ORIGINAL RESEARCH

Long-term safety and efficacy of upadacitinib or adalimumab in patients with rheumatoid arthritis: results through 3 years from the SELECT-COMPARE study

Roy Fleischmann [1], Eduardo Mysler,[2] Louis Bessette,[3] Charles G Peterfy,[4] Patrick Durez [5], Yoshiya Tanaka [6], Jerzy Swierkot,[7] Nasser Khan,[8] Xianwei Bu,[8] Yihan Li,[8] In-Ho Song[8]

For numbered affiliations see end of article.

Correspondence to
Dr Roy Fleischmann; rfleischmann@arthdocs.com

ABSTRACT

Objectives To assess the long-term safety and efficacy of the Janus kinase inhibitor upadacitinib versus adalimumab over 3 years in the ongoing long-term extension (LTE) of SELECT-COMPARE, a randomised controlled phase 3 trial of patients with active rheumatoid arthritis and inadequate response to methotrexate (MTX).

Methods Patients on stable background MTX were randomised 2:2:1 to upadacitinib 15 mg, placebo or adalimumab 40 mg. Patients with an insufficient response were switched by week 26 from placebo to upadacitinib, upadacitinib to adalimumab or adalimumab to upadacitinib. Patients who completed the 48-week double-blind period could enter an LTE for up to 10 years. Safety and efficacy results were analysed here through 3 years. Treatment-emergent adverse events (AEs) were summarised based on exposure to upadacitinib and adalimumab. Efficacy was analysed by original randomised groups (non-responder imputation), as well as separately by treatment sequence (as observed).

Results Rates of several AEs were generally comparable between upadacitinib and adalimumab, including AEs leading to discontinuation, serious infections and serious AEs, malignancies, major adverse cardiac events, venous thromboembolism and deaths. Consistent with earlier results, herpes zoster, lymphopaenia, hepatic disorder and CPK elevation were reported at higher rates with upadacitinib versus adalimumab. In terms of efficacy, upadacitinib continued to show numerically better clinical responses than adalimumab over 3 years across all endpoints, including low disease activity and remission.

Conclusion The safety profile of UPA 15 mg was consistent with previous study-specific and integrated safety reports. Higher levels of clinical response continued to be observed with upadacitinib versus adalimumab through 3 years of treatment.

Key messages

What is already known about this subject?
► Safety and efficacy of upadacitinib have been evaluated in multiple rheumatoid arthritis (RA) populations in six global phase III trials, including SELECT-COMPARE, which demonstrated improvements in the signs and symptoms of RA in favour of upadacitinib 15 mg versus adalimumab through 72 weeks.

What does this study add?
► Safety and efficacy data through 3 years, including treatment switch data are reported for a Janus kinase inhibitor versus a TNF inhibitor.
► The safety profile of upadacitinib 15 mg observed through 3 years was generally similar to adalimumab for adverse events of special interest, including malignancies, major adverse cardiac events, venous thromboembolism and deaths.
► Upadacitinib continued to show consistently better clinical responses compared with adalimumab through 3 years including rates of remission and low disease activity, physical function and pain severity; radiographic progression was inhibited to a similar extent.

How might this impact on clinical practice or further developments?
► Based on its favourable benefit–risk profile for the treatment of patients with active RA, upadacitinib 15 mg continues to be a reasonable treatment choice after an inadequate response to methotrexate.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease associated with progressive cartilage and bone damage. Affecting approximately 0.5% of the adult population worldwide,[1] RA can lead to functional impairment, loss of mobility and reduced quality of life. To counter these effects and improve long-term prognosis, the

'treat to target' strategy aims to optimise treatment until the goal of sustained remission or at least low disease activity (LDA) is met.[2 3]

In patients with an inadequate response or intolerance to methotrexate (MTX), alternative treatment options or combination therapies are usually helpful. While biological disease-modifying antirheumatic drugs (bDMARDs) have greatly improved the management of RA, upwards of 30%–40% of patients on TNF antagonists fail to achieve a satisfactory long-term clinical response,[4] indicating a need for additional treatment options. Patient surveys also highlight the importance of oral medications, with oral delivery options strongly preferred over injection by patients with RA.[5 6]

Janus kinase (JAK) inhibitors, a relatively new class of orally administered small molecule inhibitors, have emerged as an effective alternative in RA patients with insufficient response or intolerance to conventional synthetic (cs) or bDMARDs. The safety and efficacy of the JAK inhibitor upadacitinib have been evaluated in a wide range of RA patients across six global randomised phase III trials.[7–13] SELECT-COMPARE focuses on patients with active RA despite MTX treatment and uniquely includes a long-term comparator control arm with the TNF inhibitor adalimumab throughout the 10-year study. Notably, upadacitinib (15 mg orally once daily) plus MTX demonstrated statistically significant improvement in clinical and functional outcomes of RA when compared with adalimumab (40 mg subcutaneous injection every other week) plus MTX at week 12 of SELECT-COMPARE.[13] Continued improvements in favour of upadacitinib were maintained through 72 weeks.[14] Since RA is a chronic disease that requires long-term intervention, it is important to evaluate the long-term safety and efficacy of RA treatments. Here, we report the long-term safety, tolerability and efficacy of upadacitinib versus adalimumab, both in combination with MTX, over 3 years in the ongoing open-label, long-term extension (LTE) of SELECT-COMPARE.

PATIENTS AND METHODS
Patients
Study eligibility criteria and baseline demographics were described previously[13] (summarised in online supplemental table 1). In brief, patients were at least 18 years of age with active RA (and meeting the 2010 ACR/EULAR classification criteria[15]) and were on MTX therapy for ≥3 months, attaining a stable dosage of 15–25 mg/week for ≥4 weeks prior to the first dose of study drug (or at least 10 mg/week MTX if intolerant of ≥12.5 mg/week). Patients also were required to have high-sensitivity C-reactive protein (CRP) ≥5 mg/L and evidence of erosive disease and/or seropositivity (as determined by ≥3 bone erosions on X-rays of hands and feet or ≥1 bone erosion and positive rheumatoid factor/anticyclic citrullinated peptide autoantibody). All patients were naive to targeted synthetic DMARDs and adalimumab. Patients were excluded if they had an inadequate response to prior bDMARD therapy.

Study design and treatment
SELECT-COMPARE included a 26-week, double-blind, placebo-controlled period, a 48-week, double-blind, active comparator-controlled period and an ongoing open-label LTE for an overall trial length of up to 10 years (online supplemental figure 1). Patients were randomised 2:2:1 to upadacitinib 15 mg once daily, placebo or adalimumab 40 mg every other week and continued to receive their background MTX dose. Patients not achieving sufficient clinical response were blindly rescued from placebo to upadacitinib, upadacitinib to adalimumab or adalimumab to upadacitinib within the first 26 weeks of the trial. Rescue occurred at week 14, 18 and 22 (for those who did not achieve at least 20% improvement in both tender joint counts (TJC) and swollen joint counts (SJC)) or week 26 (if LDA criteria were not met, defined by Clinical Disease Activity Index (CDAI) >10). All placebo patients not rescued previously were switched to upadacitinib at week 26. Initiation of, or change in, some background RA medications (including glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen) was allowed per investigator's discretion starting at week 26; modification or initiation of csDMARDs was allowed beginning at week 48. Patients completing the 48-week period 1 could enter an ongoing LTE and continue to receive treatment with upadacitinib or adalimumab in a blinded manner until the last patient completed their week 48 visit.

Safety assessments
Safety assessments were based on available data up to week 156 for each patient. Treatment-emergent adverse events (TEAEs), including AEs of special interest (AESIs), per 100 patient-years (PY) were summarised up to 3 years based on exposure to upadacitinib or adalimumab. All patients were included in the safety analysis, with assignment of an AE based on drug exposure at the time of event. In addition, selected AESIs were summarised for the subset of patients receiving continuous upadacitinib or continuous adalimumab treatment. All safety data are reported as exposure-adjusted event rates.

Safety assessments were performed as previously described.[13 16] Major adverse cardiac events (MACE) and venous thromboembolism (VTE) events were adjudicated by an independent Cardiovascular Adjudication Committee in a blinded manner. Kaplan-Meier curves were used to examine the time to occurrence of MACE and VTE events. Laboratory parameters were evaluated through week 156, including the proportion of patients meeting criteria for potentially clinically significant (grade 3 or 4) changes during the treatment period. The assessment of AE severity was made at the investigators' discretion and in line with the study protocol. Transient AEs were determined based on the availability of an end date for that AE. A potential relationship between

lymphocyte decreases and serious and opportunistic infectious events was also explored.

Efficacy measures

Efficacy assessments included the proportions of patients achieving LDA (defined by CDAI ≤10) or clinical remission (defined by CDAI ≤2.8),[17] 28-joint Disease Activity Score-CRP (DAS28(CRP)) ≤3.2 or <2.6,[18 19] ACR/EULAR Boolean-based remission,[20] ACR20/50/70 responses,[21] and ACR components including Health Assessment Questionnaire-Disability Index (HAQ-DI) (rated on a 0–3 scale)[22] and patient's assessment of pain (scored on a 0–100 mm scale). Indicated assessments from period 1 (at weeks 4, 8, 12, 26 and 48)[13 16] are summarised here; period 2 assessments were conducted at week 60 and every 12 weeks thereafter up to week 156.

Radiographic progression up to 2 years was assessed based on reading session 3, which included X-ray images from hands and feet from baseline and weeks 26, 48 and 96, as well as from premature discontinuation or unscheduled visits prior to week 96. Per study protocol, no X-ray assessments were performed at 3 years. Results from reading session 1 (images up to 6 months) and session 2 (up to 1-year reading) were previously reported.[13 16] X-rays were evaluated by two independent readers who were blinded to treatment assignments and visit order and an adjudicator if needed. Assessments included mean change from baseline in modified Total Sharp Score (mTSS),[23 24] erosion scores and joint space narrowing, as well as the proportion of patients who showed no radiographic progression (defined as change from baseline in mTSS ≤0).

Statistical analysis

Safety data were summarised by the following two groups, with assignment of AEs based on drug exposure at the time of event: any upadacitinib (including patients who started and remained on upadacitinib as well as the upadacitinib exposure from those rescued from placebo or adalimumab to upadacitinib) and any adalimumab (including patients who started and remained on adalimumab as well as the adalimumab exposure from those rescued from upadacitinib to adalimumab).

Efficacy data up to week 156 were analysed by originally assigned randomised treatment group (intention-to-treat analysis), as well as by treatment sequence, which includes: (1) placebo to upadacitinib, (2) continuous upadacitinib, (3) continuous adalimumab, (4) adalimumab to upadacitinib switchers and (5) upadacitinib to adalimumab switchers. For analysis of binary endpoints by randomised treatment group, non-responder imputation (NRI) was applied for rescue, premature discontinuation of study drug and missing data; treatment comparisons were made using the Cochran-Mantel-Haenszel test, adjusting for the stratification factor of prior bDMARD use. For analysis of continuous endpoints by randomised treatment group, last observation carried forward was applied to data observed after rescue, and missing data

were not imputed. Analysis of continuous endpoints was conducted using the analysis of covariance model, where treatment was set as a fixed factor, and the stratification factor of prior bDMARD use and corresponding baseline value were covariates. As observed (AO) data by treatment sequence were reported without imputation for missing data. For radiographic endpoints, descriptive summaries were provided based on AO data. Patients for whom both baseline and week 96 X-ray readings were available are included in the present analysis.

RESULTS

Patient disposition

A total of 1629 patients were randomised and received at least one dose of study drug (651 to upadacitinib 15 mg, 651 to placebo and 327 to adalimumab 40 mg) (figure 1). Of the 651 patients randomised to upadacitinib, overall 252 (39%) were rescued to adalimumab between weeks 14 and 22 (if <20% improvement in TJC or SJC) or at week 26 (if CDAI >10), whereas a higher proportion of patients (159/327; 49%) randomised to adalimumab were rescued to upadacitinib. Over half of patients (342/651; 53%) randomised to upadacitinib completed period 1 on randomised therapy and entered the LTE at week 48 compared with 39% (127/327) of those randomised to adalimumab. Similarly, a higher proportion of patients randomised to upadacitinib completed 3 years of continuous treatment compared with those randomised to adalimumab (297/651 (46%) vs 111/327 (34%)). Of note, while the study was unblinded once the last patient in the study achieved the week 48 visit (end of period 1), over two-thirds of patients remained fully blinded at week 60, approximately one-third were still blinded at week 72, and the study was fully unblinded at week 156.

Safety

Through 3 years, the overall exposure to upadacitinib was approximately three-fold higher than the exposure to adalimumab (2796 PY and 948 PY, respectively). The overall rate of AEs was similar in patients receiving upadacitinib (214.9 E/100 PY) compared with adalimumab (234.2 E/100 PY) (figure 2). The most frequently reported TEAEs (>5 E/100 PY) in both groups included upper respiratory tract infection, urinary tract infection, nasopharyngitis, increased alanine aminotransferase (ALT) and bronchitis (online supplemental table 2). The exposure-adjusted event rates were numerically higher in patients randomised to adalimumab compared with upadacitinib for severe AEs (10.9 E/100 PY for upadacitinib and 14.1 E/100 PY for adalimumab), as well as AEs leading to discontinuation of study drug (5.1 E/100 PY for upadacitinib and 7.5 for adalimumab) (figure 2).

With the exception of herpes zoster (HZ), CPK elevation, hepatic disorder and lymphopaenia, which were reported at numerically higher rates with upadacitinib, AESI rates were generally comparable between upadacitinib and adalimumab (figure 2). Serious infections
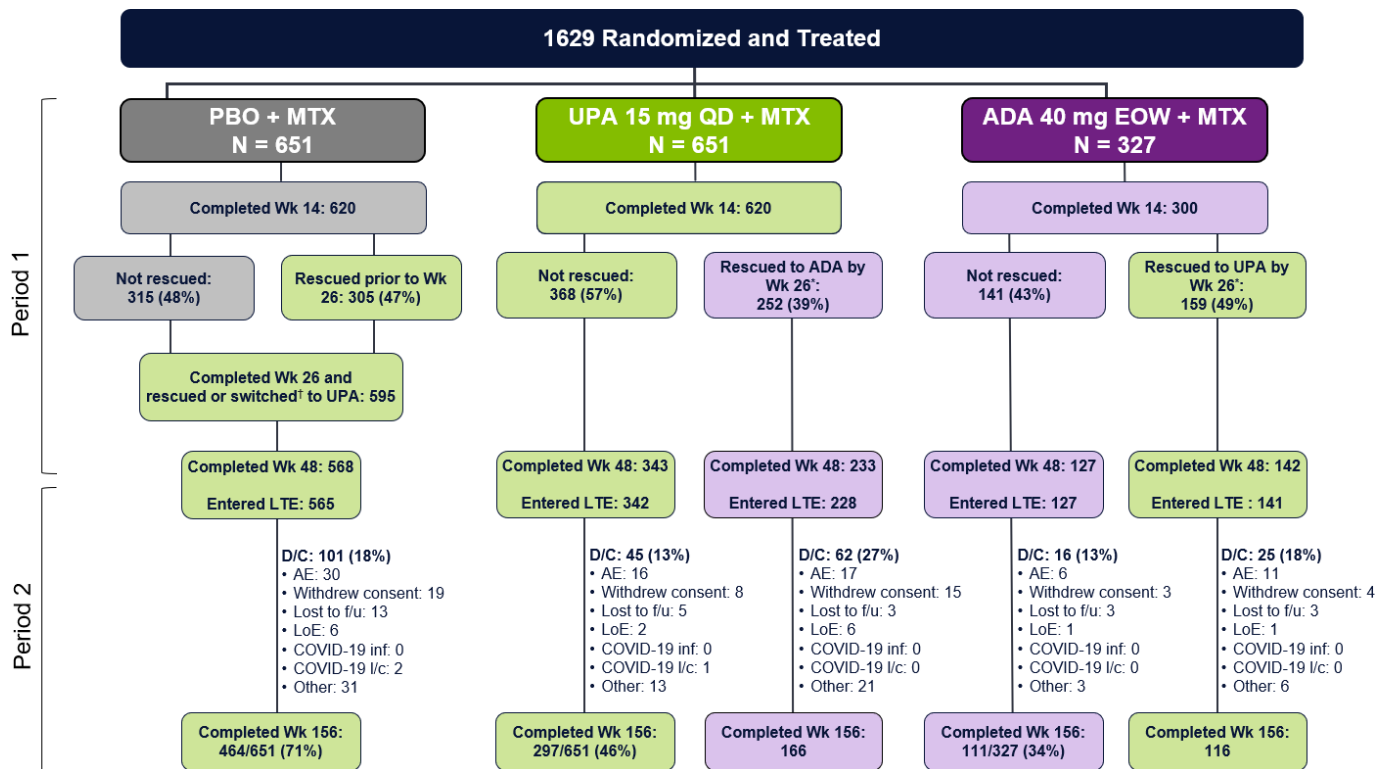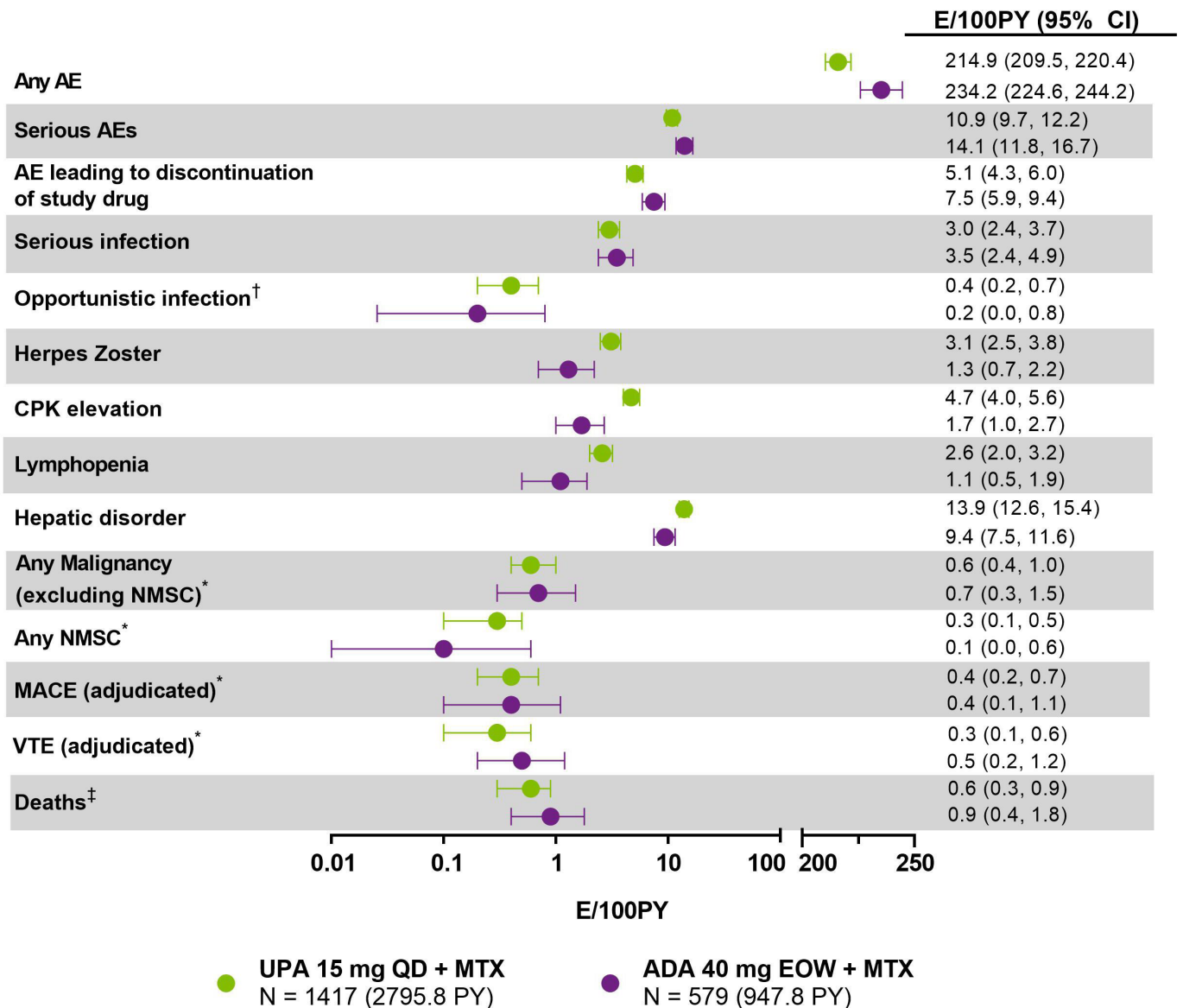
Figure 1 Disposition of patients through week 156. Numbers of patients on study drug, with primary reason for discontinuation summarised during long-term extension through week 156. *Rescue occurred only before or at week 26; no rescue was allowed after week 26. †All placebo patients not previously rescued (at weeks 14, 18 or 22) were switched to upadacitinib at week 26. ADA, adalimumab; AE, adverse event; D/C, discontinued; EOW, every other week; f/u, follow-up; l/c, logistical restrictions; LOE, lack of efficacy; MTX, methotrexate; PBO, placebo; QD, once daily; UPA, upadacitinib; Wk, week.

occurred at similar rates in patients on upadacitinib (3.0 E/100 PY) and adalimumab (3.5 E/100 PY), and the types of those infections were generally consistent with those expected in a study population comprised of patients with RA. HZ infection rates were higher on upadacitinib than adalimumab (3.1 and 1.3 E/100 PY, respectively) (figure 2). Most HZ infections were non-serious and involved one or two dermatomes (online supplemental material 1). No events were reported as having central nervous system or other non-cutaneous involvement; three events were reported as ophthalmic HZ (two on upadacitinib and one on adalimumab). Opportunistic infections (excluding tuberculosis, HZ and oral candidiasis) were reported in similar proportions of patients on either study therapy (0.4 E/100 PY on upadacitinib and 0.2 E/100 PY on adalimumab), with nonserious oesophageal candidiasis the most commonly reported (figure 2, online supplemental material 1).

The majority of CPK elevation events occurring on either upadacitinib or adalimumab were mild (68% and 50%, respectively) or moderate (25% and 44%), transient (77% and 81%), and, among the observations of increased CPK for which the presence or absence of symptoms were collected, 94% were asymptomatic; mostly transient muscle pain was reported for the remaining 6%. No case of rhabdomyolysis was observed. Most reports of hepatic disorder were based on ALT or aspartate aminotransferase (AST) elevations, with no

Hy's law case identified. The event rate for anaemia was the same for patients randomised to either upadacitinib or adalimumab (3.3 E/100 PY), and most cases were mild or moderate and transient. Through 3 years, one adjudicated GI perforation event was reported in a patient receiving upadacitinib (online supplemental material 1).

The event rates of malignancies, excluding nonmelanoma skin cancer (NMSC), were similar on upadacitinib and adalimumab through 156 weeks (0.6 and 0.7 E/100PY, respectively) (figure 2). There was no notable pattern in the types of malignancies that were observed. Malignancies in patients on upadacitinib included three malignant melanoma, three lung cancer and two breast cancer; malignancies occurring on adalimumab included three colon cancer and two lung cancer—all others on either treatment occurred in a single patient (detailed in online supplemental material 1). Nearly all malignancies took place in older patients (≥53 years of age). Malignancy (excluding NMSC) rates in the subgroup of patients receiving continuous treatment with upadacitinib or adalimumab, without rescue or switch, were also similar (0.8 and 1.1 E/100 PY, respectively) (table 1). Event rates for adjudicated MACE were equivalent on upadacitinib and adalimumab (0.4 E/100PY for each treatment) (figure 2). Adjudicated MACE in patients on upadacitinib included two non-fatal strokes, four non-fatal myocardial infarctions, four cardiovascular (CV) deaths; on adalimumab, three non-fatal strokes and

E/100PY (95% CI)

	E/100PY (95% CI)
Any AE	214.9 (209.5, 220.4)
	234.2 (224.6, 244.2)
Serious AEs	10.9 (9.7, 12.2)
	14.1 (11.8, 16.7)
AE leading to discontinuation of study drug	5.1 (4.3, 6.0)
	7.5 (5.9, 9.4)
Serious infection	3.0 (2.4, 3.7)
	3.5 (2.4, 4.9)
Opportunistic infection†	0.4 (0.2, 0.7)
	0.2 (0.0, 0.8)
Herpes Zoster	3.1 (2.5, 3.8)
	1.3 (0.7, 2.2)
CPK elevation	4.7 (4.0, 5.6)
	1.7 (1.0, 2.7)
Lymphopenia	2.6 (2.0, 3.2)
	1.1 (0.5, 1.9)
Hepatic disorder	13.9 (12.6, 15.4)
	9.4 (7.5, 11.6)
Any Malignancy (excluding NMSC)*	0.6 (0.4, 1.0)
	0.7 (0.3, 1.5)
Any NMSC*	0.3 (0.1, 0.5)
	0.1 (0.0, 0.6)
MACE (adjudicated)*	0.4 (0.2, 0.7)
	0.4 (0.1, 1.1)
VTE (adjudicated)*	0.3 (0.1, 0.6)
	0.5 (0.2, 1.2)
Deaths‡	0.6 (0.3, 0.9)
	0.9 (0.4, 1.8)

E/100PY

● **UPA 15 mg QD + MTX**
N = 1417 (2795.8 PY)

● **ADA 40 mg EOW + MTX**
N = 579 (947.8 PY)

Figure 2 Treatment-emergent adverse event summary through 156 weeks (E/100 PY (95% CI)). Data through 156 weeks include all patients receiving upadacitinib or adalimumab, including rescue groups, with assignment based on drug exposure at the time of event. The last week-156 visit was on 6 August 2020. Exposure-adjusted event rates (EAERs) are reported for all events. *Exposure-adjusted incidence rates (EAIRs) were the same as EAERs for malignancies, MACE and VTE. All events were considered AESIs except any AE, serious AEs, AE leading to discontinuation of study drug and deaths. †Opportunistic infections exclude herpes zoster, tuberculosis and oral candidiasis. Event rates for oral candidiasis and active tuberculosis were similar on upadacitinib and adalimumab (0.2 and 0.1 E/100 PY vs 0.3 and 0.2 E/100 PY, respectively). ‡Includes non-treatment emergent deaths. ADA, adalimumab; AE, adverse event; AESI, adverse event of special interest; CPK, creatine phosphokinase; EOW, every other week; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, non-melanoma skin cancer; PY, patient-years; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolism.

one CV death were reported. Most MACE occurred in patients >50 years of age (upadacitinib: 8/10; adalimumab: 4/4). All patients with MACE had at least one CV risk factor; in fact, most had at least two CV risk factors, including hypertension, diabetes mellitus and smoking (online supplemental table 3). MACE was observed across the disease activity spectrum, with few patients in CDAI remission (upadacitinib: 20%; adalimumab: 0%) at the visit preceding MACE occurrence (40% and 50% of patients on upadacitinib and adalimumab were in CDAI LDA, respectively). Event rates for adjudicated VTE were similar on upadacitinib and adalimumab (0.3 and 0.5 E/100 PY, respectively) (figure 2). Adjudicated VTE events on upadacitinib included one venous thromboembolic death, three non-fatal deep vein thrombosis (DVT), three non-fatal pulmonary embolism (PE), two concurrent DVT and PE; on adalimumab, four PE and one DVT were reported. The majority of VTE events occurred in patients over 50 years of age (upadacitinib: 6/9; adalimumab: 5/5), and all had at least 1 CV or thrombosis risk factor (online supplemental table 4). Among patients who had AEs adjudicated as VTEs, most were in high or

Table 1 Exposure-adjusted event rates of malignancy (excluding NMSC), adjudicated MACE and VTE in patients receiving continuous upadacitinib or adalimumab

Event	Continuous UPA 15 mg QD +MTX (n=398; PY=994.1) (95% CI) (events)	Continuous ADA 40 mg EOW +MTX (n=168; PY=373.0) (95% CI) (events)
Malignancy (excluding NMSC)*	0.8 (0.3 to 1.6) (8)	1.1 (0.3 to 2.7) (4)
MACE (adjudicated)*	0.1 (0.0 to 0.6) (1)	0.5 (0.1 to 1.9) (2)
VTE (adjudicated)*	0.2 (0 to 0.7) (2)	0.8 (0.2 to 2.4) (3)

*Exposure-adjusted incidence rates were the same as exposure-adjusted event rates for malignancy, MACE and VTE.
ADA, adalimumab; AE, adverse event; EOW, every other week; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, non-melanoma skin cancer; PY, patient years; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolism.

moderate disease activity (56% on upadacitinib and 60% on adalimumab; CDAI >10) at the visit preceding VTE occurrence, with few in CDAI remission (upadacitinib: 11%; adalimumab: 20%) (online supplemental figure 2). Overall, no clear pattern emerged in the timing of either MACE or VTE events during upadacitinib or adalimumab treatment (online supplemental figure 3). Event rates for adjudicated MACE and adjudicated VTE were also consistent in the subgroup of patients receiving continuous upadacitinib or adalimumab (table 1).

Twenty-five deaths (18 of which were treatment-emergent) were reported among patients who received upadacitinib (16 deaths) or adalimumab (9 deaths). The rate of deaths was generally similar on either upadacitinib or adalimumab (0.6 and 0.9 E/100 PY, respectively), and there was no detectable pattern observed in regard to the type of fatal events (online supplemental material 1).

The group mean values for haematology variables (haemoglobin, lymphocytes, neutrophils and platelets) were within normal range at baseline and at subsequent treatment visits. However, higher proportions of patients with grade 3/4 lymphocyte decreases and CPK elevation were reported on upadacitinib compared with adalimumab (table 2). There was no clear association between grade 4 lymphopaenia and the risk of infections, including serious and opportunistic infections (online supplemental table 5). The percentage of patients with a grade 3 increase in ALT/AST also occurred more frequently on upadacitinib than adalimumab.

Efficacy

The proportion of patients attaining LDA and clinical remission by CDAI, as well as the proportion of patients reaching DAS28(CRP) ≤3.2/<2.6, was consistently higher in those randomised to upadacitinib compared with adalimumab over 3 years by NRI (figure 3). At week 156, CDAI LDA/remission was achieved by 40/24% randomised to upadacitinib and 29/17% randomised to adalimumab. Moreover, DAS28(CRP) ≤3.2/<2.6 was achieved by 37/32% of patients randomised to upadacitinib vs 26/22% of those randomised to adalimumab, and 20% vs 14% achieved the ACR/EULAR Boolean-based remission definition (nominal p=0.012).

**Table 2** Grade 3/4 laboratory abnormalities through week 156

Parameter, %		UPA 15 mg QD +MTX	ADA 40 mg EOW +MTX
Haemoglobin (g/dL)	Grade 3 (decrease 2.1–2.9* or Hb ≥7.0 to <8.0)	6.5	4.2
	Grade 4 (decrease ≥3* or Hb <7.0)	2.1	2.1
Lymphocytes (x10^9/L)	Grade 3 (0.5 to <1.0)	27.0	9.0
	Grade 4 (<0.5)	2.9	0.5
Neutrophils (x10^9/L)	Grade 3 (0.5 to <1.0)	1.3	0.5
	Grade 4 (<0.5)	0.4	0.3
ALT (U/L)	Grade 3 (3.0–8.0 × ULN)	5.4	2.1
	Grade 4 (>8.0 × ULN)	0.6	0.7
AST (U/L)	Grade 3 (3.0–8.0 × ULN)	3.3	1.4
	Grade 4 (>8.0 × ULN)	0.4	0.9
CPK (U/L)	Grade 3 (>5.0 × ULN–10.0 × ULN)	2.1	0.3
	Grade 4 (>10.0 × ULN)	0.7	0.3
Creatinine (µMol/L)	Grade 3 (>3.0–6.0 × ULN)	0.2	0.2
	Grade 4 (>6.0 × ULN)	0.1	0

Data are for patients with worsening in grade severity for laboratory parameters. Grading is based on Outcome Measures in Rheumatology (OMERACT) criteria, except for CPK and creatinine, where National Cancer Institute Common Terminology Criteria (NCI CTC) criteria were used.
*Decrease from baseline. Baseline is defined as the last observation on or before the date of the first dose of study drug in the corresponding treatment group.
ADA, adalimumab; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; EOW, every other week; MTX, methotrexate; QD, once daily; ULN, upper limit of normal; UPA, upadacitinib.
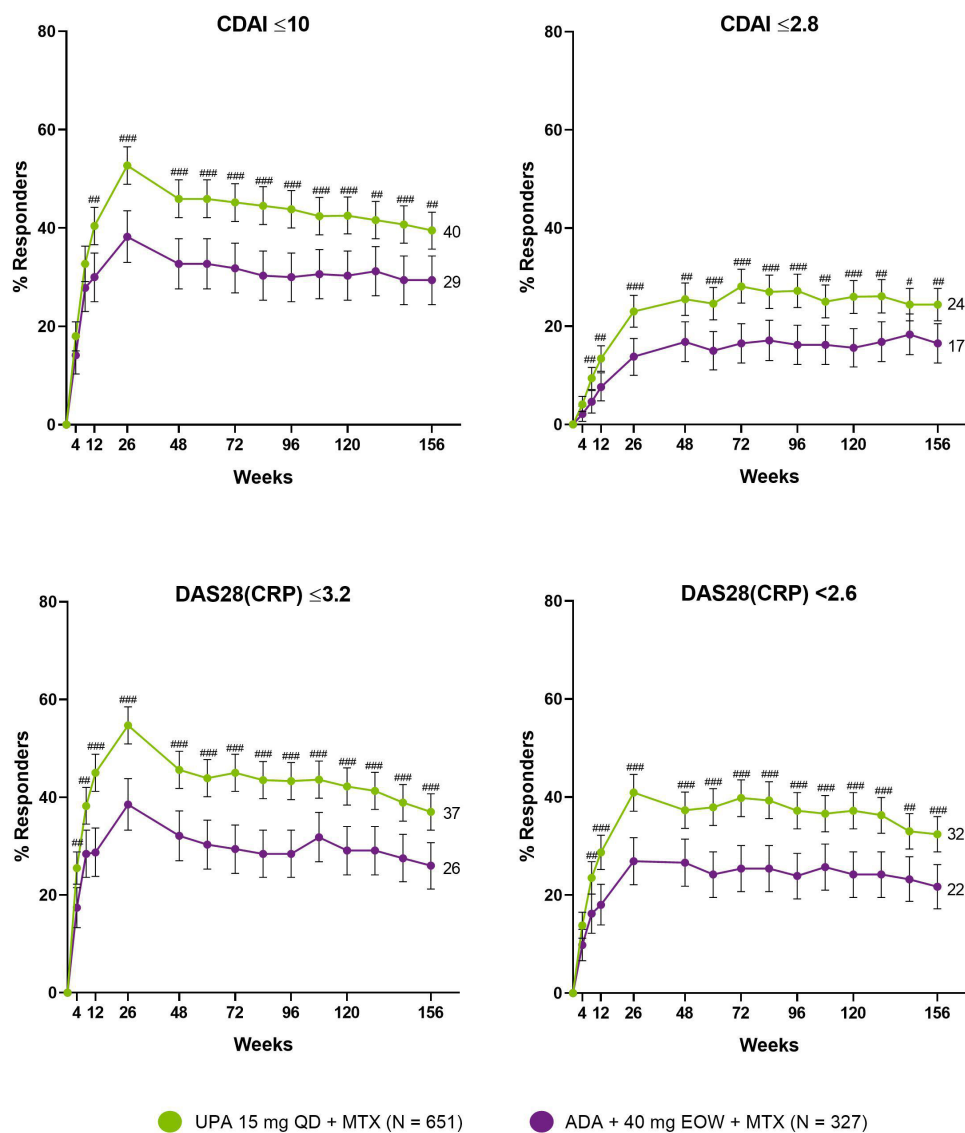
Figure 3 Proportions of patients achieving CDAI LDA/remission and DAS28(CRP) ≤3.2/<2.6 through 156 Weeks (NRI). Treatment groups are by initial randomisation. #P<0.05, ##p<0.01, ###p<0.001 for upadacitinib plus MTX versus adalimumab plus MTX. All p values are nominal. NRI was used for patients who were rescued or prematurely discontinued study drug, as well as for missing data. Data points plotted here are shown in online supplemental table 6. ADA, adalimumab; CDAI, clinical disease activity index; DAS28(CRP), 28-joint Disease Activity Score based on C-reactive protein; EOW, every other week; MTX, methotrexate; NRI, non-responder imputation; PBO, placebo; QD, once daily; UPA, upadacitinib.

Upadacitinib also demonstrated improvements over time when data were analysed by treatment group sequence (AO) (figure 4). By this approach, numerically higher proportions of patients receiving continuous upadacitinib versus continuous adalimumab—without any treatment switching—achieved CDAI LDA and remission, as well as DAS28(CRP) ≤3.2/<2.6, over 3 years. By week 156, CDAI LDA/remission was achieved by 93/57% and 92/52% of patients receiving continuous upadacitinib or adalimumab, respectively (AO). Numerically higher responses for patients who switched from adalimumab to upadacitinib vs those who switched from adalimumab to upadacitinib were also observed (figure 4).

When evaluating the results by NRI, patients randomised to upadacitinib consistently achieved higher rates of ACR20, ACR50 and ACR70 responses compared with adalimumab (42/38/32% vs 30/27/21% at week 156) (online supplemental figure 4). Similarly, when analysed by treatment sequence group (AO), numerically higher ACR20/50/70 rates were observed in patients receiving continuous upadacitinib versus continuous adalimumab over 3 years (96/88/74% vs 94/82/66% at week 156) (online supplemental figure 5). In addition, numerically higher ACR responses were observed in patients who switched from adalimumab to upadacitinib than those who switched from upadacitinib to adalimumab. Patients randomised to upadacitinib also demonstrated greater numerical improvements from baseline in HAQ-DI at week 156 (−0.75 vs −0.60, nominal p<0.01) and a greater reduction in pain relative to adalimumab (−39.8 vs −31.2 at week 156, nominal p<0.001) (figure 5). Overall consistent results were observed for other ACR
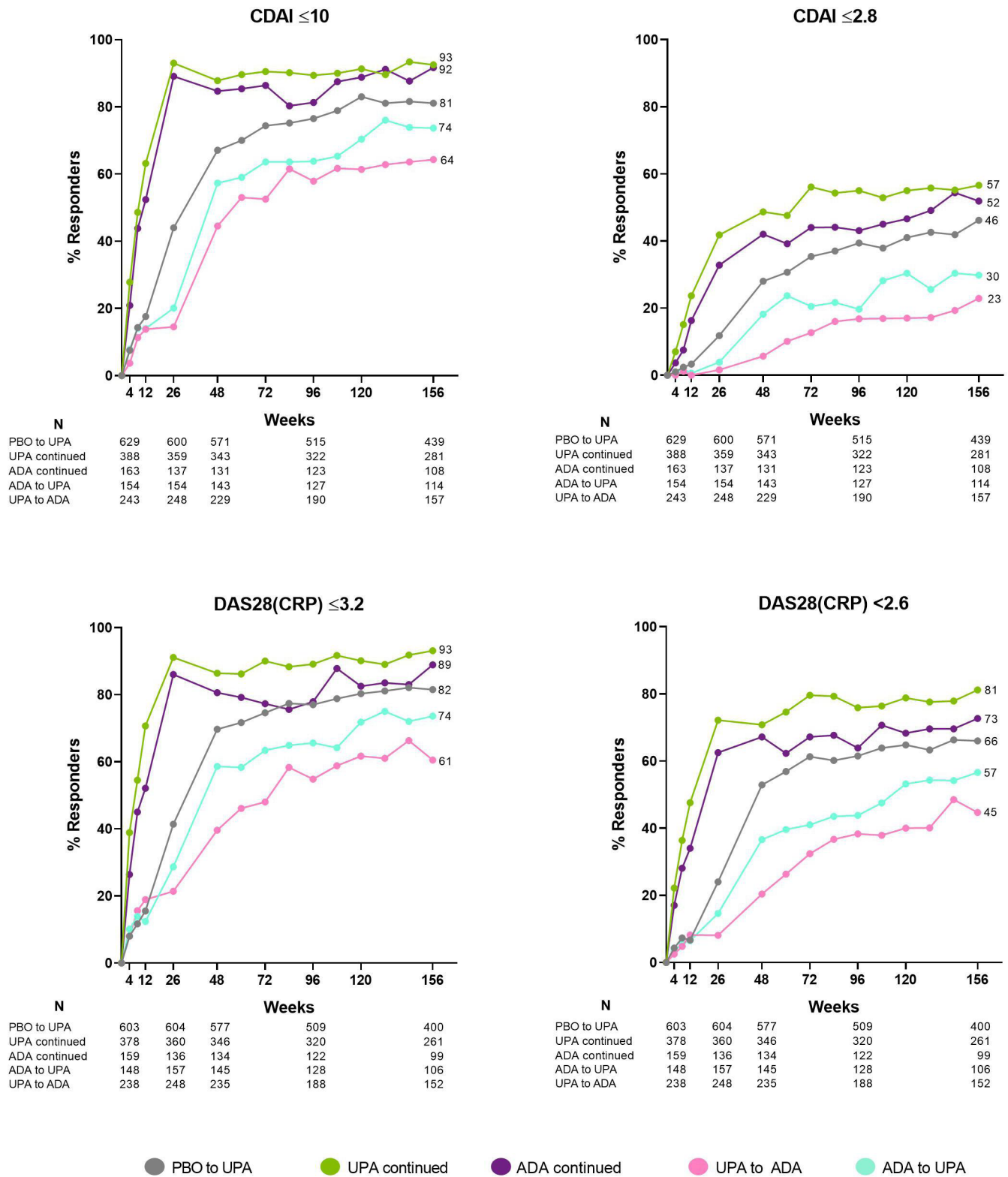
Figure 4 Proportions of patients attaining disease activity states over 156 weeks (AO). Groups are by treatment sequence AO, without imputation for missing data. All patients in the placebo group who were not previously rescued were switched to upadacitinib at week 26. ADA, adalimumab; AO, as observed; CDAI, Clinical Disease Activity Index; DAS28(CRP), 28-joint Disease Activity Score based on C-reactive protein; EOW, every other week; MTX, methotrexate; QD, once daily; UPA, upadacitinib.
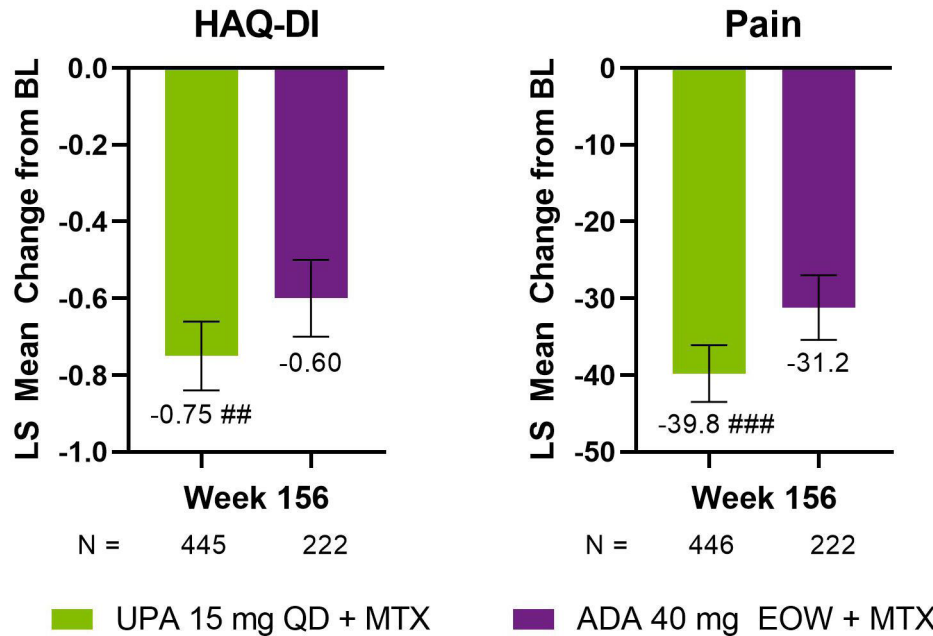
Figure 5 Mean change from baseline in HAQ-DI and pain at week 156 (LOCF). Nominal ##p<0.01, ###p<0.001 for upadacitinib plus MTX versus adalimumab plus MTX. Treatment groups are by initial randomisation. Observations after rescue were replaced with the last observation prior to rescue, and analysis was based on ANCOVA model with treatment and prior bDMARD use as fixed factors and bL value as covariate. HAQ-DI is rated on a 0–3 scale; patient's assessment of pain is scored on a 0–100 mm scale. ADA, adalimumab; bDMARD, biological disease modifying antirheumatic drug; bL, baseline; EOW, every other week; HAQ-DI, Health Assessment Questionnaire-Disability Index; LOCF, last observation carried forward; LS, least squares; MTX, methotrexate; QD, once daily; UPA, upadacitinib.

core components over 3 years, except SJC66, which was less prominent (online supplemental figure 6).

Through 2 years of treatment, similar proportions of patients administered continuous upadacitinib or continuous adalimumab demonstrated no radiographic progression (82.0% vs 75.2%, respectively, at 2 years) (figure 6A). The rate at which structural progression was inhibited was

also comparable, as measured by a mean change from baseline in mTSS, erosion score and joint space narrowing (figure 6B; online supplemental figures 7 and 8).
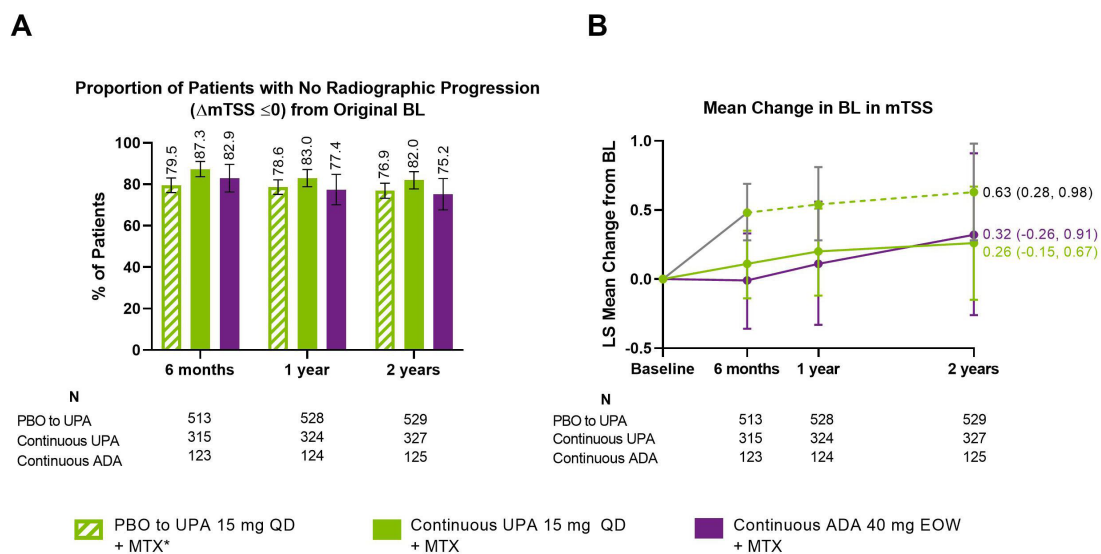
Figure 6 Radiographic outcomes at 6 months, 1 year and 2 years (AO). *Per study design, all patients in the placebo group who were not previously rescued were switched to upadacitinib at week 26. Data are reported AO. (A) Determination of no radiographic progression was assessed by a change from baseline in mTSS ≤0. (B) Least-squares mean change from baseline in mTSS. ADA, adalimumab; AO, as observed; bL, baseline; EOW, every other week; LS, least squares; MTX, methotrexate; PBO, placebo; QD, once daily; mTSS, modified Total Sharp Score; UPA, upadacitinib.

DISCUSSION

The 3-year data from the SELECT-COMPARE trial provide the unique opportunity to assess the safety and efficacy of upadacitinib compared with the active comparator adalimumab. In contrast to other head-to-head RA studies evaluating JAK inhibitors where the comparator treatment arm ended after 1 year,[25–27] SELECT-COMPARE is the only trial to our knowledge that maintains an active comparator through 3 years and longer. Given that RA is a chronic disease requiring continuing treatment, long-term safety considerations are of key clinical relevance.

The safety profile of upadacitinib 15 mg once a day observed through 3 years is consistent with prior evaluations of upadacitinib reported in SELECT-COMPARE and with the overall known safety profile of upadacitinib.[10 13 16] There were no new safety findings. The rate of serious infections was similar for upadacitinib compared with adalimumab through 156 weeks. In line with the known increased risk of HZ on JAK inhibition,[10 28–31] HZ rates were higher on upadacitinib. However, most HZ cases identified on upadacitinib were nonserious, involved one or two dermatomes, and did not result in discontinuation of treatment. Regarding geographical distribution, an integrated analysis of upadacitinib phase 3 RA data (including SELECT-COMPARE) reported that patients from Asia experience HZ more frequently.[10] The event rate for malignancies (excluding NMSC) described here is consistent with that expected in RA populations,[32–34] and results through 156 weeks were similar between upadacitinib and adalimumab. As would be expected, the vast majority of malignancies occurred in patients over 50 years of age. Event rates for MACE were also similar for both study drugs and consistent in the subgroup of patients receiving continuous upadacitinib or adalimumab without treatment switch. VTE rates reported here through week 156 were similar between upadacitinib and adalimumab (0.3 and 0.5 E/100 PY, respectively) and consistent with expected rates for patients with RA (rate of 0.3–0.8 E/100 PY).[35 36] There was also no increase in VTE risk with duration of exposure to upadacitinib compared with week 48 results.[16] All patients with MACE or thrombotic events had at least one risk factor in addition to their underlying RA. Of note, while MACE occurred in patients across the disease activity spectrum, few patients were in CDAI remission at the visit preceding the event (2/10 on upadacitinib and 0/4 on adalimumab). Given a recent cohort study suggesting that VTE risk may be associated with disease activity,[37] we also assessed patient disease activity around the time of the VTE in affected patients. Similarly, more patients enrolled in SELECT-COMPARE showed higher disease activity at the visit prior to VTE occurrence, and few VTE events occurred among patients in CDAI remission (1/9 on upadacitinib and 1/5 on adalimumab). However, due to the limited number of events, no definitive conclusion can be drawn, and further research in a much larger population of patients at risk of the events are needed to answer this question. Other factors associated with VTE risk identified from an integrated analysis of upadacitinib 15 mg trial data included higher BMI, prior history of VTE, older age and NSAID or statin use.[38]

More recently, potential safety issues were reported in ORAL Surveillance, a randomised, postmarketing safety study for another JAK inhibitor.[39] The study was prospective and randomised, with a primary endpoint comparing the incidence rate of malignancies and MACE in patients aged 50 and above with RA who had at least one CV risk factor.[39] Although not powered for these endpoints, VTE and mortality were also assessed. This study showed a numerical difference in these events of special interest favouring the TNF inhibitor over the JAK inhibitor. SELECT-COMPARE enrolled an entirely different population that was much smaller, including only a subgroup of patients who would have qualified for ORAL Surveillance and was not powered to show these safety results. Notably, we observed similar rates of these events between upadacitinib and adalimumab among patients enrolled in SELECT-COMPARE.

To summarise safety findings, with the exception of known higher rates for HZ, CPK elevation, lymphopaenia and hepatic disorder on upadacitinib, safety over 3 years remained generally comparable between upadacitinib 15 mg once a day and adalimumab and consistent with findings from the integrated phase 3 safety analysis, which incorporated data from over 3500 patients worldwide with a combined exposure of 4000 PY.[10] In addition, a post hoc analysis of SELECT-COMPARE using numbers needed to harm methodology identified comparable risks for serious infections, malignancies, MACE and VTEs among patients randomised to upadacitinib or adalimumab through 3 years.[40] However, given that SELECT-COMPARE was not designed to show such safety differences, rates of malignancies, MACEs, VTEs and deaths need to be interpreted with caution.

In terms of efficacy, upadacitinib plus MTX continued to show better clinical responses compared with adalimumab plus MTX (nominal p<0.05) consistently through 3 years across all endpoints, including rates of remission and LDA, physical function and pain severity. Similar to previously described treatment switch data,[16] numerically higher efficacy responses were consistently maintained for upadacitinib vs adalimumab over 3 years, regardless of whether patients were in the continuous upadacitinib or treatment switch group. Consistent with radiographic outcomes through 1 year,[16] structural joint damage was inhibited to a similar extent on upadacitinib versus adalimumab over 2 years, as determined by mean change in mTSS score, erosion and joint space narrowing, as well as the proportion of patients with no radiographic progression.

Limitations of this study include that it was not designed or powered to detect differences in long-term safety events nor were adjustments possible for multiple comparisons to evaluate the long-term efficacy data. Thus, long-term comparative efficacy data should be interpreted with caution. In addition, the placebo treatment ended at

week 26 for ethical reasons. Given the nature of LTEs, results based on AO data may be biased by those patients who remain in the study and who tolerate the drug and show response to drug treatment. To minimise this bias, a conservative NRI approach was also used for efficacy analysis. Regarding safety limitations, the reporting of uncommon AESIs may be biased against upadacitinib: the overall total PY of exposure was nearly threefold higher on upadacitinib versus adalimumab (2796 PY and 948 PY, respectively), providing more opportunities for rare AEs to present on upadacitinib. Nonetheless, despite these limitations, the 3-year data from this open-label LTE provide insights into the long-term benefit/risk of upadacitinib versus adalimumab in a controlled setting.

In summary, the safety profile of upadacitinib 15 mg once a day observed through 3 years was consistent with the results reported previously in SELECT-COMPARE[13 16] and with the integrated phase 3 safety analysis.[10] No new safety risks emerged. Upadacitinib continued to be effective in treating the signs and symptoms of RA over 3 years, with consistently higher proportions of patients achieving key clinical outcomes such as remission and LDA on upadacitinib vs adalimumab. Upadacitinib-treated patients also showed greater improvements in physical function and pain severity, key factors for patients given their strong influence on overall quality of life. In addition, radiographic progression through 2 years was low and similar between upadacitinib and adalimumab providing further reassurance that the disease activity was well controlled. Overall, the results from this LTE of SELECT-COMPARE continue to support a favourable benefit:risk profile for upadacitinib in the treatment of RA.

Author affiliations
[1]Metroplex Clinical Research Center, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA
[2]Organización Médica de Investigación, Buenos Aires, Argentina
[3]Department of Medicine, Laval University, Quebec City, Quebec, Canada
[4]Spire Sciences Inc, Boca Raton, Florida, USA
[5]Pôle de Recherche en Rhumatologie, Institut de Recherche Expérimentale et Clinique, UCL Saint-Luc, Brussels, Belgium
[6]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan
[7]Department of Rheumatology and Internal Medicine, Wroclaw Medical University, Wroclaw, Poland
[8]AbbVie Inc, North Chicago, Illinois, USA

ORCID iDs
Roy Fleischmann http://orcid.org/0000-0002-6630-1477
Patrick Durez http://orcid.org/0000-0002-7156-2356
Yoshiya Tanaka http://orcid.org/0000-0002-0807-7139

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