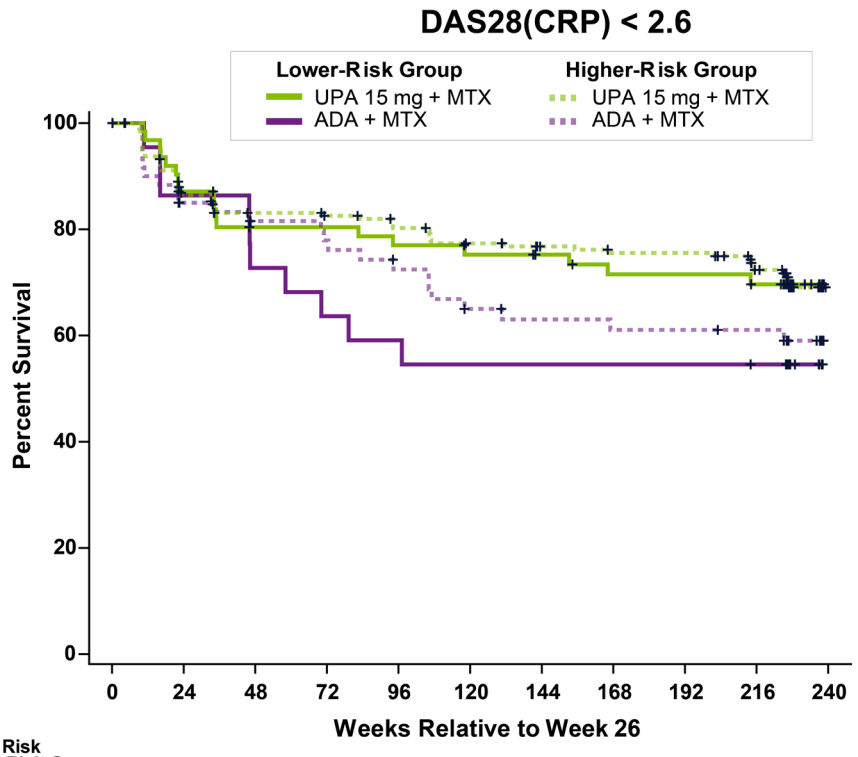


Figure 4 Proportions of patients at lower and higher CV risk achieving CDAI response through 5 years. MTX-IR patients randomised to UPA or ADA, each in combination with background MTX, were stratified into lower CV risk (<65 years of age and no CV risk factors) or higher CV risk (≥65 years of age and/or CV risk factors) groups. Efficacy was analysed by randomised group, and non-responder imputation was applied for missing data. CDAI thresholds used for remission and low disease activity were ≤2.8 and ≤10, respectively. Comparisons between UPA and ADA were based on the Cochran-Mantel-Haenszel test, adjusting for the stratification factor of prior biologic DMARD use. Nominal *p<0.05, **p<0.01, ***p<0.001. ADA, adalimumab; CDAI, Clinical Disease Activity Index; CV, cardiovascular; IR, inadequate response or intolerance; MTX, methotrexate; QD, once daily; UPA, upadacitinib.

DISCUSSION

Understanding the benefit–risk profile for patients with RA and different CV risk profiles provides valuable insights that can inform treatment decisions. In this post hoc analysis, upadacitinib 15 mg treatment generally showed comparable rates of risks of interest (except for HZ in both CV risk groups and NMSC and serious infections in the higher-risk group) and better efficacy outcomes relative to adalimumab 40 mg every other week treatment regardless of baseline CV risk status. Thus, the overall benefit–risk profile over 5 years was favourable for upadacitinib 15 mg in RA patients independent of CV risk group and treatment duration. While previous studies have evaluated the safety of JAK inhibitors in patients at elevated CV risk, this manuscript represents the first study to our knowledge that also explores benefit–risk in patients with differing CV risk profiles.

Previous studies have shed light on the risks associated with advanced RA therapies in populations at higher CV risk. While these therapeutic agents have the potential to decrease CV events and related deaths as a result of their anti-inflammatory properties,[27 28] they also have the potential for adverse events. Differential safety risks were reported in ORAL Surveillance for tofacitinib relative to TNF inhibitor therapy in a population aged ≥50 years enriched for patients with CV risk factors.[3] Subsequent analyses showed that the increased risk associated with tofacitinib compared with TNF inhibitors was most evident among patients aged ≥65 years, current or former smokers, and those with a history of coronary artery disease/atherosclerotic CV disease or prior cardiac event.[8 29] A previous integrated post hoc analysis of upadacitinib phase 3 trials including risk factors mirroring the ORAL Surveillance eligibility criteria similarly identified



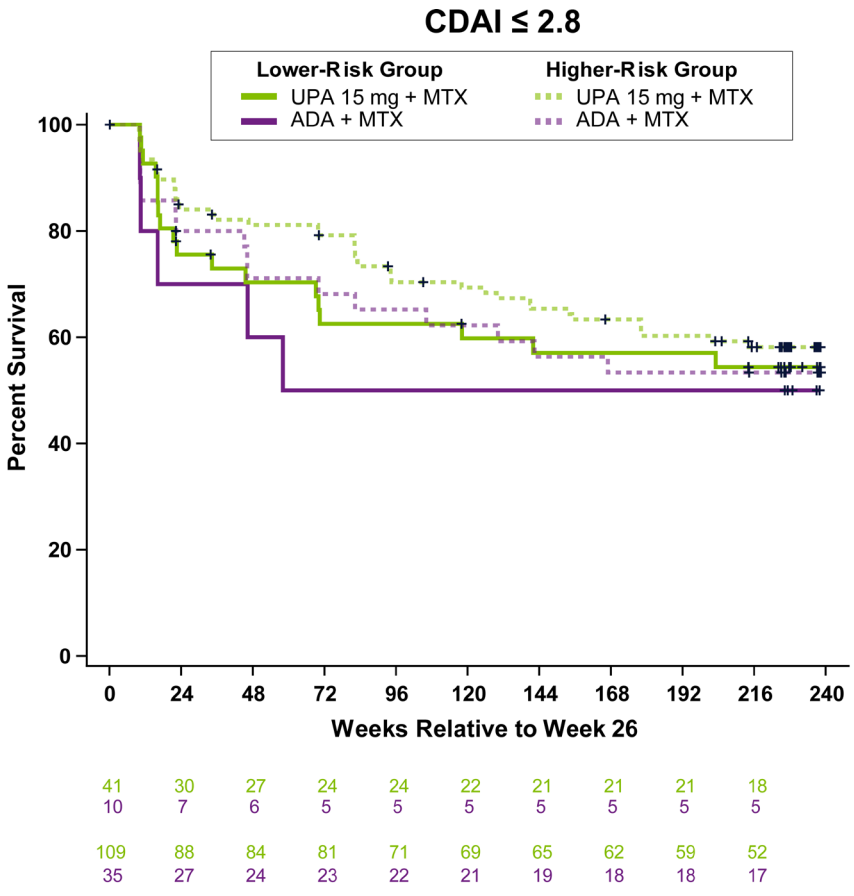
Survival Estimates

n (%) [95% CI]	Lower-Risk Group		Higher-Risk Group	
	UPA 15 mg + MTX	ADA + MTX	UPA 15 mg + MTX	ADA + MTX
Week 156	15 (75.2) [62.3, 84.3]	10 (54.5 [32.1, 72.4]	42 (77.3) [70.6, 82.7]	20 (65.0) [51.1, 75.9]
Week 264	18 (69.6) [56.1, 79.7]	10 (54.5 [32.1, 72.4]	54 (69.1) [61.4, 75.5]	23 (59.0) [44.9, 70.7]

Figure 5 Kaplan-Meier analysis of time to loss of DAS28(CRP) response through 5 years in patients at lower and higher cardiovascular risk. Data include MTX-IR patients randomised to UPA 15 mg or ADA, each in combination with background MTX, who were in DAS28(CRP)<2.6 at week 26. The time in weeks to loss of DAS28(CRP)<2.6 response was determined from the date of the week 26 visit. Patients who did not lose DAS28(CRP)<2.6 response were censored at the last observed measurement date on or prior to study day 1849 (ie, target study day for the week 264 analysis visit) or the date of discontinuation of study drug for any reason other than lack of efficacy, whichever was earlier. +indicates censored data. ADA, adalimumab; DAS28(CRP), 28-joint disease activity score based on C reactive protein; IR, inadequate response or intolerance; MTX, methotrexate; QD, once daily; UPA, upadacitinib

higher rates of most adverse events in the higher-risk group (aged ≥50 years and ≥1 CV risk factor) compared with the overall SELECT trial population.[30] Notably, however, generally similar rates of malignancy excluding NMSC, MACE and VTE were observed across upadacitinib 15 mg, adalimumab and MTX treatment groups in both the higher-risk and overall populations. In that analysis, upadacitinib did not appear to be associated with an increased risk of any examined adverse events, except for HZ and NMSC, as well as serious infections in patients aged 65 years or older. However, it is important to note that those results were from a post hoc analysis and not a prospective, controlled safety study like ORAL Surveillance; therefore, caution should be taken when comparing results. Similar to ORAL Surveillance, an increased incidence of adverse events of interest was seen in the higher-risk group compared with the lower-risk group with both treatments.

Our findings are consistent with the established safety profile of upadacitinib, as demonstrated in previous study-specific reports and integrated phase 3 safety analyses of upadacitinib in RA and other approved indications.[14 19 25 31 32] Higher rates of HZ were observed with upadacitinib versus adalimumab in both risk groups, in line with the known risk of HZ infection with JAK inhibitors.[19 23–25] Most cases of HZ were non-serious, involved a single dermatome and did not result in treatment discontinuation. For all examined adverse events in both CV risk groups, except the rate of HZ in the higher-risk group, overlapping CIs were observed between upadacitinib and adalimumab. Rates of serious infection and NMSC were numerically greater in higher CV risk patients receiving



Survival Estimates

n (%) [95% CI]	Lower-Risk Group		Higher-Risk Group	
	UPA 15 mg + MTX	ADA + MTX	UPA 15 mg + MTX	ADA + MTX
Week 156	16 (59.8) [42.9, 73.2]	5 (50.0) [18.4, 75.3]	34 (67.3) [57.4, 75.5]	13 (62.2) [43.9, 76.1]
Week 264	18 (54.4) [37.6, 68.4]	5 (50.0) [18.4, 75.3]	43 (58.1) [47.9, 67.0]	16 (53.3) [35.5, 68.3]

Figure 6 Kaplan-Meier analysis of time to loss of CDAI remission through 5 years in patients at lower and higher cardiovascular risk. Data include MTX-IR patients randomised to UPA 15 mg or ADA, each in combination with background MTX, who were in CDAI remission at week 26. The time in weeks to loss of remission was determined from the date of the week 26 visit. Patients who did not lose remission were censored at the last observed measurement date on or prior to study day 1849 (ie, target study day for the week 264 analysis visit) or the date of discontinuation of study drug for any reason other than lack of efficacy, whichever was earlier. Remission was defined as CDAI ≤2.8. +indicates censored data. ADA, adalimumab; CDAI, Clinical Disease Activity Index; IR, inadequate response or intolerance; MTX, methotrexate; QD, once daily; UPA, upadacitinib.

upadacitinib vs adalimumab. These results are consistent with the previous post hoc analysis from SELECT-COMPARE[30] and reports of NMSC risk in patients with inflammatory diseases receiving JAK inhibitors.[33–35] By contrast, a real-world study did not find a significantly higher risk of infection (either any or serious) in patients treated with JAK inhibitors compared with TNF therapy.[36]

In the present study, as expected, the higher CV risk group showed a greater susceptibility to malignancies, MACE and VTE than the lower CV risk group. Notably, rates of these risks were generally similar between upadacitinib and adalimumab, regardless of CV risk group. A post hoc analysis of the ORAL Surveillance study identified older age, prior VTE and morbid obesity as significant risk factors for VTE across treatments.[37] Moreover, most VTE events occurred in patients with residual disease activity, consistent with previous analyses supporting the association between disease activity and VTE risk.[38] No MACE occurred in the younger patient group (aged <65 years) without CV risk factors in the current analysis. Rates of death were comparable between upadacitinib and adalimumab in both risk groups.

Upadacitinib continued to demonstrate efficacy in treating the signs and symptoms of RA over 5 years. Patients treated with upadacitinib demonstrated numerically better responses than those receiving adalimumab for all endpoints evaluated at all visits, including achievement of DAS28(CRP)<2.6 and ≤3.2, clinical remission, and LDA. Higher proportions of patients receiving upadacitinib versus adalimumab also showed clinically relevant improvements in key patient-reported outcomes such as physical function and pain. These improvements

can profoundly impact overall quality of life,[39] further highlighting the potential benefits of upadacitinib therapy. Although patients in both risk groups demonstrated favourable efficacy with upadacitinib compared with adalimumab, the benefits were more apparent in the lower-risk group than in the higher-risk group. The reasons for this observation are unclear but underscore the importance of early intervention in the treatment paradigm. The positive benefit–risk profile of upadacitinib, combined with the low number of events of special interest, supports the earlier use of JAK inhibitors.[40] As always, these decisions should be made in conversation with the patient, considering their individual risk factors.

Effective control of RA disease activity plays an important role in reducing the risk of adverse events associated with inflammation.[38 41–43] In a previous post hoc assessment of patients aged ≥50 years at higher CV risk, upadacitinib-treated patients who experienced MACE or VTE showed less improvement in disease activity than those who did not experience such adverse events, whereas no significant association was noted between malignancy (excluding NMSC) and disease activity.[30] This suggests that effective disease control may help reduce the risk of some adverse events in patients with RA, reinforcing the importance of effective RA management and long-term safety. Recent studies have suggested that JAK inhibitors may also have potential cardioprotective effects due to their ability to reduce inflammation and modulate cardiotoxic factors, although the underlying mechanism is not fully understood.[27 44] Future research comparing CV biomarker profiles in patients receiving JAK inhibitors with those on other advanced therapies for RA to evaluate whether JAK inhibitors have a unique cardioprotective profile would be of interest.

Limitations of this analysis include that it was conducted post hoc and did not rely on predetermined endpoints. Additionally, not all CV risk factors identified by EMA were evaluated in the present study, primarily due to the trial design of SELECT-COMPARE, which excluded certain pre-existing conditions. SELECT-COMPARE was also not designed or powered to detect statistical differences in safety events between upadacitinib and adalimumab. Our results from a long-term extension of a randomised controlled trial may also not fully represent the real-world experience of the treatment in a broader and more diverse patient population. The effective sample size was limited for some treatment groups, particularly in the lower CV risk group. Moreover, a relatively high proportion of patients either switched therapies (resulting in their categorisation as non-responders in the efficacy analyses) or discontinued treatment over the 5-year period, thereby affecting the generalisability of the long-term findings. Lastly, the absence of glycated haemoglobin data from SELECT-COMPARE prevents an in-depth assessment of the impact of upadacitinib and adalimumab on glucose control. However, despite these limitations, our results help contextualise the benefit–risk profile of upadacitinib versus adalimumab in RA patients at lower and higher CV risk within a controlled clinical trial setting.

In summary, this analysis revealed generally comparable rates of safety risks observed over 5 years between upadacitinib and adalimumab, except for HZ; numerically higher rates of serious infections and NMSC were observed with upadacitinib in the higher-risk group. The safety profile of upadacitinib remained consistent with earlier assessments from SELECT-COMPARE and integrated safety analyses.[14 25 31 32] Upadacitinib led to consistently better clinical and functional outcomes relative to adalimumab across all examined endpoints in both short-term and long-term analyses. These benefits were observed in patients at both lower and higher CV risk groups. Given that CV risk is an important consideration for treatment selection in RA, the results of this analysis provide valuable insights into the benefit–risk balance of upadacitinib and adalimumab for patients with RA. Our findings continue to support the favourable profile of upadacitinib in MTX-IR patients with moderately to severely active RA.

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Ethics approval This study involves human participants. The study was conducted according to the International Council for Harmonisation guidelines, local regulations and guidelines governing clinical study conduct, and the Declaration of Helsinki. All patients provided written informed consent, and the study protocol and consent forms were approved by an institutional review board or independent ethics committee at each study site. The coordinating investigator (Charles Birbara of the University of Massachusetts, Worcester, Massachusetts, USA) received approval from the Advarra Institutional Review Board. Participants gave informed consent to participate in the study before taking part.

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REFERENCES

1 Jagpal A, Navarro-Millán I. Cardiovascular co-morbidity in patients with rheumatoid arthritis: a narrative review of risk factors, cardiovascular risk assessment and treatment. *BMC Rheumatol* 2018;2:10.
2 Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? *Nat Rev Rheumatol* 2015;11:390–400.
3 Ytterberg SR, Bhatt DL, Mikuls TR, *et al*. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N Engl J Med* 2022;386:316–26.
4 Food & Drug Administration. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. 2021. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death
5 Smolen JS, Landewé RBM, Bergstra SA, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023;82:3–18.
6 [Xeljanz] product information as approved by the CHMP on 10 November 2022, pending endorsement by the European commission. 2022. Available: https://www.ema.europa.eu/en/documents/referral/xeljanz-epar-product-information-approved-chmp-10-november-2022-pending-endorsement-european_en.pdf
7 European Medicines Agency. EMA confirms measures to minimise risk of serious side effects with janus kinase inhibitors for chronic inflammatory disorders 2022. 2022. Available: https://www.ema.europa.eu/en/news/ema-confirms-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic
8 Charles-Schoeman C, Buch MH, Dougados M, *et al*. Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: a post hoc analysis from ORAL Surveillance. *Ann Rheum Dis* 2023;82:119–29.
9 Hoisnard L, Pina Vegas L, Dray-Spira R, *et al*. Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors versus adalimumab: a nationwide cohort study. *Ann Rheum Dis* 2023;82:182–8.
10 Khosrow-Khavar F, Kim SC, Lee H, *et al*. Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study. *Ann Rheum Dis* 2022;81:798–804.
11 Salinas CA, Louder A, Polinski J, *et al*. Evaluation of VTE, MACE, and Serious Infections Among Patients with RA Treated with Baricitinib Compared to TNFi: A Multi-Database Study of Patients in Routine Care Using Disease Registries and Claims Databases. *Rheumatol Ther* 2023;10:201–23.
12 Genovese MC, Fleischmann R, Combe B, *et al*. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet* 2018;391:2513–24.
13 Burmester GR, Kremer JM, Van den Bosch F, *et al*. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018;391:2503–12.
14 Fleischmann R, Pangan AL, Song I-H, *et al*. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial. *Arthritis Rheumatol* 2019;71:1788–800.
15 Rubbert-Roth A, Enejosa J, Pangan AL, *et al*. Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis. *N Engl J Med* 2020;383:1511–21.
16 Smolen JS, Pangan AL, Emery P, *et al*. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet* 2019;393:2303–11.
17 Tanaka Y, Luo Y, O'Shea JJ, *et al*. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. *Nat Rev Rheumatol* 2022;18:133–45.
18 Conaghan PG, Mysler E, Tanaka Y, *et al*. Upadacitinib in Rheumatoid Arthritis: A Benefit-Risk Assessment Across a Phase III Program. *Drug Saf* 2021;44:515–30.
19 Conaghan P, Cohen S, Burmester G, *et al*. Benefit-Risk Analysis of Upadacitinib Compared with Adalimumab in the Treatment of Patients with Moderate-to-Severe Rheumatoid Arthritis. *Rheumatol Ther* 2022;9:191–206.
20 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
21 Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23:S100–8.
22 Felson DT, Anderson JJ. Methodological and statistical approaches to criteria development in rheumatic diseases. *Baillieres Clin Rheumatol* 1995;9:253–66.
23 Adas MA, Alveyn E, Cook E, *et al*. The infection risks of JAK inhibition. *Expert Rev Clin Immunol* 2022;18:253–61.
24 Bechman K, Subesinghe S, Norton S, *et al*. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)* 2019;58:1755–66.
25 Fleischmann R, Mysler E, Bessette L, *et al*. Long-term safety and efficacy of upadacitinib or adalimumab in patients with rheumatoid

arthritis: results through 3 years from the SELECT-COMPARE study. *RMD Open* 2022;8:e002012.
26 Rubbert-Roth A, Kakehasi AM, Takeuchi T, *et al*. Malignancy in the Upadacitinib Clinical Trials for Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis. *Rheumatol Ther* 2024;11:97–112.
27 Baldini C, Moriconi FR, Galimberti S, *et al*. The JAK-STAT pathway: an emerging target for cardiovascular disease in rheumatoid arthritis and myeloproliferative neoplasms. *Eur Heart J* 2021;42:4389–400.
28 Roubille C, Richer V, Starnino T, *et al*. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:480–9.
29 Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N Engl J Med* 2022;386:1766–8.
30 Fleischmann R, Curtis JR, Charles-Schoeman C, *et al*. Safety profile of upadacitinib in patients at risk of cardiovascular disease: integrated post hoc analysis of the SELECT phase III rheumatoid arthritis clinical programme. *Ann Rheum Dis* 2023;82:1130–41.
31 Burmester GR, Cohen SB, Winthrop KL, *et al*. Safety profile of upadacitinib over 15 000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis. *RMD Open* 2023;9:e002735.
32 Cohen SB, van Vollenhoven RF, Winthrop KL, *et al*. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann Rheum Dis* 2021;80:304–11.
33 Jalles C, Lepelley M, Mouret S, *et al*. Skin cancers under Janus kinase inhibitors: A World Health Organization drug safety database analysis. *Therapie* 2022;77:649–56.
34 Liu R, Wan Q, Zhao R, *et al*. Risk of non-melanoma skin cancer with biological therapy in common inflammatory diseases: a systemic review and meta-analysis. *Cancer Cell Int* 2021;21:614.
35 Wang J-L, Yin W-J, Zhou L-Y, *et al*. Risk of non-melanoma skin cancer for rheumatoid arthritis patients receiving TNF antagonist: a systematic review and meta-analysis. *Clin Rheumatol* 2020;39:769–78.
36 Aymon R, Mongin D, Gilbert B, *et al*. OP0092 INFECTIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH JAK-INHIBITORS COMPARED TO bDMARDs: FINDINGS FROM AN INTERNATIONAL COLLABORATION OF REGISTERS (THE "JAK-POT" STUDY). *Ann Rheum Dis* 2024;83:84–5.
37 Charles-Schoeman C, Fleischmann R, Mysler E, *et al*. Risk of Venous Thromboembolism With Tofacitinib Versus Tumor Necrosis Factor Inhibitors in Cardiovascular Risk-Enriched Rheumatoid Arthritis Patients. *Arthritis Rheumatol* 2024;76:1218–29.
38 Molander V, Bower H, Frisell T, *et al*. Risk of venous thromboembolism in rheumatoid arthritis, and its association with disease activity: a nationwide cohort study from Sweden. *Ann Rheum Dis* 2021;80:169–75.
39 Linde L, Sørensen J, Ostergaard M, *et al*. Health-related quality of life: validity, reliability, and responsiveness of SF-36, 15D, EQ-5D [corrected] RAQoL, and HAQ in patients with rheumatoid arthritis. *J Rheumatol* 2008;35:1528–37.
40 Szekanecz Z, Buch MH, Charles-Schoeman C, *et al*. Efficacy and safety of JAK inhibitors in rheumatoid arthritis: update for the practising clinician. *Nat Rev Rheumatol* 2024;20:101–15.
41 Innala L, Sjöberg C, Möller B, *et al*. Co-morbidity in patients with early rheumatoid arthritis - inflammation matters. *Arthritis Res Ther* 2016;18:33.
42 Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology (Oxford)* 2013;52:53–61.
43 Crowson CS, Liao KP, Davis JM, *et al*. Rheumatoid arthritis and cardiovascular disease. *Am Heart J* 2013;166:622–8.
44 Cuesta-López L, Escudero-Contreras A, Hanaee Y, *et al*. Exploring candidate biomarkers for rheumatoid arthritis through cardiovascular and cardiometabolic serum proteome profiling. *Front Immunol* 2024;15:1333995.