Efficacy and Safety of Upadacitinib Monotherapy in Methotrexate-Naive Patients With Moderately-to-Severely Active Rheumatoid Arthritis (SELECT-EARLY): A Multicenter, Multi-Country, Randomized, Double-Blind, Active Comparator–Controlled Trial

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Objective. The SELECT-EARLY trial was undertaken to study the effect of upadacitinib, an oral, reversible Janus kinase 1–selective inhibitor, as monotherapy in patients with predominantly early rheumatoid arthritis who were naive for or had limited exposure to methotrexate (MTX).

Methods. Patients (n = 947) were randomized 1:1:1 to receive once-daily doses of upadacitinib 15 mg or 30 mg or weekly MTX (7.5–20 mg/week) for 24 weeks. The primary end points were the proportion of patients who met the American College of Rheumatology 50% (ACR50) improvement criteria at week 12, and the proportion in whom a Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) of <2.6 was achieved at week 24. Data are presented through week 24.

Results. At baseline, the median disease duration was 0.5 years (range 0–44 years). A total of 840 patients (89%) completed 24 weeks of treatment. The study met both primary end points for upadacitinib 15 mg and 30 mg versus MTX (ACR50 was achieved at week 12 in 52% and 56% of patients, respectively, versus 28% [$P < 0.001$], and DAS28-CRP <2.6 was achieved at week 24 in 48% and 50% of patients, respectively, versus 19% [$P < 0.001$]). Statistically significant and clinically meaningful improvements in multiple patient-reported outcomes (PROs) were recorded for both upadacitinib doses versus MTX. Overall, 88% of patients receiving upadacitinib 15 mg and 89% of patients receiving 30 mg, respectively, had no radiographic progression (modified total Sharp score ≤0) compared to 78% of those receiving MTX ($P < 0.01$). Through week 24, the frequency of treatment-emergent adverse events was similar between the MTX arm (65%) and upadacitinib 15 mg arm (64%), but was slightly higher in the upadacitinib 30 mg arm (71%). Six deaths were reported (2 in the upadacitinib 15 mg arm, 3 in the upadacitinib 30 mg arm, and 1 in the MTX arm).

Conclusion. Our findings indicate that patients receiving either dose of upadacitinib monotherapy experienced significant improvements in clinical, radiographic, and PROs compared to patients receiving MTX.

INTRODUCTION

The primary treatment goals for rheumatoid arthritis (RA), symptom reduction and prevention of joint damage leading to permanent disability, require intervention with disease-modifying antirheumatic drugs (DMARDs), including first-line conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). Currently, methotrexate (MTX) is the most widely accepted initial therapy for RA, supported by its well-known long-term efficacy and safety profile, current guidelines and treatment recommendations from the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR), and few restrictions (i.e., cost) to patient access (1,2). However, the success of initial therapy with MTX is limited. Remission is achieved in only a minority of patients receiving MTX, and acceptable disease control is achieved in at most 60% of patients (3–5). For patients who have an insufficient initial response or are intolerant of or lose response to MTX over time (~80%), csDMARDs other than MTX or the addition of a bDMARD or tsDMARD to a csDMARD are recommended to rapidly attenuate the potentially irreversible impact of active disease (1,2,6). Previous studies in MTX-naive patients with moderately-to-severely active RA and poor prognosis (seropositivity for rheumatoid factor [RF] and anti–citrullinated protein antibodies [ACPAs] and radiographic damage at baseline) have shown that MTX monotherapy was less effective than its combination treatments (7).

The Janus kinase (JAK) enzymes (JAK1, JAK2, JAK3, and TYK2) are important mediators of multiple cytokine-signaling pathways for normal cellular processes as well as for immune-mediated inflammation (8,9). Orally administered JAK inhibitors (tsDMARDs) are approved for their established efficacy as monotherapy (10,11) and combination therapy (with csDMARDs), versus bDMARDs, across diverse RA patient populations (12–14).

Upadacitinib, a potent, reversible JAK1-selective inhibitor (15), met all primary and ranked secondary end points in each of the pivotal phase III trials, both as monotherapy and in combination with csDMARDs, across the spectrum of MTX-exposed patients with established RA via the SELECT clinical development program: NEXT (16), BEYOND (17), MONOTHERAPY (18), and COMPARE (19). The SELECT-EARLY MTX-controlled trial was designed to study the safety and efficacy of upadacitinib as monotherapy in patients with moderately-to-severely active RA and poor prognostic features who are either naive for or had limited exposure to MTX.

PATIENTS AND METHODS

Study design and participants. SELECT-EARLY (ClinicalTrials.gov identifier: NCT02706873) was conducted at 236 sites in 43 countries. Eligible patients were ≥18 years of age, had active RA, had symptoms consistent with RA for ≥6 weeks, and fulfilled the ACR/EULAR 2010 classification criteria for RA (20). Active disease was defined as ≥6 swollen joints in a 66-joint count and ≥6 tender joints in a 68-joint count at the screening and baseline visits, with a high-sensitivity C-reactive protein (CRP) concentration of ≥5 mg/liter (upper limit of normal 2.87 mg/liter), and ≥1 bone erosion on radiography (as determined by a local reader) or positivity for both RF and ACPAs at screening.

Patients were either naive for MTX or had received ≤3 weekly doses of MTX and completed a 4-week washout period before receiving the first dose of study drug. Patients may have received prior csDMARD(s) other than MTX and completed a predefined washout period. Key exclusion criteria were prior intolerance of MTX and prior exposure to any JAK inhibitor or any bDMARD. The study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations, and the Declaration of Helsinki. All study-related documents were approved by independent ethics committees and institutional review boards. All patients provided written informed consent.

Randomization and masking. SELECT-EARLY is a double-blind, randomized, phase III study comprising a 48-week active comparator–controlled period followed by an open-label long-term extension period of up to 4 years (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract). Patients in the global study were randomized 1:1:1 to receive either once-daily upadacitinib (15 mg or 30 mg as monotherapy), or weekly MTX (starting at 10 mg/week

[7.5 mg/week for patients in China and Japan] and titrated up to a maximum of 20 mg/week [15 mg/week for patients in Japan] through week 8, as tolerated). MTX dose increment was 5 mg/4 weeks with a minimum of 15 mg/week as the final dose, if intolerance of 20 mg/week was documented. To meet the requirements of the Pharmaceuticals and Medical Devices Agency, Japan, a substudy with a Japan-only fourth arm of once-daily upadacitinib 7.5 mg was included, the results of which will be reported elsewhere. Herein, the results of the global study through week 24 (including the primary end points) are reported. Randomization was stratified by geographic region (North America, South/Central America, Western Europe, Eastern Europe, and Asia/Other). Based on a randomization schedule, patients were randomized using an Interactive Response Technology. The investigators and sponsor were blinded with regard to treatment assignment during this 24-week period. After all patients completed the week 48 visit, the treatment assignment was unblinded to the sites and patients.

Procedures. Patients received either a once-daily extended-release oral formulation of upadacitinib or once-weekly oral MTX with or without food. Blinding was accomplished with each patient taking 2 identical capsules once weekly (MTX and/or matching placebo) and a tablet once daily (upadacitinib or matching placebo). If doses had been stable for ≥1 week prior to baseline, patients were allowed to continue taking nonsteroidal antiinflammatory drugs, acetaminophen, and glucocorticoids (prednisone ≤10 mg/day or equivalent). Oral folic acid was administered throughout the study. Rescue therapy (nonsteroidal antiinflammatory drugs, low-potency analgesics, or low-dose glucocorticoids [oral ≤10 mg/day prednisone equivalent or prednisone equivalent ≤0.5 mg/kg/day for 3 consecutive days] but not DMARDs) was offered to patients in whom ≥20% improvement from baseline in both tender and swollen joint counts was not achieved at 2 consecutive visits beginning at week 12.

Efficacy, laboratory data, adverse events (AEs), and vital signs were assessed at baseline and at weeks 2, 4, 8, 12, 16, 20, and 24. Patient-reported outcomes (PROs) of fatigue and physical health status were assessed by questionnaires, namely, the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) (21) and the Short Form 36 (SF-36) physical component summary (PCS) (22), at baseline and at weeks 12 and 24. Additionally, physical function and health-related quality of life were evaluated via the Health Assessment Questionnaire (HAQ) disability index (DI) (23), which was completed at baseline and weeks 2, 4, 8, 12, 16, 20, and 24. Patient assessment of pain as well as patient and physician global assessment of disease activity were evaluated according to a visual analog scale, which was completed at baseline and weeks 2, 4, 8, 12, 16, 20, and 24. Bilateral radiographs of the hands and feet were obtained during screening and at week 24. Blood samples were collected for pharmacokinetic analysis at weeks 2, 4, 12, 16, 20, and 24.

Outcome measures. Two separate primary end points comparing upadacitinib monotherapy at doses of 15 mg and 30 mg with MTX were assessed to meet regulatory requirements: 1) the proportion of patients who met the American College of Rheumatology 50% (ACR50) improvement criteria (24) at week 12, to meet the requirement of the US Food and Drug Administration (FDA) and 2) the proportion of patients in whom a Disease Activity Score in 28 joints using the CRP level (DAS28-CRP) (25) of <2.6 was achieved at week 24, to meet the requirements of the European Medicines Agency (EMA) of the European Union (EU).

Key secondary end points at weeks 12 and 24 included the following: change from baseline in DAS28-CRP, HAQ DI, and SF-36 PCS, and the proportions of patients in whom a DAS28-CRP of ≤3.2, an ACR20 response, or an ACR70 response was achieved. Key secondary end points at week 24 only were the ACR50 response rate, change from baseline in modified total Sharp score (26), the proportion of patients in whom a DAS28-CRP of <2.6 was achieved (FDA only), and the proportion of patients with no radiographic progression (change from baseline in modified total Sharp score ≤0) as determined by central readers. Additional efficacy end points are provided in the Supplementary material, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract.

AEs, physical examinations, vital signs, electrocardiograms, and laboratory findings (hematology, chemistry, and urinalysis) were monitored throughout the study and for 30 days after study drug discontinuation. Treatment-emergent AEs (TEAEs) were coded using preferred terms from the Medical Dictionary for Regulatory Activities (version 19.1). The Rheumatology Common Toxicity Criteria (version 2.0) developed by the Outcome Measures in Rheumatology Drug Safety Working Group (27) was used to classify the severity of AEs and changes in laboratory findings, except creatine phosphokinase (CPK) and creatinine levels, which were classified using the Common Toxicity Criteria of the National Cancer Institute (28).

The TEAEs of special interest (listed in the Supplementary material, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract) were summarized. These events were selected due to their higher prevalence in RA populations, and they were identified as either known or emerging risks associated with other JAK inhibitors. Major adverse cardiovascular events (MACE) and noncardiac, non–central nervous system thromboembolic events (venous thromboembolic events) were adjudicated by an independent cardiovascular adjudication committee in a blinded manner. MACE were defined as cardiovascular death,

nonfatal myocardial infarction, and nonfatal stroke. A venous thromboembolic event was defined as deep vein thrombosis and/or pulmonary embolism.

Statistical analysis. A sample size of 900 patients was planned to provide ≥90% power for the primary end points: 20% difference in ACR50 response (assuming a week 12 ACR50 response rate of 20% in the MTX group) and 16% difference in DAS28-CRP <2.6 (assuming a week 24 DAS28-CRP <2.6 response rate of 24% in the MTX group), with a 2-sided alpha level of 0.025 and a 10% dropout rate. The sample size was also planned to provide ~80% power to detect a difference of 0.58 in change from baseline in modified total Sharp score (assuming an SD of 2.2) and ≥90% power for other ranked key

secondary end points at a 2-sided alpha level of 0.025. The overall Type I error rates for the primary and ranked key secondary end points for both upadacitinib doses were strongly controlled using a graphical multiplicity testing procedure, once each for the US FDA and EU EMA (29) (Supplementary Figure 9). The resulting adjusted P values (considered statistically significant at <0.05) in addition to nominal P values for the primary and ranked key secondary end points based on the testing procedure for US FDA and EU EMA were provided. Both upadacitinib doses were intended to be compared with MTX independently (pairwise); hence, no structural correlation was considered when calculating the sample size. Efficacy and safety analyses included patients who received ≥1 dose of the study drug.
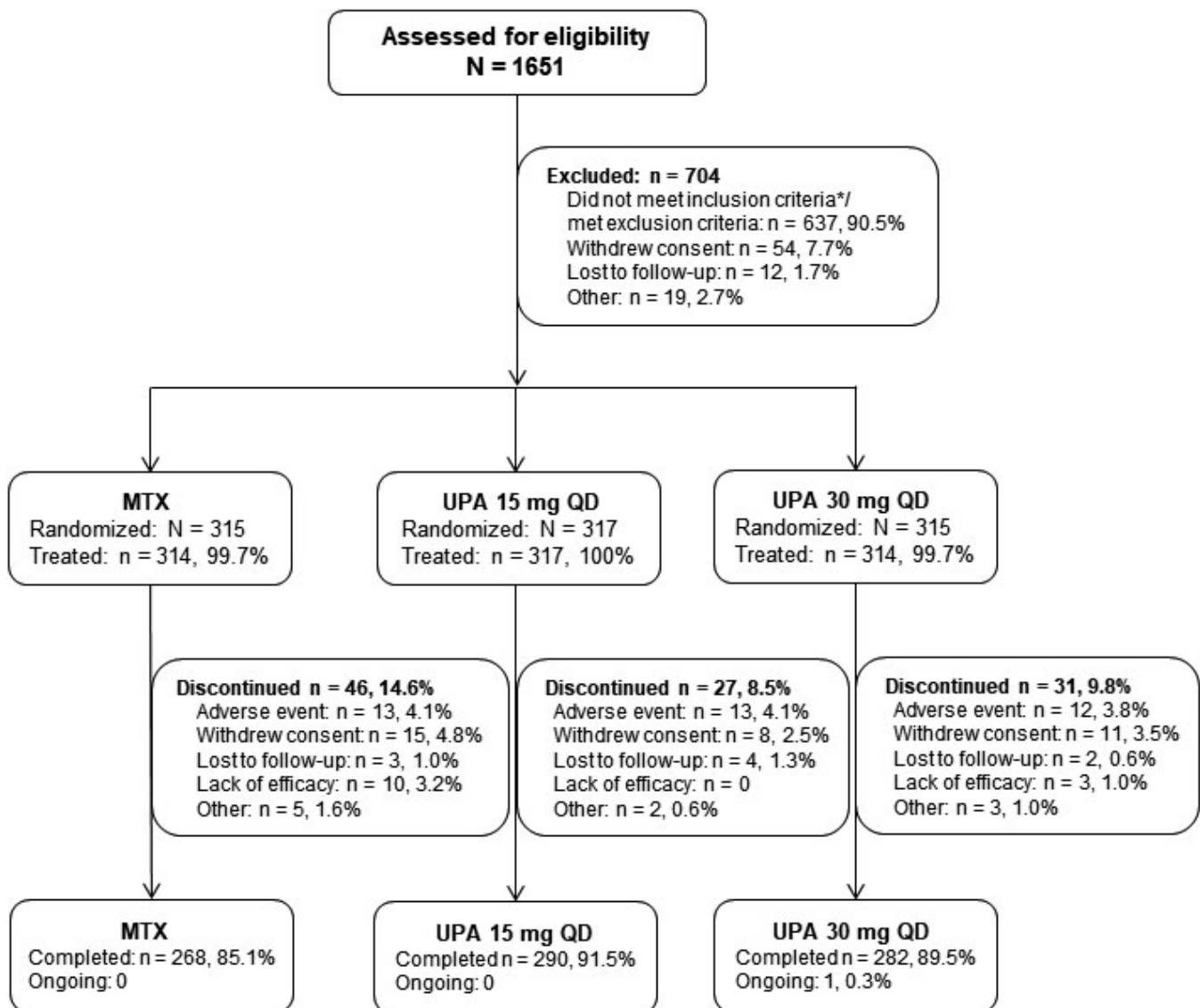
Figure 1. Profile of the SELECT-EARLY trial of upadacitinib (UPA) 15 mg once daily (QD) and upadacitinib 30 mg once daily compared to methotrexate (MTX) in patients with rheumatoid arthritis. Only primary reasons for discontinuation are listed. One patient (ongoing) in the upadacitinib 30 mg arm completed week 24 after the cutoff date and was not included in these analyses. *The most frequent reason for screening failure was not meeting the inclusion criterion for high-sensitivity C-reactive protein.

Efficacy end points. For binary nonradiographic end points, each upadacitinib arm was compared with the MTX arm, and *P* values were constructed using the Cochran-Mantel-Haenszel test, adjusted for geographic region. For primary analysis, nonresponder imputation was used for missing data imputation. Patients who met the rescue criteria at week 16 or 20 were treated as nonresponders at visits post rescue. Sensitivity analyses were performed using observed cases or as observed (without imputation or rescue handling) for primary and key secondary end points at weeks 12 or 24.

For all continuous nonradiographic end points, statistical inference was drawn using analysis of covariance (ANCOVA) with treatment and geographic region as the fixed factors and the corresponding baseline value as covariates. Data after rescue in patients who met the rescue criteria at week 16 or 20 were overwritten by the last observation carried forward. The as-observed data, regardless of missing data or rescue handling, were also summarized for all continuous key secondary end points.

For the radiographic binary end point at week 24 (percentage of patients with no radiographic progression [modified total Sharp score ≤0]), the upadacitinib and MTX arms were compared, and *P* values were constructed using the Cochran-Mantel-Haenszel test, and adjusted for geographic region with linear extrapolation and as-observed approaches. The continuous radiographic end points were analyzed using ANCOVA with linear extrapolation and as-observed approaches, with treatment and geographic region as the fixed factors and the corresponding baseline value as covariates. Linear extrapolation results were used for the purpose of multiplicity control.

Safety end points. The numbers and percentages of patients experiencing TEAEs, including those that led to premature discontinuation, serious AEs, and AEs of special interest, were tabulated by treatment groups. The numbers and percentages of patients meeting the criteria for grade 3 or 4 laboratory findings were also summarized.

Protocol amendments. All protocol amendments were done to meet requests from regulatory agencies (US FDA and EU EMA) or external experts (rheumatologists). The major protocol amendments are listed in the Supplementary Material, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract).

RESULTS

Between February 23, 2016, and March 15, 2018, 1,651 patients from 236 sites in 43 countries were screened, of whom 704 were excluded (Figure 1) and 947 were randomized to receive MTX (n = 315), upadacitinib 15 mg (n = 317), or upadacitinib 30 mg (n = 315). In total, 945 patients (99.8%) received ≥1 dose of study drug. Two patients, 1 each from the MTX and upadacitinib 30 mg arms, did not receive study drug after randomization.

While 1 did not meet the inclusion criteria of ≥6 swollen and tender joints at baseline, the other was considered "not suitable" by the investigator. Patients in the MTX arm received a mean of 19.2 mg MTX per week.

Of those randomized, 840 (89%) completed the 24-week treatment period. One patient in the upadacitinib 30 mg arm completed week-24 treatment after the cutoff date for analysis and hence was not included in the analysis. AEs were the most frequent of the primary reasons for discontinuation of treatment in all 3 treatment arms (3.8–4.1%). Withdrawal of consent and lack of efficacy were more frequent in the MTX arm than in the upadacitinib 15 mg and 30 mg arms (4.8% versus 2.5% and 3.5%, respectively, for withdrawal of consent and 3.2% versus 0% and 1.0%, respectively, for lack of efficacy). The most common International Council for Harmonisation–defined protocol deviation was violation of the disease activity inclusion criteria of having ≥6 tender and swollen joints (n = 10 [1.1%]) (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract). A total of 50 patients (5.3%) had received rescue medication by week 24.

At baseline, all demographic characteristics and most disease characteristics were well balanced across the treatment arms (Table 1). Disease activity and physical function scores were similar across the treatment arms. These scores were consistent with moderately-to-severely active RA. The mean baseline DAS28-CRP was 5.9, and 78% of the patients had a DAS28-CRP score of >5.1, consistent with high disease activity (30). The study population also had risk factors for structural progression: 69% of the patients were positive for both RF and ACPA, and erosions were present in ≥50% of the patients, with a mean ± SD modified total Sharp score of 16.2 ± 35.9.

Enrolled patients were predominantly from South or Central America (n = 272 [29%]) and Eastern Europe (n = 259 [27%]) (Supplementary Figure 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract). Most were recently diagnosed as having RA (median disease duration 0.5 years [range 0–44 years]). Less than 10% of the patients had received MTX prior to study start (≤3 lifetime weekly doses; 6% in the MTX arm, 9.5% in the upadacitinib 15 mg arm, and 7.0% in the upadacitinib 30 mg arm); ~25% had previously received a non-MTX csDMARD, primarily hydroxychloroquine or sulfasalazine (8.6% each).

At week 12, ACR50 (the primary end point for US FDA) was achieved in significantly higher proportions of patients receiving either dose of upadacitinib monotherapy versus MTX (52% [95% confidence interval (95% CI) 47, 58] for upadacitinib 15 mg and 56% [95% CI 51, 62] for upadacitinib 30 mg versus 28% [95% CI 23, 33] for MTX) (Figure 2). The difference for upadacitinib 15 mg versus MTX was 24% (95% CI 16, 31) (*P* < 0.001) and for upadacitinib 30 mg versus MTX was 28% (95% CI 21, 35) (*P* < 0.001). Similarly, at week 24, DAS28-CRP <2.6 (the primary end point

Table 1. Baseline demographic and disease characteristics of the study patients (full analysis set)*

	MTX (n = 314)	Upadacitinib 15 mg once daily (n = 317)	Upadacitinib 30 mg once daily (n = 314)
Time since RA diagnosis, years			
Mean ± SD	2.6 ± 5.1	2.9 ± 5.4	2.8 ± 5.6
Median (range)	0.5 (0.0–38.0)	0.5 (0.0–36.5)	0.6 (0.0–44.0)
Sex, no. (%) female	240 (76.4)	241 (76.0)	240 (76.4)
Age, years	53.3 ± 12.9	51.9 ± 12.6	54.9 ± 12.6
Previous csDMARD exposure, no. (%)	79 (25.2)	80 (25.2)	80 (25.5)
MTX exposure, no. (%)	19 (6.1)	30 (9.5)	22 (7.0)
Dose at week 24, mg	19.2 ± 2.1	–	–
Oral glucocorticoid use, no. (%)	163 (51.9)	147 (46.4)	137 (43.6)
Oral glucocorticoid dose, mg/day†	6.4 ± 2.4	6.4 ± 3.1	6.9 ± 2.9
Immunization history, no (%)			
Bacillus Calmette–Guérin vaccination‡	118 (47.2)	130 (52.2)	93 (41.0)
Hepatitis B immunization§	34 (11.9)	40 (14.3)	35 (13.3)
Herpes zoster immunization¶	4 (1.3)	7 (2.3)	8 (2.8)
Disease characteristics			
RF and ACPA positive, no. (%)	213 (67.8)	230 (72.6)	212 (67.7)
RF and/or ACPA positive, no. (%)	255 (81.2)	279 (88.3)	252 (80.5)
Tender joint count (68 joints evaluated)	26.4 ± 16.2	25.4 ± 14.4	25.2 ± 15.0
Swollen joint count (66 joints evaluated)	16.9 ± 10.6	16.9 ± 10.4	15.7 ± 9.7
PtGA (0–100 mm VAS)#	65.8 ± 21.5	66.6 ± 22.0	64.9 ± 21.6
PhGA (0–100 mm VAS)**	68.7 ± 16.5	67.1 ± 17.0	65.3 ± 16.6
Pain (0–100 mm VAS)#	65.7 ± 21.5	68.4 ± 20.6	65.3 ± 21.5
hsCRP, mg/liter	21.2 ± 22.1	23.0 ± 27.4	19.4 ± 22.6
DAS28-CRP#	5.9 ± 1.0	5.9 ± 1.0	5.8 ± 1.0
Clinical Disease Activity Index	40.5 ± 13.3	40.4 ± 13.3	39.3 ± 13.5
Simplified Disease Activity Index††	42.6 ± 14.0	42.7 ± 13.9	41.3 ± 14.4
Modified total Sharp score‡‡	13.3 ± 30.6	18.1 ± 38.2	17.2 ± 38.3
Erosion score‡‡	6.1 ± 15.5	8.6 ± 19.3	8.0 ± 18.9
JSN score‡‡	7.2 ± 16.2	9.6 ± 20.1	9.3 ± 20.3
Morning stiffness			
Duration, minutes§§	128.5 ± 134.2	168.9 ± 227.5	136.4 ± 166.5
Severity (0–10 scale)§§	6.3 ± 2.3	6.6 ± 2.3	6.4 ± 2.2
HAQ DI#	1.6 ± 0.7	1.6 ± 0.7	1.5 ± 0.7
FACIT-F¶¶	26.6 ± 11.7	26.4 ± 11.9	27.8 ± 11.1
SF-36 PCS##	33.1 ± 7.5	32.7 ± 7.7	33.7 ± 7.2

* Patients who had a missing baseline value or whose values were unknown for a variable were not counted in the denominator for that measure. Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; csDMARD = conventional synthetic disease-modifying antirheumatic drug; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; PtGA = patient global assessment of disease activity; VAS = visual analog scale; PhGA = physician global assessment of disease activity; hsCRP = high-sensitivity C-reactive protein; DAS28-CRP = Disease Activity Score in 28 joints using the CRP level; JSN = joint space narrowing; HAQ DI = Health Assessment Questionnaire disability index; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue scale; SF-36 PCS = Short Form 36 physical component summary.
† Based on prednisone equivalent dose. Only patients who were receiving oral steroids at baseline were evaluated.
‡ Data were available for 250 patients in the methotrexate (MTX) arm, 249 patients in the upadacitinib 15 mg arm, and 227 patients in the upadacitinib 30 mg arm.
§ Data were available for 286 patients in the MTX arm, 280 patients in the upadacitinib 15 mg arm, and 264 patients in the upadacitinib 30 mg arm.
¶ Data were available for 299 patients in the MTX arm, 298 patients in the upadacitinib 15 mg arm, and 287 patients in the upadacitinib 30 mg arm.
# Data were available for 314 patients in the MTX arm, 317 patients in the upadacitinib 15 mg arm, and 311 patients in the upadacitinib 30 mg arm.
** Data were available for 299 patients in the MTX arm, 301 patients in the upadacitinib 15 mg arm, and 304 patients in the upadacitinib 30 mg arm.
†† Data were available for 299 patients in the MTX arm, 301 patients in the upadacitinib 15 mg arm, and 303 patients in the upadacitinib 30 mg arm.
‡‡ Data were available for 309 patients in each treatment arm.
§§ Data were available for 313 patients in the MTX arm, 316 patients in the upadacitinib 15 mg arm, and 313 patients in the upadacitinib 30 mg arm.
¶¶ Data were available for 314 patients in the MTX arm, 316 patients in the upadacitinib 15 mg arm, and 310 patients in the upadacitinib 30 mg arm.
Data were available for 313 patients in the MTX arm, 315 patients in the upadacitinib 15 mg arm, and 312 patients in the upadacitinib 30 mg arm.
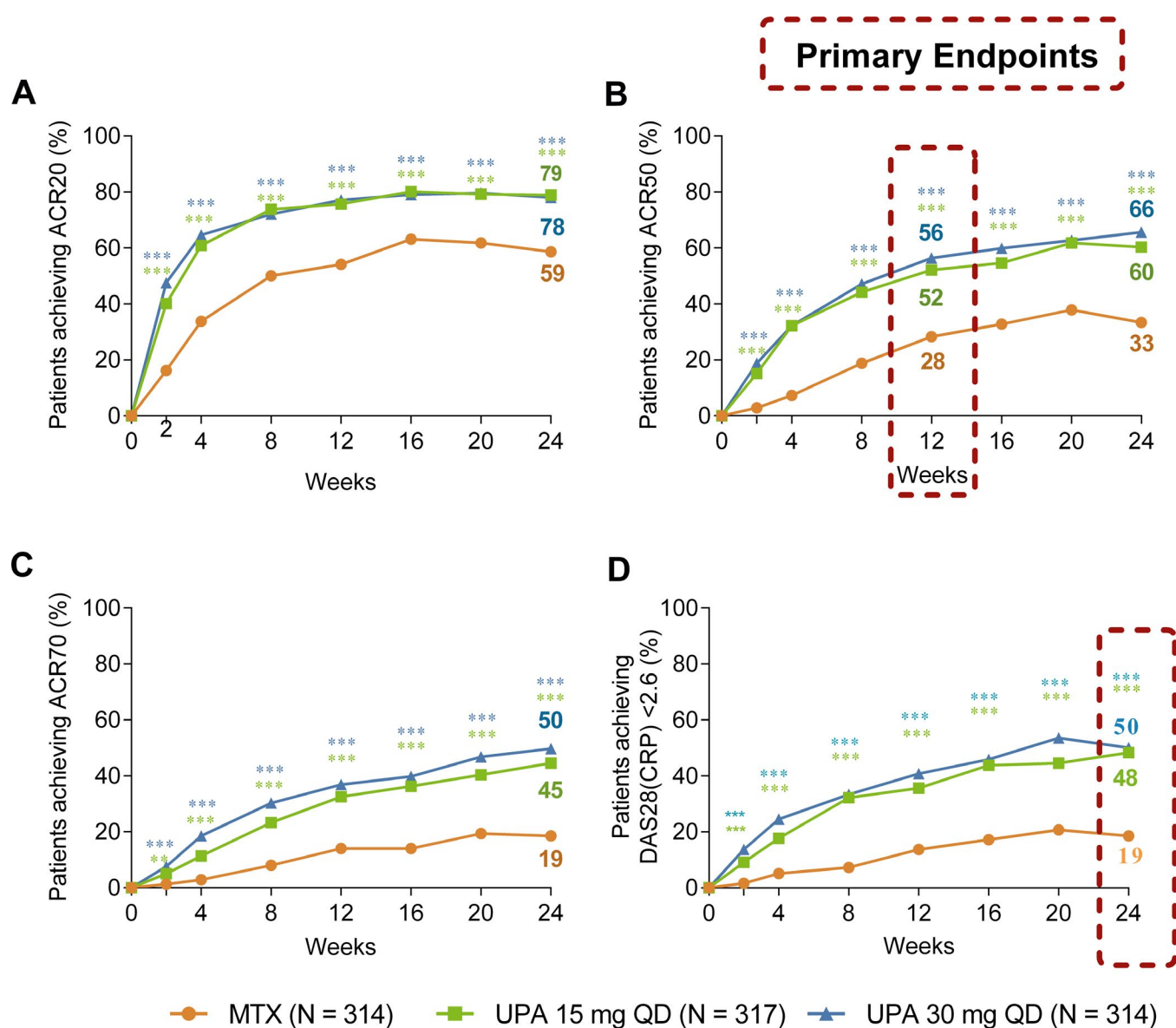
Figure 2. Proportions of patients receiving methotrexate (MTX), upadacitinib (UPA) 15 mg once daily (QD), and upadacitinib 30 mg once daily who met the end points of American College of Rheumatology criteria for 20% improvement (ACR20) (**A**), 50% improvement (ACR50) (**B**), and 70% improvement (ACR70) (**C**), and a Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) of <2.6 (**D**) over 24 weeks. The primary end points for this study were the ACR50 response rate at week 12 and DAS28-CRP <2.6 at week 24. Missing data were imputed using the nonresponder imputation method. Patients who met the rescue criteria at week 16 or week 20 were treated as nonresponders at all visits after the first visit at which rescue medication was received. ** = $P < 0.01$; *** = $P < 0.001$, versus MTX.

for EU EMA) was achieved in significantly higher proportions of patients receiving either dose of upadacitinib monotherapy versus MTX (48% [95% CI 43, 54] for upadacitinib 15 mg and 50% [95% CI 45, 56] for upadacitinib 30 mg versus 19% [95% CI 14, 23] for MTX) (Figure 2). The difference for upadacitinib 15 mg versus MTX was 30% (95% CI 23, 37) ($P < 0.001$) and for upadacitinib 30 mg versus MTX was 32% (95% CI 25, 39) ($P < 0.001$). Sensitivity analyses for both primary end points yielded consistent results (Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/ abstract). The differences between each upadacitinib group and

MTX for both end points were significant at the first postbaseline visit (week 2) and persisted through week 24 ($P < 0.001$) (Figure 2).

At weeks 12 and 24, ACR20 was achieved in significantly more patients receiving upadacitinib 15 mg (76% at week 12 [95% CI 71, 80] and 79% at week 24 [95% CI 74, 83]) and upadacitinib 30 mg (77% at week 12 [95% CI 72, 82] and 78% at week 24 [95% CI 73, 83]) than MTX (54% at week 12 [95% CI 49, 60] and 59% at week 24 [95% CI 53, 64]) ($P < 0.001$ for both comparisons). Similarly, an ACR70 response was achieved at weeks 12 and 24 in significantly more patients receiving upadacitinib 15 mg (33% at week 12 [95% CI 27, 38] and 45%

at week 24 [95% CI 39, 50]) and upadacitinib 30 mg (37% at week 12 [95% CI 32, 42] and 50% at week 24 [95% CI 44, 55]) than MTX (14% at week 12 [95% CI 10, 18] and 19% at week 24 [95% CI 14, 23]) ($P < 0.001$ for both comparisons) (Figure 2). Differences between upadacitinib (both doses) and MTX for all ACR responses, their core components, and DAS28-CRP ≤3.2 were significant at the first postbaseline visit (week 2) and persisted through week 24 ($P < 0.001$) (Supplementary Figures 3 and 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract). Similarly, the change from baseline in DAS28-CRP was also significantly greater for both upadacitinib doses than MTX through week 24 ($P < 0.001$) (Supplementary Figure 4).

Low disease activity and remission according to the Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) were achieved at week 24 in significantly higher proportions of patients receiving either dose of upadacitinib compared to patients receiving MTX ($P < 0.001$ for all comparisons) (Figure 3). ACR/EULAR Boolean-based remission was achieved at week 24 in up to 25% of patients receiving upadacitinib (24% [95% CI 20, 29] for upadacitinib 15 mg and 25% [95% CI 20, 30] for upadacitinib 30 mg versus 7% [95% CI 4, 10] for MTX); $P < 0.001$ for

both comparisons) (Figure 3). Treatment with upadacitinib 15 mg or 30 mg led to significantly greater improvements in the HAQ DI than treatment with MTX at all visits throughout the 24-week treatment period ($P < 0.001$) (Figure 4). The proportions of patients in whom a clinically meaningful change in HAQ DI (minimum clinically important difference ≤ –0.22 [31]) was achieved were significantly greater in both upadacitinib arms than in the MTX arm at all visits from week 2 through week 24 ($P < 0.001$) (Figure 4 and Supplementary Table 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract). Similarly, significantly greater improvements were recorded for other PROs, such as SF-36 PCS ($P < 0.001$), FACIT-F, and the severity and duration of morning stiffness, through week 24 (Supplementary Table 4 and Supplementary Figure 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract).

At week 24, least squares mean changes from baseline in modified total Sharp scores were significantly lower in patients receiving either dose of upadacitinib than those receiving MTX ($P < 0.01$ for upadacitinib 15 mg versus MTX; $P < 0.001$ for upadacitinib 30 mg versus MTX), as were least squares mean changes from baseline in joint space narrowing and joint erosion scores

Figure 3. Proportions of patients receiving methotrexate (MTX), upadacitinib (UPA) 15 mg once daily (QD), and upadacitinib 30 mg once daily in whom low disease activity and remission according to the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI), and American College of Rheumatology/European League Against Rheumatism Boolean remission, was achieved over 24 weeks. For calculation of the CDAI, SDAI, and Boolean remission rates at each visit, all missing data were imputed using the nonresponder imputation method. Patients who met the rescue criteria at week 16 or week 20 were treated as nonresponders at all visits after the first visit at which rescue medication was received. Boolean remission is defined as a tender joint count of ≤1, swollen joint count of ≤1, C-reactive protein level of ≤1 mg/dl, and patient global assessment of disease activity of ≤1 (on a 0–10 scale) at any time point. * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$, versus MTX.
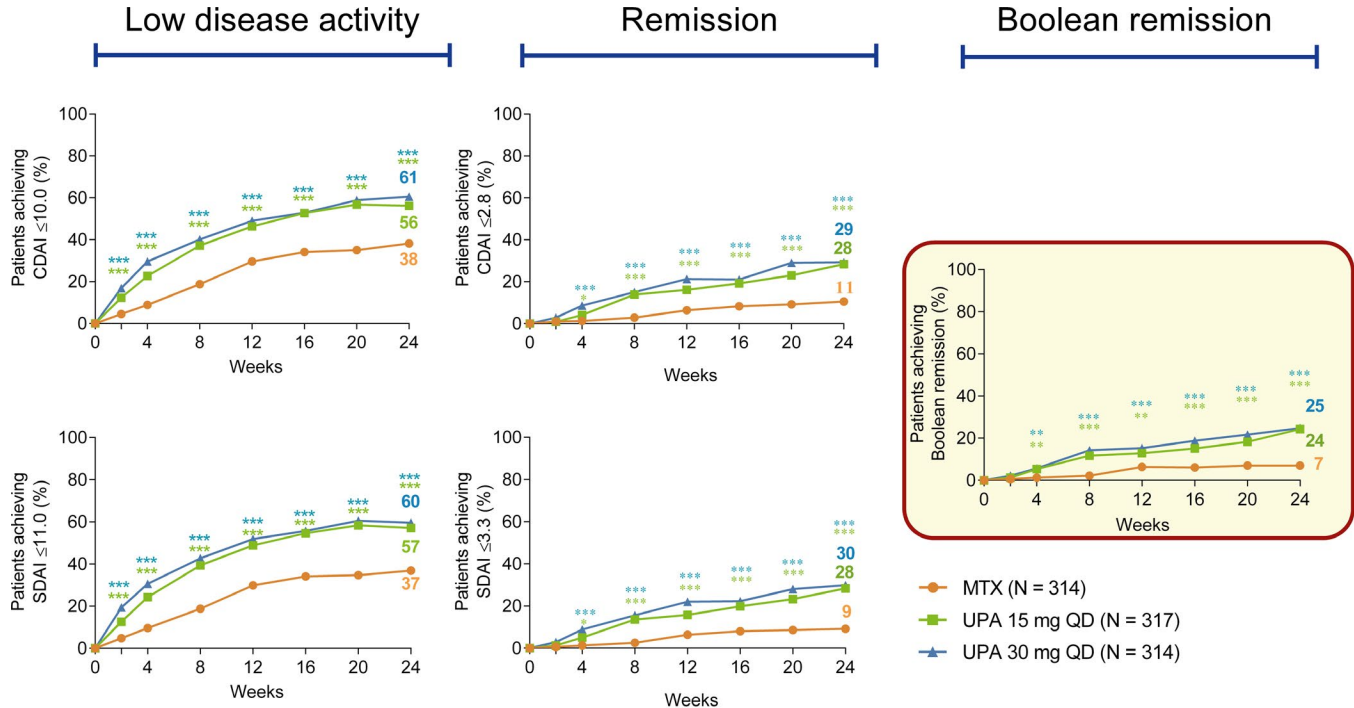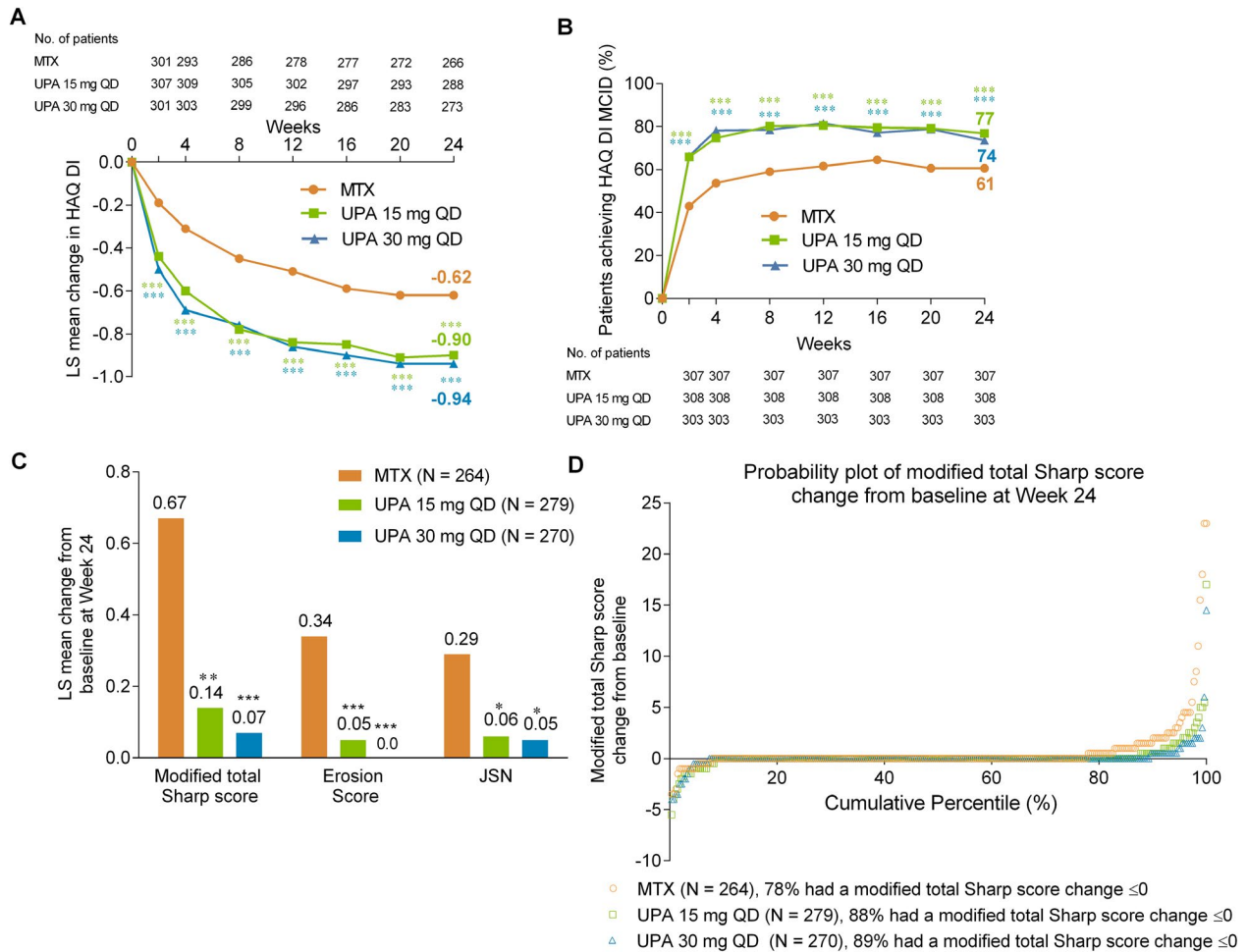
Figure 4. Physical function and radiographic structural damage in patients receiving methotrexate (MTX), upadacitinib (UPA) 15 mg once daily (QD), and upadacitinib 30 mg once daily. **A** and **B**, Least squares (LS) mean change in the Health Assessment Questionnaire (HAQ) disability index (DI) (**A**) and the proportion of patients in whom a minimum clinically important difference (MCID) in HAQ DI was achieved (**B**) over 24 weeks. **C** and **D**, LS mean change from baseline in modified total Sharp score (mTSS), erosion score, and joint space narrowing (JSN) (**C**) and the probability of change from baseline in modified total Sharp score (**D**) at week 24. The LS mean changes from baseline are based on the analysis of covariance model with geographic region as fixed factors and baseline value as covariate. The last observation carried forward method was used for mean change from baseline in HAQ DI for patients who received rescue medication; nonresponder imputation was used for MCID in HAQ DI. Linear extrapolation was used for change from baseline in modified total Sharp score, erosion score, and JSN. Analyses of the MCID in HAQ DI included only patients with a baseline HAQ DI of ≥0.22. * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$, versus MTX.

($P < 0.05$) (Figure 4). Additionally, the proportions of patients with no radiographic progression (modified total Sharp score ≤0) at week 24 were significantly higher in both upadacitinib arms than in the MTX arm (88% [95% CI 84, 91] in the upadacitinib 15 mg arm and 89% [95% CI 86, 93] in the upadacitinib 30 mg arm versus 78% [95% CI 73, 83] in the MTX arm; $P < 0.01$ and $P < 0.001$, respectively) (Figure 4).

During the 24-week period, the frequencies of TEAEs were similar in the MTX arm (65%) and upadacitinib 15 mg arm (64%), but higher in the upadacitinib 30 mg arm (71%) (Table 2). A similar trend was observed in the frequency of serious AEs; the following were reported in ≥1 patient in any treatment arm: acute myocardial infarction (in 2 patients in the MTX arm and 1 patient in the upadacitinib 30 mg arm), pneumonia (in 2 patients in the MTX

arm, 1 patient in the upadacitinib 15 mg arm, and 3 patients in the upadacitinib 30 mg arm), and osteoarthritis (in 2 patients in the upadacitinib 30 mg arm). The frequencies of TEAEs leading to discontinuation of study drug were comparable across the 3 treatment arms (5.1% in the MTX arm, 4.4% in the upadacitinib 15 mg arm, and 3.8% in the upadacitinib 30 mg arm).

Over 24 weeks, infections occurred in approximately one-third of the patients in each treatment arm. Rates of serious infections were highest in the upadacitinib 30 mg arm (2.5%) but comparable between the upadacitinib 15 mg and MTX arms (1.6% and 1.3%, respectively). Pneumonia was the most frequent serious infection in any treatment arm (in 2 patients in the MTX arm, 1 patient in the upadacitinib 15 mg arm, and 3 patients in the upadacitinib 30 mg arm). One patient in each upadacitinib arm

Table 2. Summary of treatment-emergent AEs (safety analysis set)*

	MTX (n = 314)	Upadacitinib 15 mg once daily (n = 317)	Upadacitinib 30 mg once daily (n = 314)	Difference (95% CI)	
				Upadacitinib 15 mg once daily vs. MTX	Upadacitinib 30 mg once daily vs. MTX
Any AE	205 (65.3)	203 (64.0)	224 (71.3)	−1.2 (−8.7, 6.2)	6.1 (−1.2, 13.3)
Any SAE	13 (4.1)	15 (4.7)	20 (6.4)	0.6 (−2.6, 3.8)	2.2 (−1.3, 5.7)
Any AE leading to discontinuation of study drug	16 (5.1)	14 (4.4)	12 (3.8)	−0.7 (−4.0, 2.6)	−1.3 (−4.5, 2.0)
Death†	1 (0.3)	2 (0.6)	3 (1.0)	0.3 (−0.8, 1.4)	0.6 (−0.6, 1.9)
Infection	103 (32.8)	104 (32.8)	115 (36.6)	0.0 (−7.3, 7.3)	3.8 (−3.6, 11.3)
Serious infection	4 (1.3)	5 (1.6)	8 (2.5)	0.3 (−1.5, 2.2)	1.3 (−0.9, 3.4)
Opportunistic infection‡	0 (0)	1 (0.3)	1 (0.3)	0.3 (−0.3, 0.9)	0.3 (−0.3, 0.9)
Herpes zoster	1 (0.3)	7 (2.2)	7 (2.2)	1.9 (0.2, 3.6)	1.9 (0.2, 3.7)
Hepatic disorder	17 (5.4)	19 (6.0)	14 (4.5)	0.6 (−3.0, 4.2)	−1.0 (−4.3, 2.4)
Anemia	6 (1.9)	9 (2.8)	13 (4.1)	0.9 (−1.4, 3.3)	2.2 (−0.4, 4.9)
Elevated CPK	3 (1.0)	9 (2.8)	35 (11.1)	1.9 (−0.2, 4.0)	10.2 (6.5, 13.8)
Gastrointestinal perforations§	0 (0)	0 (0)	2 (0.6)	0	0.6 (−0.2, 1.5)
Malignancy (including nonmelanoma skin cancer)¶	1 (0.3)	3 (0.9)	0 (0)	0.6 (−0.6, 1.9)	−0.3 (−0.9, 0.3)
MACE (adjudicated)#	1 (0.3)	1 (0.3)	2 (0.6)	−0.0 (−0.9, 0.9)	0.3 (−0.8, 1.4)
Venous thromboembolic event (adjudicated)	1 (0.3)	0 (0)	1 (0.3)	−0.3 (−0.9, 0.3)	0.0 (−0.9, 0.9)
Pulmonary embolism	1 (0.3)	0 (0)	0 (0)	–	–
Deep vein thrombosis	0 (0)	0 (0)	1 (0.3)	–	–
Laboratory variables**					
Hemoglobin, gm/liter					
Mean ± SD change from baseline to week 24††	0.9 ± 10.0	2.3 ± 10.6	−0.7 ± 12.0	1.5 (−0.4, 3.3)	−1.6 (−3.4, 0.3)
Grade 3 (70 to <80 or a decrease of 21 to <30)	16 (5.1)	10 (3.2)	25 (8.0)‡‡	–	–
Grade 4 (<70 or a decrease of ≥30)	5 (1.6)	1 (0.3)	10 (3.2)‡‡	–	–
Platelets, × 10⁹/liter					
Mean ± SD change from baseline up to week 24§§	−16.5 ± 66.2	−26.9 ± 78.3	−9.6 ± 73.6	−10.4 (−22.6, 1.9)	6.9 (−5.5, 19.3)
Grade 3 (20 to <50)¶¶	0 (0)	0 (0)	0 (0)	–	–
Grade 4 (<20)¶¶	0 (0)	0 (0)	1 (0.3)	–	–
Leukocytes, × 10⁹/liter					
Mean ± SD change from baseline to week 24††	−1.0 ± 2.2	−1.4 ± 2.5	−1.4 ± 2.2	−0.5 (−0.8, −0.1)	−0.4 (−0.80, 0.0)
Grade 3 (1.0 to <2.0)	0 (0)	0 (0)	2 (0.6)‡‡	–	–
Grade 4 (<1.0)	0 (0)	0 (0)	2 (0.6)‡‡	–	–
Neutrophils, × 10⁹/liter					
Mean ± SD change from baseline to week 24##	−0.8 ± 1.9	−1.4 ± 2.4	−1.4 ± 2.1	−0.6 (−0.9, −0.2)	−0.6 (−0.9, −0.2)
Grade 3 (0.5 to <1.0)	0 (0)	1 (0.3)	5 (1.6)	–	–
Grade 4 (<0.5)	0 (0)	0 (0)	1 (0.3)	–	–

(Continued)

Table 2. (Cont'd)

	MTX (n = 314)	Upadacitinib 15 mg once daily (n = 317)	Upadacitinib 30 mg once daily (n = 314)	Difference (95% CI)	
				Upadacitinib 15 mg once daily vs. MTX	Upadacitinib 30 mg once daily vs. MTX
Lymphocytes, × 10⁹/liter					
Mean ± SD change from baseline to week 24##	−0.1 ± 0.7	0.1 ± 0.7	0.1 ± 0.7	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)
Grade 3 (0.5 to <1.0)	43 (13.8)	29 (9.2)	38 (12.3)	–	–
Grade 4 (<0.5)	2 (0.6)	0 (0)	2 (0.6)	–	–
ALT, units/liter					
Grade 3 (3.0 to <8 × ULN)	11 (3.5)	4 (1.3)	5 (1.6)	–	–
Grade 4 (>8 × ULN)	3 (1.0)	2 (0.6)	0 (0)	–	–
AST, units/liter					
Grade 3 (3.0 to <8 × ULN)	8 (2.6)	1 (0.3)	4 (1.3)	–	–
Grade 4 (>8 × ULN)	0 (0)	2 (0.6)	0 (0)	–	–

* Except where indicated otherwise, values are the number (%). AEs = adverse events; 95% CI = 95% confidence interval; SAE = serious AE; CPK = creatine phosphokinase; ALT = alanine transaminase; ULN = upper limit of normal; AST = aspartate transaminase.

† Including non–treatment-emergent deaths, in the methotrexate (MTX) arm there was 1 death due to acute myocardial infarction (MI), in the upadacitinib 15 mg arm there was 1 death due to nonfatal MI and hypoxic ischemic encephalopathy and 1 death due to metastatic malignant melanoma, and in the upadacitinib 30 mg arm there was 1 sudden cardiovascular (CV) death, 1 death due to pneumonia and sepsis, and 1 death due to peritonitis.

‡ One patient in the upadacitinib 15 mg arm had cryptococcal pneumonia, and 1 patient in the upadacitinib 30 mg arm had a positive cytomegalovirus (CMV) test (and was asymptomatic).

§ Determined by Gastrointestinal Perforations Standardised Medical Dictionary for Regulatory Activities Queries. In the upadacitinib 30 mg arm 1 patient had a large intestinal perforation and 1 patient had peritonitis.

¶ In the MTX arm 1 patient had ovarian cancer, and in the upadacitinib 15 mg arm there was 1 case each of metastatic malignant melanoma, squamous cell carcinoma of the lung, and uterine carcinoma in situ. There were no cases of nonmelanoma skin cancer.

Adjudicated major adverse cardiovascular events (MACE) included 1 CV death in the MTX arm, 1 nonfatal MI, and 1 CV death due to other CV causes (both events occurring in the same patient) in the upadacitinib 15 mg arm, and 1 nonfatal MI and 1 CV death (sudden) in the upadacitinib 30 mg arm.

** Includes patients with worsening in grade at any time during the study, including single isolated values. Grading is based on Outcome Measures in Rheumatoid Arthritis Clinical Trials criteria. Except where indicated otherwise, n = 312 in the MTX arm, 315 in the upadacitinib 15 mg arm, and 310 in the upadacitinib 30 mg arm.

†† Data were available for 266 patients in the MTX arm, 286 patients in the upadacitinib 15 mg arm, and 272 patients in the upadacitinib 30 mg arm.

‡‡ Data were available for 311 patients.

§§ Data were available for 264 patients in the MTX arm, 284 patients in the upadacitinib 15 mg arm, and 270 patients in the upadacitinib 30 mg arm.

¶¶ Data were available for 311 patients in the MTX arm, 314 patients in the upadacitinib 15 mg arm, and 311 patients in the upadacitinib 30 mg arm.

Data were available for 266 patients in the MTX arm, 285 patients in the upadacitinib 15 mg arm, and 271 patients in the 30 mg arm.

had an opportunistic infection (1 patient receiving the 15 mg dose had pneumonia cryptococcal, and 1 patient receiving the 30 mg dose had a positive cytomegalovirus test with no symptoms). The frequencies of herpes zoster were similar in the 2 upadacitinib arms (2.2%), which were higher than that in the MTX arm (0.3%). Higher percentages of patients had anemia and CPK elevations in the upadacitinib 30 mg arm than in the 15 mg arm (2.8% receiving the 15 mg dose and 4.1% receiving the 30 mg dose had anemia; 2.8% receiving the 15 mg dose and 11.1% receiving the 30 mg dose had elevated CPK levels). Most hepatic disorders were nonserious, and transient transaminase elevations occurred with similar frequencies across the 3 treatment arms (6.0% in the upadacitinib 15 mg arm and 4.5% in the upadacitinib 30 mg arm versus 5.4% in the MTX arm). There were 3 malignancy events (0.9%) in the upadacitinib 15 mg arm compared to 1 in the MTX arm and none in the upadacitinib 30 mg arm. The frequencies of adjudicated MACE, adjudicated venous thromboembolic event, and gastrointestinal perforations were comparable across treatment groups. There were no events of nonmelanoma skin cancer, active/latent tuberculosis, or lymphoma throughout the 24-week period (Table 2).

Six deaths occurred over the 24-week period. One death in the MTX arm was attributed to acute myocardial infarction by the cardiovascular adjudication committee. Of the 2 deaths in the upadacitinib 15 mg group, 1 was attributed to hypoxic ischemic encephalopathy following myocardial infarction (by the cardiovascular adjudication committee), while the other was due to metastatic malignant melanoma and tumor infiltration of the hepatic vein (not considered a venous thromboembolic event by the cardiovascular adjudication committee). This second patient had a history of malignant melanoma prior to study entry. One of the 3 deaths in the upadacitinib 30 mg arm was adjudicated by the cardiovascular adjudication committee as a sudden cardiovascular death, the second was due to pneumonia and sepsis, and the third was due to peritonitis. This third patient had a history of gastrointestinal bleeding prior to study entry.

The mean values for all hematologic parameters in each treatment arm were within normal limits at baseline and remained so for some parameters at all subsequent visits. However, higher proportions of patients had grade 3 or 4 decreases in hemoglobin, neutrophil, leukocyte, and platelet values in the upadacitinib 30 mg arm compared to the upadacitinib 15 mg and MTX arms (Table 2). The proportions of patients with grade 3 or 4 decreases in lymphocytes were higher in the MTX arm compared to both upadacitinib arms. The proportion of patients with elevated alanine transaminase (ALT; grade 3) was higher in the MTX arm (3.5%) and comparable between the upadacitinib arms (1.3% and 1.6% in the 15 mg and 30 mg arms, respectively), while the proportions of patients with grade 3 aspartate transaminase (AST) elevations were highest in the MTX arm (2.6%), followed by the upadacitinib 30 mg and 15 mg arms (1.3% and 0.3%, respectively). Few patients had grade 4 ALT and AST elevations (Table 2).

Treatment with upadacitinib 15 mg or upadacitinib 30 mg resulted in numerically greater mean increases from baseline in low-density and high-density lipoprotein cholesterol at week 24 compared with treatment with MTX (0.2–1.1 mmoles/liter) (Supplementary Figure 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract).

Within 24 hours of dosing, mean plasma upadacitinib concentrations ranged from 26.7 ng/ml (around peak time) to 5.89 ng/ml (close to trough time) for 15 mg once daily and from 78.8 ng/ml (around peak time) to 12.3 ng/ml (close to trough time) for 30 mg once daily. These concentrations were consistent with observations in other upadacitinib studies in RA (16,17) and with the predicted plasma concentrations based on prior assessments of upadacitinib pharmacokinetics (32,33).

DISCUSSION

In this SELECT-EARLY trial in MTX-naive patients with RA, both doses of upadacitinib were superior to MTX in all efficacy outcomes, including multiple definitions of clinical remission and PROs. The clinical remission response rates were similar between the 15 mg and 30 mg doses (~30% for CDAI and SDAI at week 24; ≥24% for Boolean remission at week 24). Favorable responses to upadacitinib treatment were rapid (as early as the first postbaseline visit at week 2, at which MTX had not been fully titrated), and persisted through 24 weeks across both patient- and physician-reported measures. Additionally, both upadacitinib doses prevented progression of structural damage over 24 weeks in ~90% of patients. Results for the primary and all ranked key secondary end points remained statistically significant after multiplicity adjustments (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract). Sensitivity analyses for primary and key secondary end points were consistent with the primary analyses (Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41384/abstract). With 945 patients treated, SELECT-EARLY is among the largest global, double-blind trials ever conducted in MTX-naive patients.

In this population, the primary treatment target is remission, or at least a state of low disease activity, within 6 months as described in the ACR guidelines and EULAR recommendations (1,2,34). SELECT-EARLY is the first trial to demonstrate achievement of Boolean remission by week 24 in 24–25% of MTX-naive patients receiving a JAK inhibitor. Importantly, ~90% of the patients in this trial had no radiographic progression of joint damage (modified total Sharp score ≤0), with no progression previously reported in ~76% of similar patients treated with a JAK inhibitor (11), though no head-to-head comparison is available.

This head-to-head comparison of upadacitinib with MTX allowed for a robust examination of the safety profile of upadacitinib versus MTX. The data are consistent with those reported

previously in other phase III upadacitinib trials (16–19). AEs generally occurred at frequencies similar to or numerically less with 15 mg than with the active comparator MTX, with the exception of herpes zoster. Grade 3 and 4 changes occurred more frequently with upadacitinib 30 mg for hemoglobin and neutrophil values and more frequently with MTX for lymphocyte and transaminase values.

The trial has some limitations. While a majority of patients had a relatively short duration of RA, a sizeable minority had disease for longer durations but had not been treated with MTX. However, 25% were previously treated with non-MTX csDMARDs. In addition, this trial was limited to patients with risk factors for radiographic progression, thus limiting the generalization of these data to all MTX-naive patients with RA. Patients with active disease of very recent onset, recruited from an early arthritis clinic, may differ somewhat from those studied here.

While MTX is the most widely accepted "initial therapy for RA," it is appropriate nonetheless to point out its limitations. MTX achieves remission—the consensus treatment target in early RA—in only a minority of patients (<20% in this trial), and achieves acceptable disease control in at most 60% of patients (3–5). It may not be an appropriate treatment of choice in certain patient populations (e.g., patients with significant alcohol intake). In addition, weekly MTX is associated with the relatively frequent occurrence of nonserious but inconvenient AEs, such as nausea, oral ulcers and other gastrointestinal symptoms, alopecia, and general malaise. It is also associated with the potential for more serious events, with hepatotoxicity and myelosuppression being relatively common and interstitial pneumonitis uncommon but potentially life-threatening (35). Recently, a large controlled study of MTX for cardiovascular disease prevention demonstrated negative findings and unexpectedly revealed an increased risk of non–basal cell skin cancer (36,37). Thus, MTX is not always the ideal treatment for all patients, and the search for alternative therapies is legitimate.

In summary, 15 mg and 30 mg once-daily doses of upadacitinib demonstrated achievement of superior clinical and radiographic outcomes and PROs versus MTX in MTX-naive RA patients who are at increased risk of structural damage. Treatment with upadacitinib 15 mg once daily resulted in a plateau of efficacy and a safety profile generally comparable to that of MTX. Treatment with upadacitinib 30 mg was associated with minimal additional efficacy compared to 15 mg, and a higher rate of certain serious AEs and infection, including serious infection. These head-to-head data provide consistent evidence of the efficacy of this JAK1-selective inhibitor versus the gold standard of initial RA therapy, supporting the potential of upadacitinib as a new therapeutic option for patients with RA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. van Vollenhoven had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. van Vollenhoven, Takeuchi, Pangan, Friedman, Mohamed, Chen, Strand.
Acquisition of data. Chen, Rischmueller, Blanco, Xavier.
Analysis and interpretation of data. van Vollenhoven, Takeuchi, Pangan, Friedman, Mohamed, Chen.

ROLE OF THE STUDY SPONSOR

REFERENCES

1. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1–26.

2. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.

3. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372:375–82.

4. Van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, van Zeben D, Kerstens PJ, Gerards AH, et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Ann Rheum Dis 2007;66:1356–62.

5. Van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Cöster L, Waltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (SWEFOT trial): 1-year results of a randomised trial. Lancet 2009;374:459–66.

6. Bello AE, Perkins EL, Jay R, Efthimiou P. Recommendations for optimizing methotrexate treatment for patients with rheumatoid arthritis [review]. Open Access Rheumatol 2017;9:67–79.

7. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJ, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: a network meta-analysis [review]. Cochrane Database Syst Rev 2016;2016:CD010227.

8. Rawlings JS, Rosler KM, Harrison DA. The JAK/STAT signaling pathway. J Cell Sci 2004;117:1281–3.

9. Walker JG, Smith MD. The Jak–STAT pathway in rheumatoid arthritis. J Rheumatol 2005;32:1650–3.

10. Fleischmann RM, Huizinga TW, Kavanaugh AF, Wilkinson B, Kwok K, DeMasi R, et al. Efficacy of tofacitinib monotherapy in methotrexate-naive

patients with early or established rheumatoid arthritis. RMD Open 2016;2:e000262.

11. Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Rheumatol 2017;69:506–17.

12. Van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–19.

13. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Morales LD, Gonzaga JR, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 2017;376:652–62.

14. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017;390:457–68.

15. Serhal L, Edwards CJ. Upadacitinib for the treatment of rheumatoid arthritis [review]. Expert Rev Clin Immunol 2018;15:13–25.

16. Burmester GR, Kremer JM, van den Bosch F, Kivitz A, Bessette L, Li Y, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying antirheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:2503–12.

17. Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying antirheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet 2018;391:2513–24.

18. Smolen JS, Pangan AL, Emery P, Rigby W, Tanaka Y, Vargas JI, 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.

19. Fleischmann R, Pangan AL, Song IH, Mysler E, Bessette L, Peterfy C, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase 3, double-blind, randomized controlled trial. Arthritis Rheumatol 2019;71:1788–800.

20. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:1580–8.

21. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol 2005;32:811–9.

22. Ware JE Jr, Kosinski M, Keller SK. SF-36 physical and mental health summary scales: a user's manual. Boston: The Health Institute, New England Medical Center; 1994.

23. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.

24. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.

25. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.

26. Sharp JT, Young DY, Bluhm GB, Brook A, Brower AC, Corbett M, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum 1985;28:1326–35.

27. Woodworth T, Furst DE, Alten R, Bingham CO III, Yocum D, Sloan V, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol 2007;34:1401–14.

28. US DPHHS. NIH. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 4.0. June 2010. URL: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

29. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009;28:586–604.

30. Tymms K, Zochling J, Scott J, Bird P, Burnet S, de Jager J, et al. Barriers to optimal disease control for rheumatoid arthritis patients with moderate and high disease activity. Arthritis Care Res (Hoboken) 2014;66:190–6.

31. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993;20:557–60.

32. Mohamed MF, Zeng J, Marroum PJ, Song IH, Othman AA. Pharmacokinetics of upadacitinib with the clinical regimens of the extended-release formulation utilized in rheumatoid arthritis phase 3 trials. Clin Pharmacol Drug Dev 2019;8:208–16.

33. Klunder B, Mohamed MF, Othman AA. Population pharmacokinetics of upadacitinib in healthy subjects and subjects with rheumatoid arthritis: analyses of phase I and II clinical trials. Clin Pharmacokinet 2018;57:977–88.

34. Van Vollenhoven R. Treat-to-target in rheumatoid arthritis: are we there yet [review]? Nat Rev Rheumatol 2019;15:180–6.

35. FDA.gov. Methotrexate tablets, USP. January 2016. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008085s066lbl.pdf.

36. Van Vollenhoven RF, Nurmohamed M. Methotrexate for prevention of cardiovascular events [letter]. N Engl J Med 2019;380:2276–7.

37. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med 2019;380:752–62.