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ORIGINAL RESEARCH

Upadacitinib *versus* placebo or adalimumab with background methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate: a subgroup analysis of a phase III randomized controlled trial in Central and Eastern European patients

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Abstract

Background: In the randomized, phase III, global SELECT-COMPARE study, upadacitinib 15 mg demonstrated efficacy at week 12 *versus* placebo and adalimumab with methotrexate (MTX) in patients with rheumatoid arthritis and inadequate response to MTX, which was maintained over 48 weeks. This post hoc analysis of SELECT-COMPARE reports the efficacy and safety of upadacitinib in Central and Eastern European (CEE) patients.

Methods: Patients were randomized 2:2:1 to upadacitinib 15 mg once daily, placebo, or adalimumab 40 mg every other week, and continued MTX. Efficacy and safety were assessed through 48 weeks. Primary endpoints were the achievement of ≥20% improvement in American College of Rheumatology response criteria and Disease Activity Score in 28 joints with C-reactive protein <2.6 responses at week 12 for upadacitinib *versus* placebo. No statistical comparisons were conducted.

Results: A total of 596 patients from 12 CEE countries were randomized. At week 12, a numerically greater proportion of patients receiving upadacitinib *versus* placebo or adalimumab achieved ≥20% improvement in American College of Rheumatology response criteria (72% *versus* 33% and 59%), Disease Activity Score in 28 joints with C-reactive protein <2.6 (26% *versus* 4% and 11%), low disease activity and remission, and improved physical function, with results maintained over 48 weeks. Upadacitinib treatment numerically inhibited structural progression *versus* placebo at week 26. Serious infection and herpes zoster rates were numerically higher with upadacitinib *versus* adalimumab (2.7 *versus* 1.7 and 2.3 *versus* 1.1 events/100 patient-years, respectively) over 48 weeks.

Conclusion: Consistent with the global population of patients with rheumatoid arthritis and an inadequate response to MTX, in CEE patients, upadacitinib 15 mg demonstrated clinical and functional improvements *versus* placebo and adalimumab, radiographic improvements *versus* placebo, and reasonable safety, over 48 weeks.

Keywords: Eastern Europe, rheumatoid arthritis, safety, treatment efficacy, upadacitinib.

Citation

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic immune-mediated inflammatory disease characterized by joint pain and swelling, impaired physical function, and systemic inflammation, often associated with fatigue and joint damage if left untreated.[1] According to the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) recommendations, preferably methotrexate (MTX) or, alternatively, a conventional synthetic disease-modifying antirheumatic drug (csDMARD), is recommended as the first-line treatment for RA.[1,2] However, in patients with an inadequate response to MTX (MTX-IR), a second csDMARD or, particularly in patients with poor prognostic factors, a biologic disease-modifying antirheumatic drug (bDMARD) or a targeted synthetic disease-modifying antirheumatic drug should be added to the background csDMARD.[1,2]

Upadacitinib is an orally administered selective and reversible Janus kinase (JAK) inhibitor that preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal *via* pairs of JAK2 in human cellular assays.[3] Upadacitinib has demonstrated a generally favorable benefit–risk profile across various patient populations in phase III trials.[4–9] The molecule has recently been approved for the treatment of RA by the European Medicines Agency and the US Food and Drug Administration.[3,10]

SELECT-COMPARE is an ongoing phase III, randomized, placebo- and active-controlled, double-blind trial that has evaluated the safety and efficacy of upadacitinib 15 mg once daily (QD) *versus* placebo or adalimumab 40 mg every other week , each in combination with stable background MTX, in patients with MTX-IR RA.[7,11] Upadacitinib 15 mg QD achieved both primary endpoints, ≥20% improvement in ACR response criteria (ACR20) and Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) <2.6 at week 12 *versus* placebo, and was superior *versus* adalimumab in ranked, multiplicity-adjusted endpoints of ≥50% improvement in ACR response criteria (ACR50) and change from baseline in pain and Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 12. In addition, upadacitinib 15 mg QD achieved significantly greater inhibition in van der Heijde's modification of the Total Sharp Score (mTSS) *versus* placebo at week 26. Upadacitinib continued to demonstrate significantly greater clinical and patient-reported outcome (PRO)-related responses *versus* placebo and adalimumab as well as maintained significant radiographic inhibition, over 48 weeks. The safety profile of upadacitinib over 48 weeks was similar to that of adalimumab except for higher rates of herpes zoster (HZ) and creatine phosphokinase elevations.[7,11] The increased rates of HZ observed with upadacitinib are consistent with previous reports of HZ across approved JAK inhibitors, including tofacitinib and baricitinib.[12–14]

In Central and Eastern European (CEE) countries, the prevalence of RA is estimated to be 0.35–0.90%.[15,16] Although EULAR recommendations suggest that patients with RA and an unacceptable disease activity switch to a bDMARD or targeted synthetic disease-modifying antirheumatic drug after failure of ≥2 csDMARDs if poor prognostic factors are absent and after 1 csDMARD if poor prognostic factors are present, restrictive local reimbursement criteria in CEE countries may limit access to these treatments.[1,16,17] While this situation facilitates greater enrolment in RA clinical trials from these regions, it can also affect the baseline characteristics profile of the patient population involved, for example, longer disease duration, greater level of radiographic damage, and comorbidities as well as clinical response and safety outcomes. The significant differences in the reporting of response rates and adverse events (AEs) between countries in the CEE region, Latin America, Asia, and the USA across RA trials suggest regional differences in investigator or patient behavior or patient characteristics.[18] Together with the increased placebo response observed in RA trials globally over the last two decades,[19] the need for separate analyses of regional data is justified. Currently, there are limited data available on the efficacy and safety of upadacitinib in CEE patients to inform clinical decision-making and national reimbursement bodies.

Randomization was stratified by geographic region in the SELECT-COMPARE study. As a result, this provided a balanced distribution of patients across treatment arms to evaluate the clinical efficacy and safety of upadacitinib in the one-third of patients enrolled from the CEE region.[7] This post hoc analysis of SELECT-COMPARE reports, for the first time, the efficacy and safety of upadacitinib 15 mg in combination with MTX in patients from the CEE region with MTX-IR RA compared with placebo or adalimumab with MTX up to 48 weeks of follow-up.

Methods

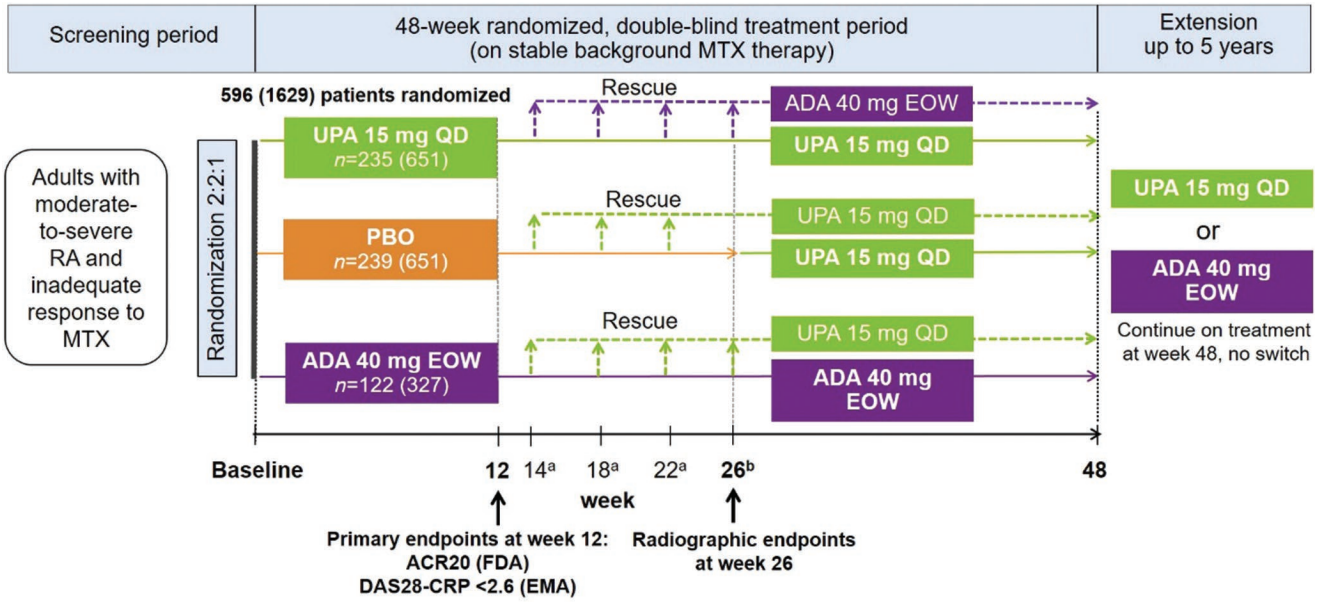
Patients

This is a post hoc subgroup analysis of patients from 12 CEE countries (Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Lithuania, Poland, Russian Federation, Serbia, Slovakia, and Ukraine) who were enrolled in the SELECT-COMPARE upadacitinib study (NCT02629159; https://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02629159). Inclusion and exclusion criteria have been described previously.[7,11] In brief, patients were ≥18 years of age with active RA (swollen joint count [SJC] ≥6, tender joint count [TJC] ≥6, high-sensitivity C-reactive protein [hsCRP] ≥5 mg/L, and evidence of radiographic erosion and/or seropositivity). Up to 20% of patients exposed to one bDMARD (except for adalimumab) were permitted to enter the study, providing they had <3 months' exposure or discontinued the bDMARD due to intolerance. Patients with an inadequate response to a prior bDMARD or with prior exposure to a JAK inhibitor were excluded.

Study design

Patients were randomized 2:2:1 to upadacitinib 15 mg QD, placebo, or adalimumab 40 mg every other week, with stable background MTX (Figure 1). Patients continued to receive oral or

Figure 1. Study design of the SELECT-COMPARE Central and Eastern European subgroup analysis.



Randomization is stratified by prior exposure to biologic disease-modifying antirheumatic drug (yes/no) and geographic region. Number of Central and Eastern European patients randomized are shown with number of global patients randomized in brackets.
[a]At weeks 14, 18, and 22, patients were rescued if <20% improvement in tender joint count and swollen joint count.
[b]At week 26, all remaining PBO patients were switched to UPA, and patients receiving UPA or ADA were switched to ADA and UPA, respectively, if Clinical Disease Activity Index >10.
ACR20, ≥20% improvement in American College of Rheumatology criteria; ADA, adalimumab; DAS28-CRP, Disease Activity Score in 28 joints using CRP level; EMA, European Medicines Agency; EOW, every other week; FDA, US Food and Drug Administration; MTX, methotrexate; PBO, placebo; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib.

parenteral MTX at a stable dosage (15–25 mg/week; or ≥10 mg/week in patients who could not tolerate MTX at ≥12.5 mg/week) for at least 4 weeks before commencement of the study, with dose reductions permitted for safety reasons only. Patients receiving stable doses of non-steroidal anti-inflammatory drugs and acetaminophen ≥1 week prior to the first dose of study drug or oral steroids (≤10 mg prednisone or equivalent per day) ≥4 weeks prior to the first dose of study drug were allowed to continue these medications. Starting at week 26 (after week 26 assessments have been performed) and thereafter, two intra-articular, intramuscular, intravenous, trigger point or tender point, intrabursa, and intratendon sheath injections of corticosteroids, dosage and frequency per standard of care, were allowed.

Randomization was stratified by prior exposure to bDMARD (yes/no) and geographic region. Patients with <20% improvement from baseline in SJC or TJC were eligible for rescue treatment (and switched from placebo or adalimumab to upadacitinib, and upadacitinib to adalimumab) at weeks 14, 18, or 22. At week 26, all remaining patients randomized to placebo were switched to upadacitinib; in patients who did not meet Clinical Disease Activity Index (CDAI) ≤10, those receiving adalimumab were rescued to upadacitinib and those receiving upadacitinib were rescued to adalimumab.

Investigators and patients remained blinded with regard to treatment until all patients had completed week 48, after which patients were eligible to enter an open-label extension for up to 5 years.

The study was conducted in accordance with the International Conference on Harmonization guidelines, applicable regulations, and the Declaration of Helsinki. Study-related documents were approved by institutional ethics committees and review boards. All patients provided written informed consent.

Efficacy assessments

The primary endpoints and ranked secondary endpoints of the SELECT-COMPARE study have been previously described.[7] In brief, the two primary endpoints were the proportion of patients who achieved ACR20 and the proportion of patients who achieved DAS28-CRP <2.6 *versus* placebo at week 12 (Figure 1). Key ranked secondary endpoints included change in mTSS[20,21] and the proportion of patients with no radiographic progression (mTSS ≤0) *versus* placebo at week 26, non-inferiority *versus* adalimumab according to ACR50 and DAS28-CRP ≤3.2 response rate at week 12, and superiority *versus* adalimumab according to ACR50 response rate and mean change from baseline in pain severity and HAQ-DI score at week 12.

In this analysis, efficacy through week 48 was evaluated for the following outcomes by initial randomized group: DAS28-CRP <2.6 and ≤3.2 (remission and low disease activity [LDA] criteria, respectively, used by the European Medicines Agency for regulatory filing); remission defined by CDAI ≤2.8, Simplified Disease Activity Index (SDAI) ≤3.3, and ACR/EULAR Boolean remission (SJC ≤1, TJC ≤1, hsCRP ≤1 mg/dL, Patient Global Assessment of Disease Activity ≤1 on a 0–10 visual analog scale [VAS]); LDA defined by CDAI ≤10 and SDAI ≤11; the proportions of patients achieving ACR20, ACR50, and ACR70 responses (defined by ≥20%, ≥50%, and ≥70% improvement in ACR criteria) and a HAQ-DI minimal clinically important difference (MCID) of ≥0.22; and mean change from baseline in HAQ-DI, 36-Item Short Form (SF-36) physical component summary (PCS), pain VAS, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and morning stiffness VAS.

Radiographic assessments of the hands and feet were conducted at baseline and weeks 14 (rescued patients), 26, and 48. The mean change from baseline in mTSS, joint space narrowing score, and joint erosion score as well as the proportion of patients with no radiographic progression from baseline (mTSS ≤0), at weeks 26 and 48, were reported.

Safety assessments

Physical examinations, vital signs, electrocardiogram findings, and findings from laboratory tests (hematology, chemistry, and urinalysis) were monitored during the study. AEs were coded according to the Medical Dictionary for Regulatory Activities, Version 19.1, and AEs and laboratory changes were graded using the Rheumatology Common Toxicity Criteria Version 2.0.[7] Cardiovascular events, including major adverse cardiovascular events (MACE) and venous thromboembolic events (VTE), were blindly adjudicated by an independent, external Cardiovascular Adjudication Committee using predefined event definitions.

The proportion (%) of patients with treatment-emergent adverse events (TEAEs) is reported by initial randomized groups up to week 26 (censored at treatment switching). Exposure-adjusted event rates (EAERs) are reported (events/100 patient-years [PYs]) for any upadacitinib-treated and any adalimumab-treated patients up to week 48. Investigator-reported TEAEs are summarized for upadacitinib and adalimumab based on the treatment received at the time of the event (i.e., events observed at or after the first dose of study drug and up to 30 days after the last dose of upadacitinib or placebo, and 70 days for adalimumab, if subjects were prematurely discontinued from the study).

Statistical analysis

Efficacy analyses were conducted using the full analysis set of CEE patients, including all randomized patients who had received ≥1 dose of study treatment in the CEE subpopulation. For binary endpoints, non-responder imputation was used for missing data and for observations after rescue treatment for patients rescued at weeks 14, 18, or 22; the last observation carried forward was used for patients rescued at week 26. For continuous endpoints, the last observation carried forward was used for observations after rescue treatment for patients rescued at weeks 14–26. The safety analysis included all patients who received ≥1 dose of study treatment (placebo, upadacitinib, or adalimumab). As this was a post hoc analysis, no sample size calculation was performed; analyses were not powered for statistical comparison between treatment arms and are purely descriptive. No statistical comparisons between regional and global datasets were conducted.

Results

Patient disposition

In total, 596 patients from the CEE region originally randomized in the SELECT-COMPARE study were included in this analysis. Among CEE patients, 239, 235, and 122 were randomized to receive placebo, upadacitinib 15 mg, and adalimumab 40 mg, respectively (Figure 1). Patient numbers were balanced across the three treatment arms as randomization was stratified by geographic region in the SELECT-COMPARE study.[7] Among all CEE patients included in these analyses, the majority were from Russia (*n*=118; 20%), Poland (*n*=109; 18%), Ukraine (*n*=84; 14%), and Hungary (*n*=64; 11%) (Figure 2).

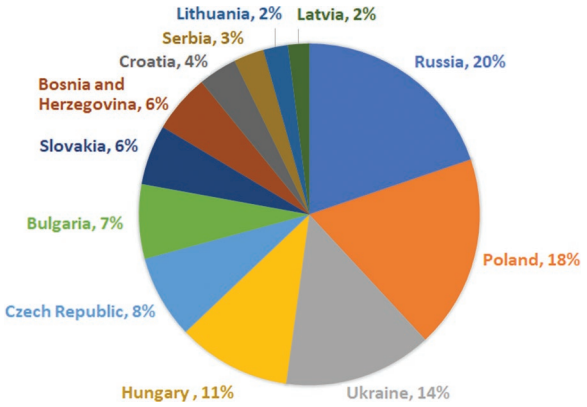
In total, 531 (89%) patients completed the 48-week study period on study drug, including patients who were rescued to upadacitinib or adalimumab. The most common reasons for discontinuation were patient withdrawal of consent (5%) and AEs (4%). At weeks 14, 18, and 22, 116 (49%) and 26 (21%) patients had <20% improvement in SJC or TJC and were rescued from placebo and adalimumab, respectively, to upadacitinib, while 45 (19%) patients were rescued from upadacitinib to adalimumab. At week 26, 63 (27%) and 40 (33%) patients with CDAI >10 were rescued from upadacitinib to adalimumab and adalimumab to upadacitinib, respectively, per protocol. A total of 214 (91%) and 100 (82%) patients (including rescued patients) randomized to upadacitinib and adalimumab, respectively, completed 48 weeks of treatment. Figure 3 depicts the full patient disposition and reasons for discontinuation.

Baseline demographics and clinical characteristics were generally similar across treatment arms, as randomization was stratified by geographic region. However, there was less structural damage (mTSS) and longer duration of morning stiffness in the adalimumab group compared with the placebo and upadacitinib groups (Table 1).

Efficacy by randomized groups

Overall, patients receiving upadacitinib experienced numerically greater clinical and radiographic improvements compared with adalimumab and placebo at weeks 12 and 26 (Table 2). At week 12, ACR20 was achieved by 72%, 59%, and 33% of patients receiving upadacitinib, adalimumab, and placebo, respectively, while DAS28-CRP <2.6 was achieved by

Figure 2. Patient distribution by country in Central and Eastern European subgroup analysis of SELECT-COMPARE (*n*=596).



26%, 11%, and 4%. At week 48, ACR20/50/70 was achieved by 68%/52%/37% and 57%/42%/22% of patients randomized to upadacitinib and adalimumab, respectively (Table 2).

Clinical remission and LDA, irrespective of definition used, were consistently achieved by a numerically greater proportion of patients in the upadacitinib group compared with placebo and adalimumab from week 8 through week 26 (Table 2; Figure 4). At week 48, DAS28-CRP ≤3.2 was achieved by 49% and 36% of patients in the upadacitinib and adalimumab groups, respectively, DAS28-CRP <2.6 by 38% and 24%, and Boolean remission by 22% and 11% (Table 2; Figure 4A, B, G). Similar trends were observed with CDAI and SDAI remission and LDA (Table 2; Figure 4C–F).

In patients treated with upadacitinib, there was numerically less radiographic progression at week 26 as measured by mTSS as well as joint erosion and joint space narrowing compared with those receiving placebo (Table 2). A numerically greater proportion of patients receiving upadacitinib had no radiographic progression (mTSS ≤0) compared with placebo at week 26 (87% and 71%, respectively). Using linear extrapolation, mean changes from baseline in mTSS in the upadacitinib and adalimumab groups were –0.23 (95% CI –1.31 to 0.84) and 0.17 (95% CI –1.14 to 1.49), respectively, at week 48. At week 48, 87% and 89% of patients in the upadacitinib and adalimumab groups, respectively, did not have radiographic progression. No radiographic comparisons were made between adalimumab and placebo or upadacitinib.

Mean improvements from baseline in HAQ-DI were –0.56 (95% CI –0.64 to –0.47), –0.49 (95% CI –0.60 to –0.38), and –0.26 (95% CI –0.34 to –0.17) in the upadacitinib, adalimumab, and placebo groups, respectively, at week 12; with 73%, 74%, and 53% of patients, respectively, achieving a MCID improvement of ≥0.22 (Table 2). Mean improvements from baseline in HAQ-DI were –0.77 (95% CI –0.89 to –0.64) and –0.64 (95% CI –0.78 to –0.49) in the upadacitinib and adalimumab groups, respectively, at week 48; with 64% and 54% of patients, respectively, achieving a MCID improvement of ≥0.22. Patients in the upadacitinib group also experienced numerically greater improvements in other PROs, including SF-36 PCS, pain VAS, FACIT-F, and morning stiffness VAS compared with patients in the placebo group at weeks 12 and 26 (Table 2). At week 48, mean improvements from baseline in the upadacitinib and adalimumab groups were 10.58 (95% CI 8.84 to 12.33) and 8.80 (95% CI 6.77 to 10.83) in SF-36 PCS, 12.38 (95% CI 10.51 to 14.25) and 11.12 (95% CI 8.95 to 13.30) in pain VAS, 11.03 (95% CI 9.20 to 12.85) and 9.46 (95% CI 7.32 to 11.59) in FACIT-F, and –3.81 (95% CI –4.31 to –3.31) and –3.68 (95% CI –4.26 to –3.10) in morning stiffness VAS, respectively.

Safety

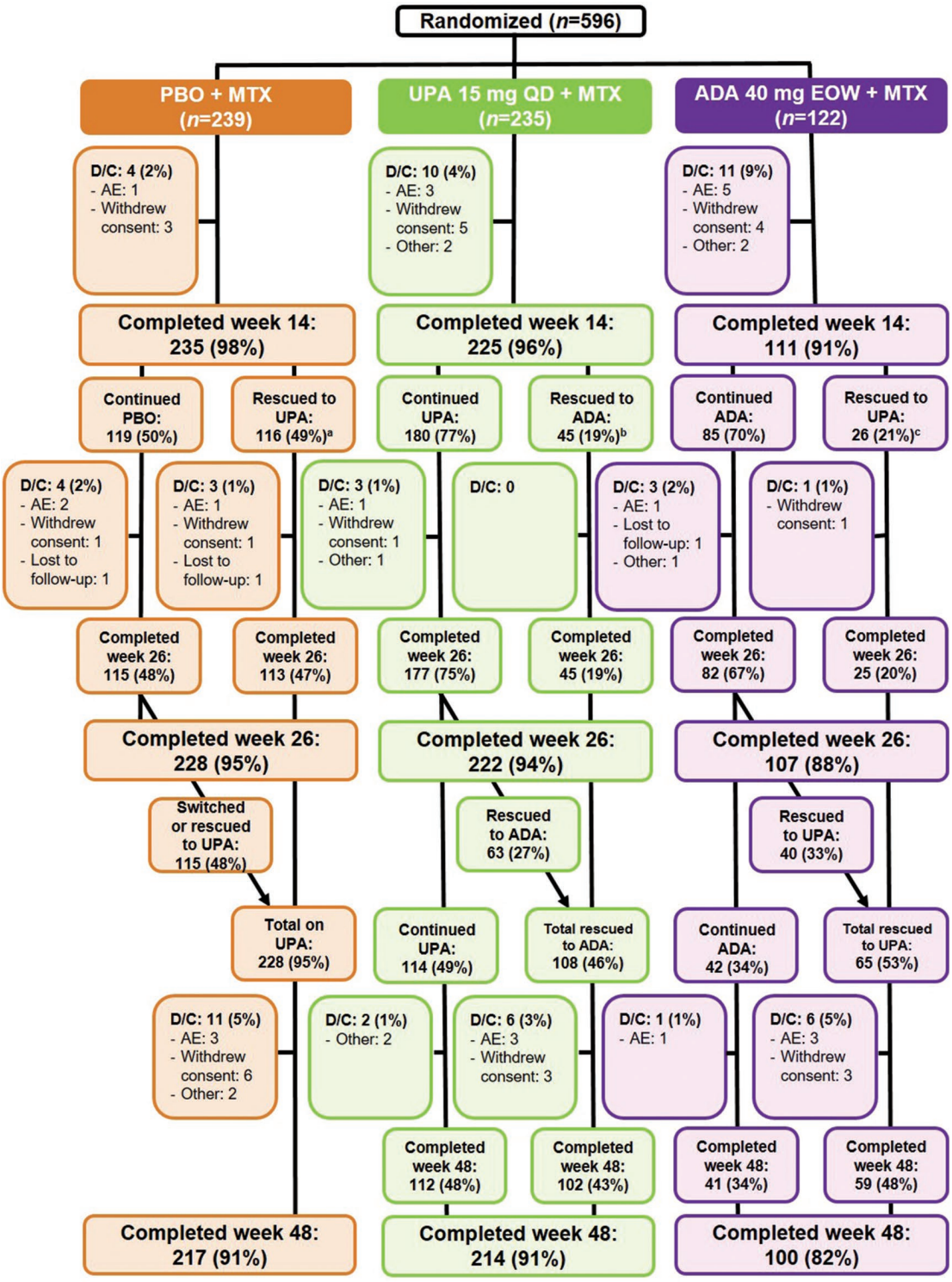
At week 26, the proportions of patients with TEAEs and serious AEs (SAEs) were generally similar across treatment arms (Table 3). AEs leading to discontinuation were reported in 1.7%, 2.6%, and 4.9% of patients randomized to placebo, upadacitinib, and adalimumab, respectively. At week 48, the cumulative exposures for patients receiving any upadacitinib and any adalimumab were 478.9 PY and 181.4 PY, respectively. EAERs reported with upadacitinib and adalimumab, respectively, were 193.8 and 216.6 per 100 PY for TEAEs, 10.2 and 10.5 per 100 PY for SAEs, and 6.1 and 9.9 per 100 PY for AEs leading to discontinuation (Table 3). The most frequently reported TEAEs at weeks 26 and 48 were infections.

Three deaths, all due to TEAEs that were not thought to be related to study treatment by the investigators, were reported. The one death with upadacitinib was due to cardiac failure. One of the deaths with adalimumab was due to left ventricular failure and the other due to craniocerebral injury caused by a traffic accident.

At week 26, the proportions of patients with serious infections and opportunistic infections were 0.4%, 1.3%, and 0 in the placebo, upadacitinib, and adalimumab groups, respectively (Table 3). At week 48, rates of infections were 64.7 and 57.9 per 100 PY and rates of serious infections were 2.7 and 1.7 per 100 PY with upadacitinib and adalimumab, respectively. These included 13 serious infections in patients treated with upadacitinib (three cases of pneumonia, two cases of gastroenteritis, and one case each of appendicitis, atypical pneumonia, erysipelas, injection-site abscess, latent tuberculosis (TB), meningitis, upper respiratory tract infection, and viral infection) and three cases in the adalimumab group (uveitis, erysipelas, and pneumonia). The opportunistic infection rate was 0.8 per 100 PY with upadacitinib; this included two cases of oral candidiasis and two cases of esophageal candidiasis. No opportunistic infections were observed with adalimumab.

Up to week 26, there was one case of latent TB in the upadacitinib group only and no cases of active TB in any treatment group. Up to week 48, there were 18 cases of latent

Figure 3. Disposition of Central and Eastern European patients included in the SELECT-COMPARE subgroup analysis over 48 weeks.



At weeks 14, 18, and 22, patients were rescued if they had <20% improvement in tender joint count and swollen joint count. At week 26, all remaining PBO patients were switched to UPA, and patients receiving UPA or ADA were switched to ADA and UPA, respectively, if Clinical Disease Activity Index >10.
[a]*n*=101 at week 14, *n*=10 at week 18, and *n*=5 at week 22.
[b]*n*=31 at week 14, *n*=8 at week 18, and *n*=6 at week 22.
[c]*n*=19 at week 14, *n*=6 at week 18, and *n*=1 at week 22.
ADA, adalimumab; AE, adverse event; D/C, discontinuation; EOW, every other week; MTX, methotrexate; PBO, placebo; QD, once daily; UPA, upadacitinib.

Table 1. Baseline demographics and clinical characteristics.

Mean ± SD[a]	PBO + MTX (*n*=239)	UPA 15 mg QD + MTX (*n*=235)	ADA 40 mg EOW + MTX (*n*=122)
Female, *n* (%)	177 (74)	185 (79)	99 (81)
RA duration since diagnosis, years	8.3±7.8	7.8±7.3	7.2±7.2
Age, years	54.7±12.0	55.0±11.8	53.5±12.0
RF+ and/or anti-CCP+, *n* (%)	212 (89)	204 (87)	110 (90)
MTX dose, mg/week	16.6±3.6	16.6±4.0	16.6±3.7
Prior bDMARD exposure, *n* (%)	22 (9)	18 (8)	13 (11)
Oral glucocorticoid use, *n* (%)	128 (54)	131 (56)	72 (59)
Oral glucocorticoid dose, mg[b]	6.5±2.6	6.4±2.4	6.9±2.3
TJC68	24.9±12.7	23.7±13.0	24.6±13.4
SJC66	15.6±8.3	16.1±9.6	15.8±8.7
PtGA[c]	65.0±19.2	63.4±22.0	67.8±18.9
PhGA[d]	67.3±15.7	66.5±16.2	66.4±16.3
Pain VAS[c]	66.0±18.8	65.6±20.6	67.0±17.2
CRP, mg/L	19.7±23.1	20.1±23.8	20.0±20.2
DAS28-CRP[c]	5.9±1.0	5.8±1.0	6.0±0.9
DAS28-ESR[c]	6.6±1.0	6.4±1.1	6.7±0.9
CDAI[d]	40.9±12.3	39.3±12.7	41.3±11.6
SDAI[d]	42.8±13.2	41.4±13.7	43.3±12.0
HAQ-DI[e]	1.6±0.6	1.6±0.6	1.6±0.5
mTSS[f]	45.5±59.4	45.5±59.1	33.6±46.5
Erosion score[f]	21.3±31.6	22.5±32.2	15.7±24.6
JSN score[f]	24.3±29.9	22.9±28.5	17.8±24.1
Duration of morning stiffness, minutes	158.8±166.1	146.5±181.8	171.9±187.5
Morning stiffness VAS	6.3±2.2	6.1±2.2	6.1±1.9
FACIT-F score[e]	26.6±10.8	26.8±10.4	26.5±11.0
SF-36 PCS score[g]	31.9±6.0	32.2±7.1	31.7±6.1

[a]Unless otherwise stated.
[b]Based on prednisone or equivalent daily dose; PBO, *n*=128; UPA, *n*=131; ADA, *n*=72.
[c]PBO, *n*=237; UPA, *n*=234; ADA, *n*=120.
[d]PBO, *n*=223; UPA, *n*=218; ADA, *n*=111.
[e]PBO, *n*=237; UPA, *n*=233; ADA, *n*=120.
[f]PBO, *n*=238; UPA, *n*=230; ADA, *n*=122.
[g]PBO, *n*=237; UPA, *n*=233; ADA, *n*=122.
ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; CCP, anti-cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28-CRP, Disease Activity Score in 28 joints using CRP level; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; EOW, every other week; FACIT-F, Functional Assessment of Chronic Illnesses Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; JSN, joint space narrowing; mTSS, van der Heijde's modification of the Total Sharp Score; MTX, methotrexate; PBO, placebo; PCS, physical component summary; PhGA, Physician Global Assessment of Disease Activity; PtGA, Patient Global Assessment of Disease Activity; QD, once daily; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SDAI, Simplified Disease Activity Index; SF-36, 36-Item Short Form; SJC66, swollen joint count of 66 joints; TJC68, tender joint count of 68 joints; UPA, upadacitinib; VAS, visual analog scale.

Table 2. Clinical responses (NRI/LOCF)[a], radiographic response (linear extrapolation), and mean change from baseline in radiographic progression and patient-reported outcomes (LOCF) at weeks 12, 26, and 48.

	Week 12			Week 26			Week 48	
All + background MTX	PBO (*n*=239)	UPA 15 mg QD (*n*=235)	ADA 40 mg EOW (*n*=122)	PBO (*n*=239)	UPA 15 mg QD (*n*=235)	ADA 40 mg EOW (*n*=122)	UPA 15 mg QD (*n*=235)	ADA 40 mg EOW (*n*=122)
Responders, *n* (%), NRI/LOCF[a]								
ACR20	78 (33)	168 (72)	72 (59)	84 (35)	163 (69)	73 (60)	160 (68)	70 (57)
ACR50	31 (13)	97 (41)	28 (23)	47 (20)	128 (55)	53 (43)	122 (52)	51 (42)
ACR70	7 (3)	56 (24)	10 (8)	17 (7)	79 (34)	27 (22)	86 (37)	27 (22)
DAS28-CRP ≤3.2	27 (11)	102 (43)	28 (23)	38 (16)	128 (55)	46 (38)	114 (49)	44 (36)
DAS28-CRP <2.6	9 (4)	60 (26)	13 (11)	21 (9)	93 (40)	27 (22)	90 (38)	29 (24)
CDAI ≤10	31 (13)	87 (37)	30 (25)	50 (21)	119 (51)	44 (36)	105 (45)	41 (34)
CDAI ≤2.8	3 (1)	25 (11)	3 (3)	9 (4)	50 (21)	12 (10)	58 (25)	14 (12)
SDAI ≤11	30 (13)	84 (36)	28 (23)	49 (21)	120 (51)	46 (38)	106 (45)	42 (34)
SDAI ≤3.3	2 (1)	20 (9)	2 (2)	9 (4)	55 (23)	12 (10)	58 (25)	16 (13)
Boolean remission	2 (1)	22 (9)	0	9 (4)	43 (18)	6 (5)	51 (22)	14 (11)
ΔHAQ-DI ≤ −0.22 *versus* baseline[b]	122 (52)	165 (73)	88 (74)	81 (35)	146 (64)	68 (57)	146 (64)	64 (54)
ΔHAQ-DI ≤ −0.3 *versus* baseline[c]	103 (45)	137 (61)	72 (62)	68 (29)	138 (61)	64 (55)	137 (61)	59 (50)
No radiographic progression[d]	NR	NR	NR	162 (71)	187 (87)	95 (89)	188 (87)	96 (89)
LS mean change from baseline (95% CI), LOCF								
mTSS[d]	NR	NR	NR	1.01 (0.44 to 1.59)	−0.13 (−0.72 to 0.46)	0.09 (−0.63 to 0.81)	−0.23 (−1.31 to 0.84)	0.17 (−1.14 to 1.49)
Erosion score[d]	NR	NR	NR	0.50 (0.16 to 0.83)	−0.11 (−0.46 to 0.23)	0.16 (−0.26 to 0.58)	−0.20 (−0.83 to 0.44)	0.29 (−0.49 to 1.06)
JSN score[d]	NR	NR	NR	0.37 (0.07 to 0.67)	0.06 (−0.25 to 0.37)	0.00 (−0.38 to 0.38)	0.09 (−0.47 to 0.65)	0.02 (−0.66 to 0.71)
HAQ-DI	*n*=233	*n*=223	*n*=113	*n*=227	*n*=221	*n*=106	*n*=213	*n*=100
	−0.26 (−0.34 to −0.17)	−0.56 (−0.64 to −0.47)	−0.49 (−0.60 to −0.38)	−0.31 (−0.41 to −0.21)	−0.66 (−0.76 to −0.56)	−0.59 (−0.71 to −0.47)	−0.77 (−0.89 to −0.64)	−0.64 (−0.78 to −0.49)
SF-36 PCS	*n*=234	*n*=222	*n*=115	*n*=227	*n*=220	*n*=107	*n*=213	*n*=101
	4.03 (2.87 to 5.20)	8.39 (7.18 to 9.61)	6.11 (4.66 to 7.55)	4.54 (3.15 to 5.92)	9.92 (8.50 to 11.34)	7.95 (6.20 to 9.71)	10.58 (8.84 to 12.33)	8.80 (6.77 to 10.83)
Pain VAS	*n*=234	*n*=222	*n*=115	*n*=227	*n*=220	*n*=107	*n*=213	*n*=101
	5.11 (3.83 to 6.40)	10.28 (8.94 to 11.61)	8.06 (6.47 to 9.65)	5.67 (4.17 to 7.18)	11.39 (9.85 to 12.94)	10.34 (8.44 to 12.25)	12.38 (10.51 to 14.25)	11.12 (8.95 to 13.30)

(Continued)

Table 2. (*Continued*)

	Week 12			Week 26			Week 48	
All + background MTX	PBO (*n*=239)	UPA 15 mg QD (*n*=235)	ADA 40 mg EOW (*n*=122)	PBO (*n*=239)	UPA 15 mg QD (*n*=235)	ADA 40 mg EOW (*n*=122)	UPA 15 mg QD (*n*=235)	ADA 40 mg EOW (*n*=122)
LS mean change from baseline (95% CI), LOCF								
FACIT-F	*n*=234	*n*=220	*n*=113	*n*=227	*n*=220	*n*=106	*n*=213	*n*=99
	4.15 (2.67 to 5.63)	9.81 (8.28 to 11.35)	6.75 (4.91 to 8.59)	5.08 (3.51 to 6.64)	10.68 (9.07 to 12.28)	8.33 (6.34 to 10.32)	11.03 (9.20 to 12.85)	9.46 (7.32 to 11.59)
Morning stiffness VAS	*n*=235	*n*=225	*n*=115	*n*=229	*n*=223	*n*=106	*n*=216	*n*=101
	−1.83 (−2.21 to −1.45)	−3.39 (−3.78 to −3.00)	−2.98 (−3.45 to −2.52)	−2.07 (−2.49 to −1.65)	−3.83 (−4.26 to −3.40)	−3.61 (−4.14 to −3.08)	−3.81 (−4.31 to −3.31)	−3.68 (−4.26 to −3.10)

[a]Patients who were rescued at weeks 14, 18, or 22 were considered non-responders; LOCF was used for patients rescued at week 26. Double-blinding was maintained after rescue up to week 48.
[b]PBO, *n*=233; UPA, *n*=227; ADA, *n*=119.
[c]PBO, *n*=231; UPA, *n*=225; ADA, *n*=117.
[d]Change in baseline in mTSS ≤0 by linear extrapolation. In week 26, PBO, *n*=227; UPA, *n*=215; ADA, *n*=107; in week 48, UPA, *n*=217; ADA, *n*=108.
ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology response criteria; ADA, adalimumab; CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28-CRP, Disease Activity Score in 28 joints using CRP level; EOW, every other week; FACIT-F, Functional Assessment of Chronic illnesses Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; JSN, joint space narrowing; LOCF, last observation carried forward; LS, least squares; mTSS, van der Heijde's modification of the Total Sharp Score; MTX, methotrexate; NR, not reported; NRI, non-responder imputation; PBO, placebo; PCS, physical component summary; QD, once daily; SDAI, Simplified Disease Activity Index; SF-36, 36-Item Short Form; UPA, upadacitinib; VAS, visual analog scale.

TB recorded, including 10 cases with upadacitinib-treated patients (three cases in Russia, two cases each in Croatia and Poland, and one case each in Czech Republic, Latvia, and Ukraine), and eight cases with adalimumab-treated patients (two cases each in Russia and Poland; one case each in Bosnia and Herzegovina, Bulgaria, Czech Republic, and Ukraine). One case of latent TB reported with upadacitinib was considered a SAE by the investigator and led to treatment discontinuation due to symptoms of bronchial inflammation without evidence of a positive TB test with serology and sputum culture. The other latent TB cases involved seroconversion in patients who had a positive TB test but did not have any symptoms of active TB. There were no cases of active TB reported through week 48; rates of latent TB were 2.1 and 4.4 per 100 PY with upadacitinib and adalimumab, respectively.

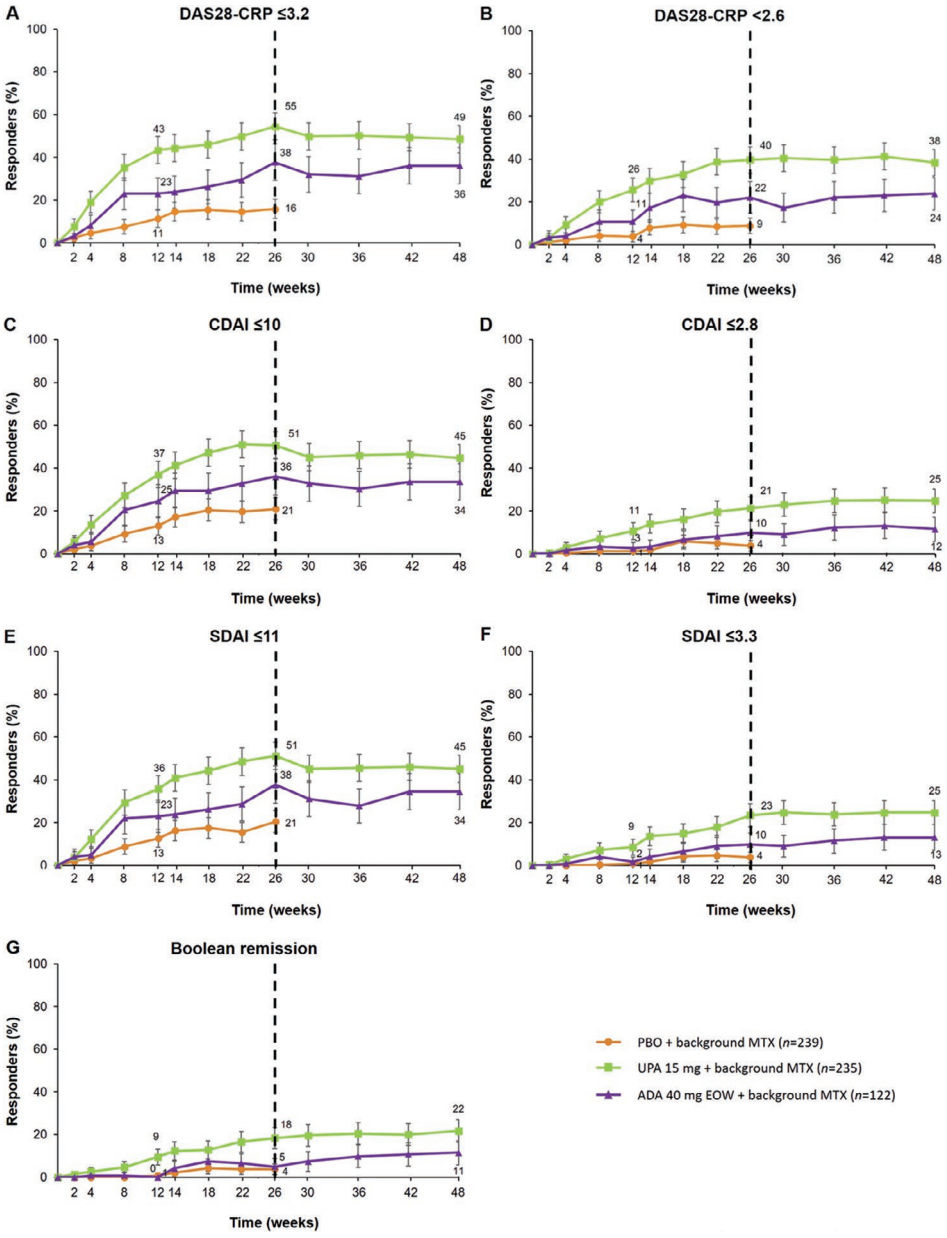
Up to week 26, there were no cases of HZ in any treatment group. At week 48, rates of HZ were 2.3 and 1.1 per 100 PY with upadacitinib and adalimumab, respectively. Most HZ cases involved a single dermatome and were non-serious. There was one case of ophthalmic HZ (rash and pain in dermatome V1 of the left eye) reported with upadacitinib in Croatia, which led to treatment discontinuation. This patient did not have a history of HZ or HZ vaccination, but they did have prior (but not current) systemic corticosteroid use. No cases of central nervous system involvement were reported.

There were no cases of malignancies and one case of non-melanoma skin cancer (NMSC) in the placebo group up to week 26 (Table 3). At week 48, EAERs for malignancy with upadacitinib were 0.2 per 100 PY for NMSC and 0.6 per 100 PY for any malignancy excluding NMSC. Malignancies excluding NMSC were one case of gastric adenocarcinoma, one case of colon adenocarcinoma, and one case of laryngeal cancer, all of which led to treatment discontinuation. No malignancies, including NMSC, were observed with adalimumab.

Up to week 26, hepatic disorders (primarily elevations of liver enzymes) were reported in 7.1%, 8.5%, and 4.9% of patients in the placebo, upadacitinib, and adalimumab groups, respectively. At week 48, rates of hepatic disorders were 20.9 and 15.4 per 100 PY, respectively, with upadacitinib and adalimumab.

There were no gastrointestinal (GI) perforations reported in any of the treatment groups up to week 26. Up to week 48, one case of non-spontaneous GI perforation (anal fistula for which treatment was temporarily interrupted for surgical treatment) was reported with upadacitinib; the rate of GI perforation with

Figure 4. Proportions of patients achieving DAS28-CRP ≤3.2 (A) and <2.6 (B), CDAI- and SDAI-defined low disease activity and remission (C–F), and Boolean remission[a] (G), over 48 weeks (NRI/LOCF[b]).



The vertical line at week 26 indicates the end of the PBO-controlled period. Error bars indicate 95% CI.

[a]ACR/EULAR Boolean remission defined as SJC28 ≤1, TJC28 ≤1, hsCRP ≤1 mg/dL, and PtGA ≤1 (on a 0–10 cm VAS).

[b]Patients who were rescued at weeks 14, 18, or 22 were considered non-responders; LOCF was used for patients rescued at week 26. Treatment groups are by initial randomization and double-blinding was maintained after rescue up to week 48.

ACR, American College of Rheumatology; ADA, adalimumab; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score in 28 joints using CRP level; EOW, every other week; EULAR, European League Against Rheumatism; hsCRP, high-sensitivity C-reactive protein; LOCF, last observation carried forward; MTX, methotrexate; NRI, non-responder imputation; PBO, placebo; PtGA, Patient Global Assessment of Disease Activity; QD, once daily; SDAI, Simplified Disease Activity Index; SJC28, swollen joint count of 28 joints; TJC28, tender joint count of 28 joints; UPA, upadacitinib; VAS, visual analog scale.

Table 3. Safety summary through week 48.

	Week 26[a], *n* (%)			Week 48, E/100 PY (95% CI)	
	PBO + MTX (*n*=239)	**UPA 15 mg QD + MTX (*n*=235)**	**ADA 40 mg EOW + MTX (*n*=122)**	**Any UPA 15 mg QD + MTX (*n*=531, PY=478.9)**	**Any ADA 40 mg EOW + MTX (*n*=230, PY=181.4)**
Any AE	108 (45.2)	127 (54.0)	65 (53.3)	193.8 (181.5–206.7)	216.6 (195.8–239.2)
Any serious AE	5 (2.1)	7 (3.0)	4 (3.3)	10.2 (7.6–13.5)	10.5 (6.3–16.4)
Any AE leading to discontinuation of study drug	4 (1.7)	6 (2.6)	6 (4.9)	6.1 (4.1–8.7)	9.9 (5.9–15.7)
Deaths[b]	0	0	2 (1.6)	0.2 (0.0–1.2)	1.1 (0.1–4.0)
Infection	47 (19.7)	55 (23.4)	28 (23.0)	64.7 (57.7–72.4)	57.9 (47.3–70.1)
Serious infection	1 (0.4)	3 (1.3)	0	2.7 (1.4–4.6)	1.7 (0.3–4.8)
Opportunistic infection	1 (0.4)	3 (1.3)	0	0.8 (0.2–2.1)	0
Active/latent TB	0	1 (0.4)	0	2.1 (1.0–3.8)	4.4 (1.9–8.7)
Herpes zoster	0	0	0	2.3 (1.1–4.1)	1.1 (0.1–4.0)
Anemia	7 (2.9)	3 (1.3)	4 (3.3)	4.0 (2.4–6.2)	6.1 (3.0–10.9)
Neutropenia	1 (0.4)	8 (3.4)	2 (1.6)	3.3 (1.9–5.4)	6.1 (3.0–10.9)
Lymphopenia	7 (2.9)	5 (2.1)	2 (1.6)	3.1 (1.8–5.2)	4.4 (1.9–8.7)
Creatine phosphokinase elevation	6 (2.5)	6 (2.6)	0	5.2 (3.4–7.7)	0.6 (0.0–3.1)
Renal dysfunction	0	0	0	0	1.1 (0.1–4.0)
Hepatic disorder	17 (7.1)	20 (8.5)	6 (4.9)	20.9 (17.0–25.4)	15.4 (10.3–22.3)
Gastrointestinal perforation	0	0	0	0.2 (0.0–1.2)	0
Any malignancy (excluding NMSC)	0	0	0	0.6 (0.1–1.8)	0
NMSC	1 (0.4)	0	0	0.2 (0.0–1.2)	0
MACE (adjudicated)[c]	0	0	1 (0.8)	0.2 (0.0–1.2)	0.6 (0.0–3.1)
Venous thromboembolic event (adjudicated)[d]	0	0	1 (0.8)	0.2 (0.0–1.2)	0.6 (0.0–3.1)

[a]Censored at initiation of rescue treatment.
[b]Including non-treatment-emergent deaths.
[c]Defined as cardiovascular death (includes acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular hemorrhage, fatal stroke, pulmonary embolism, and other cardiovascular causes), non-fatal myocardial infarction, and non-fatal stroke.
[d]Includes fatal and non-fatal deep vein thrombosis and pulmonary embolism.
ADA, adalimumab; AE, adverse event; E/100 PY, events per 100 patient-years; EOW, every other week; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, non-melanoma skin cancer; PBO, placebo; PY, patient-years; QD, once daily; TB, tuberculosis; UPA, upadacitinib.

upadacitinib at week 48 was 0.2 per 100 PY. No GI perforations were reported with adalimumab.

Up to week 26, there was one case of adjudicated MACE (left ventricular failure leading to death) and one case of VTE (pulmonary embolism leading to treatment discontinuation), both reported in the adalimumab group. Up to week 48, an additional case of adjudicated MACE (myocardial infarction) and an additional case of VTE (deep vein thrombosis and pulmonary embolism) were reported with upadacitinib, and both cases led to treatment discontinuation. Both patients with adjudicated MACE had more than one cardiovascular risk factor, including age, obesity, and diabetes mellitus; the patient who experienced a VTE with upadacitinib had a history of venous thrombosis of the right lower limb. At week 48, rates of adjudicated MACE were 0.2 and 0.6 per 100 PY and adjudicated VTE were 0.2 and 0.6 per 100 PY with upadacitinib and adalimumab, respectively.

At week 26, anemia, neutropenia, and lymphopenia were uncommon across placebo, upadacitinib, and adalimumab groups (Table 3). Creatine phosphokinase elevations

occurred in 2.6% and 2.5% of upadacitinib and placebo groups, respectively, while no cases were reported in the adalimumab group. Similar trends were observed at week 48 for upadacitinib and adalimumab.

Discussion

This post hoc analysis of the phase III SELECT-COMPARE study is the first efficacy and safety report of upadacitinib for the treatment of RA in patients from the CEE region. Results suggest that treatment with upadacitinib in combination with MTX was associated with numerically greater improvement in signs and symptoms of RA, physical function, and radiographic outcomes compared with placebo in combination with MTX over 26 weeks in patients from CEE countries. Treatment with upadacitinib was consistently associated with numerically greater proportions of patients achieving LDA and clinical remission *versus* placebo over 26 weeks. In addition, upadacitinib was associated with a numerically greater ACR50 response and numerically greater improvements in physical function and pain, *versus* adalimumab, both in combination with MTX. Improvement in clinical and functional responses with upadacitinib and adalimumab were sustained over 48 weeks.

In general, the efficacy and safety data reported in this subgroup analysis of CEE patients were consistent with those observed in the global SELECT-COMPARE study.[7,11] Compared with the global population, the CEE subpopulation had shorter disease duration, slightly greater structural damage, and longer morning stiffness duration at baseline.[7] At baseline, a slightly lower percentage of CEE patients was treated with oral glucocorticoids, compared with the global patient population. Placebo response rates observed in this analysis were generally similar to those reported in the global data. There appeared to be a slight delay in onset of action with adalimumab in the CEE subgroup compared with the global population in DAS28-CRP <2.6 response and CDAI remission; however, response rates were comparable by week 26. Inhibition of radiographic progression was numerically greater in the CEE cohort (mTSS at week 48: –0.23 and 0.17 in patients randomized to upadacitinib and adalimumab, respectively) compared with that observed in the global dataset (0.28 and 0.39). This was despite the higher baseline mTSS score for the upadacitinib group in the CEE cohort *versus* the global population (45.5 and 34.0).

Upadacitinib was associated with a generally favorable safety profile, broadly consistent with that of adalimumab, in CEE patients. However, upadacitinib was associated with numerically higher rates of serious infections, including HZ, than adalimumab. Higher rates of HZ have similarly been observed for other JAK inhibitors compared with bDMARDs.[22] Although the overall safety profile of the CEE subpopulation was broadly consistent with that of the global population, numerically lower rates of TEAEs, SAEs, and infections were reported in the CEE subgroup compared with the global dataset.[7,11] Notably, serious infection rates were numerically lower in the CEE subgroup (2.7 and 1.7 per 100 PY with upadacitinib and adalimumab, respectively) compared with the global population (4.1 and 4.3 per 100 PY). The reasons for this difference are unclear and it is difficult to draw any conclusions due to the smaller sample size in the subgroup analysis. No cases of active TB were observed in the CEE subpopulation, compared with the globally reported rates of 0.1 and 0.2 per 100 PY with upadacitinib and adalimumab, respectively. HZ infection in the upadacitinib group appeared to be slightly less common in the CEE population than in the global population (2.3 *versus* 3.1 per 100 PY). This may be expected as the global population includes Asian patients who have a known increased risk of HZ infection with JAK inhibitors,[9,23,24] whereas there were no Asian patients included in the CEE population.

Malignancy and adjudicated MACE were uncommon in this study and were observed at similar rates across patients receiving upadacitinib and adalimumab. Data suggest that JAK inhibitors may increase the risk of VTE.[3,25–27] However, the current analysis, although not powered to address this question, shows that rates of VTE were similar with upadacitinib and adalimumab. Furthermore, rates of adjudicated MACE (0.2 *versus* 0.4 per 100 PY) and VTE (0.2 *versus* 0.3 per 100 PY) with upadacitinib in this CEE subpopulation were similar to those observed in the global population.[11]

The main limitation of this subgroup analysis was that it was not powered for statistical comparisons across treatments or between the CEE subpopulation and the global population; therefore, any comparisons are purely descriptive and should be interpreted with caution. This analysis was conducted specifically in patients with MTX-IR RA on background MTX; thus, the results may not be generalized to other CEE patient populations. Further analysis would be required to assess the efficacy and safety of upadacitinib monotherapy and in patients naïve to MTX or with inadequate response to bDMARDs. Another limitation was that not all patients remained on the initially assigned randomized treatment for the entire study and no long-term data are available for upadacitinib *versus* placebo after week 26. This was due to rescue with upadacitinib/adalimumab from adalimumab/upadacitinib between weeks 14 to 22 (<20% improvement in SJC or TJC) and at week 26 (CDAI >10), and the switching of all patients receiving placebo to upadacitinib at week 26.[7,11]

Conclusion

In conclusion, upadacitinib 15 mg QD in combination with background MTX demonstrated sustained clinical, radiographic, and functional improvements compared with placebo over 26 weeks in patients from the CEE region. Clinical efficacy with upadacitinib and adalimumab, both in combination with MTX, were maintained through week 48. The safety profile of upadacitinib in CEE patients was generally similar to that of adalimumab and no new safety signals were associated with upadacitinib in the CEE subpopulation.

Trial registration number: NCT02629159.

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