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Original article

Upadacitinib improves patient-reported outcomes *vs* placebo or adalimumab in patients with rheumatoid arthritis: results from SELECT-COMPARE

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Abstract

Objective. To evaluate the impact of upadacitinib *vs* placebo and adalimumab treatment, on patient-reported outcomes (PROs) in SELECT-COMPARE in an active RA population with inadequate responses to MTX (MTX-IR).
Methods. PROs in patients receiving upadacitinib (15 mg QD), placebo, or adalimumab (40 mg EOW) while on background MTX were evaluated over 48 weeks. PROs included Patient Global Assessment of Disease Activity (PtGA) and pain by visual analogue scale (VAS), the HAQ Disability Index (HAQ-DI), the 36-Item Short Form Survey (SF-36), morning (AM) stiffness duration and severity, the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), and work instability. Least squares mean (LSM) changes and proportions of patients reporting improvements $\geq$ minimal clinically important differences (MCIDs) and scores $\geq$ normative values were evaluated.
Results. Upadacitinib and adalimumab resulted in greater LSM changes from baseline *vs* placebo across all PROs ($P < 0.05$) at week 12, and pain and AM stiffness severity ($P < 0.05$) at week 2. More upadacitinib- *vs* placebo-treated ($P < 0.05$) and similar percentages of upadacitinib- *vs* adalimumab-treated patients reported improvements $\geq$ MCID across all PROs at week 12. Upadacitinib *vs* adalimumab resulted in greater LSM changes from baseline in PtGA, pain, HAQ-DI, stiffness severity, FACIT-F, and the SF-36 Physical Component Summary (PCS) (all $P < 0.05$) at week 12. More upadacitinib- *vs* adalimumab-treated patients reported scores $\geq$ normative values in HAQ-DI and SF-36 PCS ($P < 0.05$) at week 12. More upadacitinib- *vs* adalimumab-treated patients maintained clinically meaningful improvements in PtGA, pain, HAQ-DI, FACIT-F, and AM stiffness through 48 weeks.
Conclusion. In MTX-IR patients with RA, treatment with upadacitinib resulted in statistically significant and clinically meaningful improvements in PROs equivalent to or greater than with adalimumab.
Trial registration. ClinicalTrials.gov, http://clinicaltrials.gov, NCT02629159.

Key words: rheumatoid arthritis, outcome measures, quality of life, inflammation, DMARDs

CLINICAL SCIENCE

Rheumatology key messages

- We evaluated the impact of treatment with upadacitinib *vs* placebo and adalimumab on patient-reported outcomes (PROs).
- Upadacitinib- and adalimumab-treated patients reported early improvements in PROs at 2 weeks after treatment initiation.
- Upadacitinib treatment resulted in improvements across all PROs vs placebo that met or exceeded treatment with adalimumab.

Introduction

RA is a chronic inflammatory disease associated with substantial clinical burden, reduced health-related quality of life (HRQOL), and shortened life expectancy [1]. When untreated or inadequately treated, progressive functional impairments may lead to reductions in HRQOL [1]. Symptoms commonly associated with RA that negatively impact HRQOL include pain, fatigue, and morning (AM) stiffness [2–4]; these symptoms may also substantially impair work productivity and participation in

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family/social and leisure activities [3, 5, 6]. It is important to consider the benefits of RA treatment from patients' perspectives when evaluating therapies.

Current treatment options include NSAIDs , glucocorticoids, conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and more recently, targeted synthetic DMARDs (tsDMARDs) [1, 7, 8]. Despite major progress in the treatment of RA, there remains a large unmet need, because a minority of patients with RA achieve or maintain remission or low disease activity (LDA) with stringent metrics [1, 9]. Novel therapies as well as different ways to utilize existing therapies are therefore needed to complement available interventions to address the unmet need.

Janus kinase (JAK) inhibitors, a class of tsDMARDs, are approved for use in patients with RA [7, 8, 10]. Upadacitinib (UPA) is a potent JAK inhibitor with preferential activity towards JAK-1, and it has recently been approved for the treatment of RA [11, 12]. The efficacy of UPA in patients with active RA and an inadequate response to methotrexate (MTX-IR) was shown in the phase 3 randomized controlled trial (RCT), SELECT-COMPARE [13]. In SELECT-COMPARE, a significantly greater American College of Rheumatology (ACR) 20 response was achieved in patients treated with UPA 15 mg compared with placebo (PBO) (71% *vs* 36%, respectively; $P < 0.0001$) [13]. Compared with PBO, significantly greater ACR20 responses were demonstrated in UPA (15 mg)-treated patients with an inadequate response to a csDMARD (csDMARD-IR) (64% *vs* 36%, respectively; $P < 0.0001$) [14], and in patients with an inadequate response to a bDMARD (bDMARD-IR) (65% *vs* 28%, respectively; $P < 0.0001$) [15]. UPAD has also shown efficacy as combination therapy and monotherapy in MTX-IR patients [16].

Improvements in patient-reported outcomes (PROs) are important for evaluating the efficacy and benefits of RA treatments [17, 18]. Improvements in PROs with UPA were reported in csDMARD-IR and bDMARD-IR populations in the phase 3 program [19, 20]; however, the effect of UPA on PROs in comparison with widely used therapies such as ADA is not well known. This analysis evaluated the impact of UPA *vs* PBO and *vs* ADA (active comparator) on PROs in SELECT-COMPARE, an RCT in an active MTX-IR RA population.

Patients and methods

Study design and participants

The full study design of SELECT-COMPARE, a phase 3, double-blind, parallel-group, placebo-controlled, and active-comparator trial (NCT02629159), has been reported previously [21]. Patients ≥18 years of age with moderate to severely active RA for ≥3 months and MTX-IR were randomized 2:2:1 to receive UPA (15 mg once daily, $n = 651$), matching PBO ($n = 651$), or the active comparator, ADA (40 mg every other week, $n = 327$), while receiving stable background MTX therapy. Eligible patients had received MTX therapy for ≥3 months and were on a stable dose of MTX for ≥4 weeks prior to the first dose of the study drug. The median (range) and mean MTX dose at baseline was 15.0 (7.5–25.0) mg and 17.0 mg weekly, respectively. Up to 20% of patients with prior exposure to ≥ one bDMARD were included if patients had <3 months exposure or discontinued bDMARD treatment due to intolerance; only 9% ($n = 151$) of enrolled patients had prior bDMARD exposure [21]. bDMARD-IR patients were excluded, as were those with prior exposures to JAK inhibitors or ADA or other bDMARDs therapy for ≥3 months.

At weeks 14, 18 and 22, patients with <20% improvement in tender or swollen joints were switched from PBO or ADA to UPA, or from UPA to ADA (rescue therapy). At week 26, all patients receiving PBO were switched to UPA, and any patient not achieving LDA (Clinical Disease Activity Index ≤10) were switched from UPA to ADA or from ADA to UPA, if not rescued earlier in the study.

The protocol was specifically approved for this study by Advarra Institutional Review Board (Columbia, MD, USA) and St Luke's Hospital Institutional Review Board (Duluth, MN, USA). The study was conducted in accordance with the Declaration of Helsinki and was consistent with International Conference on Harmonization Good Clinical Practice and Good Epidemiology Practices, along with all applicable local regulatory requirements. Patient data were de-identified and fully compliant with patient confidentiality requirements. All participants provided written informed consent before enrolment.

Patient-reported outcomes

Clinically relevant PROs were collected to evaluate the impact of UPA in comparison with PBO or ADA. Clinically meaningful responses for each PRO were defined as changes from baseline ≥ minimum clinically important difference (MCID) or defined as scores ≥ normative values. The proportion of patients treated with UPA or ADA who maintained improvements ≥ MCID at later time points were also determined.

Patient Global Assessment of Disease Activity (PtGA) and pain were assessed by visual analogue scale (VAS) (range 0–100 mm; higher scores indicate greater disease activity or worse pain) [17, 22, 23], with MCIDs defined as reductions ≥10 mm [17, 23, 24]. Normative values are not available for pain VAS. The HAQ-Disability Index (HAQ-DI) assessed patients' physical function (scores range from 0 to 3, where higher scores indicate impaired physical function) [25], with an MCID of ≥0.22 units [17, 23] and normative value defined as ≤0.25 [26]. The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) assessed fatigue (scores range from 0 to 52; higher scores indicate less fatigue), with an MCID defined as an increase of ≥4 points [23, 27] and a normative value of ≥43.6 [19].

The 36-Item Short Form Health Survey (SF-36) consists of two aggregate [Physical (PCS) and Mental Component Summary (MCS)] scores based on eight

domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), measured on a scale of 0–100, where higher scores indicate better health [28, 29]. MCIDs for SF-36 are defined as increases of ≥2.5 points in PCS and MCS scores [17, 23] and ≥5.0 points for each of the eight SF-36 domains [17]. Normative values for both PCS and MCS are defined as 50 [30]. Normative values as a benchmark comparison utilizing US normative values age- and gender-matched to the protocol population were used for the SF-36 domains [31].

Duration of AM stiffness was measured in minutes, and severity of AM stiffness by a numeric rating scale (scores range from 0 to 10; higher scores indicate greater severity). A predefined MCID was not available in the literature for AM stiffness; therefore, we defined it as one-half (S.D.) of the mean baseline value for duration and a reduction of ≥1 point for severity of AM stiffness [17, 32]. The Work Instability Scale for RA (RA-WIS) identified patients at risk for disease-associated work instability (scores range from 0 to 23; higher scores reflect a greater risk of leaving work); MCID was defined as a reduction of ≥5 points [33], and the normative value as ≤10 (low instability) [33].

Statistical analyses

All patients included in the intention-to-treat population of the trial were eligible for this analysis. Least squares mean (LSM) changes from baseline to week 12 were calculated based on a mixed-effect repeated measures model. The proportions of patients reporting improvements ≥ MCID in PROs from baseline to week 12 and scores ≥ normative values were determined for UPA, PBO, and ADA treatment groups. LSM changes from baseline to week 2, the first post-baseline visit and earliest time point data were available, and proportions of patients reporting improvements ≥ MCID from baseline to week 2 were determined for pain VAS and severity and duration of AM stiffness to evaluate rapid onset and response to treatment. LSM changes from baseline to weeks 26 and 48 were calculated for all PROs with 95% CIs using an analysis of covariance (ANCOVA) model. The last observation carried forward was used for observations after initiation of rescue therapy in patients rescued at week 26. Among patients treated with UPA and ADA who reported improvements ≥ MCID in PROs at week 12, the proportion who reported maintaining clinically meaningful improvements at weeks 26 and 48 were determined. Non-responder imputation (NRI) was utilized for imputation of missing responses and for observations after initiation of rescue therapy at weeks 14, 18 or 22. Comparisons between groups used χ^2 tests, with statistical significance at the 5% level without adjustment for multiple comparisons. In this analysis, the number needed to treat (NNT) measured treatment impact as the number of patients required to be treated to achieve one additional responder (improvements ≥ MCID from baseline), and it was calculated based on the reciprocal of the response rate difference between treatment (UPA and ADA) *vs* PBO groups for each PRO at week 12. Time to response was assessed by Kaplan–Meier analysis and compared using the log-rank test.

Results

Study population

Patient disposition and demographic information have been published in full [21]. Briefly, the study included 1629 patients, of whom, 651 were randomized to UPA, 651 to PBO, and 327 to ADA. The mean age was 54 years, 79% were female, and 54% had RA for ≥5 years. In this MTX-IR population, mean disease duration since initial RA diagnosis was ∼8 years. Mean DAS28 (CRP) scores were indicative of high disease activity and were similar across the treatment groups (5.8, 5.8 and 5.9 for the UPAD 15 mg, PBO and ADA 40 mg groups, respectively).

Baseline PRO scores were similar across the three treatment groups (Table 1) and reflected the impact of RA in patients with long disease duration (mean 8.1–8.3 years). Decrements from age/gender-adjusted norms indicate that patients had substantial impairments in HRQOL at baseline (Fig. 1).

Patient-reported outcomes at week 12

LSM changes and patients reporting improvements ≥ MCID at week 12

At week 12, UPA treatment resulted in statistically significant larger LSM changes from baseline *vs* PBO across all PROs (Table 2). UPA treatment also resulted in statistically significant larger LSM changes from baseline *vs* ADA in PtGA, pain, HAQ-DI, AM stiffness severity, FACIT-F, SF-36 PCS and six of eight domain scores (Table 2).

Improvements in PCS scores with UPA at week 12 (7.89) were significantly larger *vs* PBO [3.56 ($P < 0.001$)] and ADA [6.27 ($P = 0.002$)] (Table 2). LSM change in MCS score at week 12 was 6.39 with UPA, which was significantly greater *vs* PBO [3.67 ($P < 0.001$)] and numerically, but not statistically, greater than ADA [5.39 ($P = 0.085$)] (Table 2). At 12 weeks, mean changes from baseline in domain scores with UPA treatment exceeded PBO across all eight SF-36 domains ($P < 0.001$) (Table 2) and were statistically significantly different compared with ADA across six domains ($P < 0.001$, 15 mg *vs* ADA: role-physical, bodily pain, general health; $P = 0.005$: vitality; $P = 0.007$: social functioning; and $P = 0.03$: physical functioning) (Fig. 1, Table 2).

Compared with PBO at week 12, significantly more UPA-treated patients reported improvements ≥ MCID in PtGA, pain, HAQ-DI, duration and severity of AM stiffness, FACIT-F, and PCS and MCS scores ($P < 0.05$), with NNTs <10 (range 4.5–9.6) for most PROs (Fig. 2A and B). At week 12, the proportions of UPA-treated patients reporting improvements ≥ MCID were similar or numerically, but not statistically, greater than ADA-treated patients (Fig. 2A and B), with the exception of the SF-36 role-physical domain ($P < 0.05$).

Table 1 Baseline characteristics and PRO scores

Characteristics	UPA 15 mg (n = 651)	PBO (n = 651)	ADA 40 mg (n = 327)
Age, mean (S.D.)	54.2 ± 12.1	53.6 ± 12.2	53.7 ± 11.7
Female, n (%)[a]	521 (80.0)	512 (78.6)	259 (79.2)
White, n (%)[a]	576 (88.5)	561 (86.2)	292 (79.2)
Duration of RA diagnosis, mean (S.D.)	8.1 ± 7.7	8.3 ± 8.0	8.3 ± 8.4
MTX dose ≥15 mg at baseline, n (%)[a]	568 (87.4)	584 (89.8)	294 (90.2)
RF positive, n (%)[a]	521 (80.0)	517 (79.4)	265 (81.0)
Anti-CCP positive, n (%)[a]	525 (80.6)	529 (81.5)	264 (80.7)
DAS28 (CRP), mean (S.D.)	5.8 ± 1.0	5.8 ± 0.9	5.9 ± 1.0
PRO scores, mean (S.D.)			
PtGA	64.3 ± 21.8	63.8 ± 21.5	65.8 ±21.1
Pain VAS	65.7 ± 21.0	65.0 ± 20.7	66.2 ± 20.5
HAQ-DI	1.6 ± 0.6	1.6 ± 0.6	1.6 ± 0.6
AM stiffness duration[b]	141.5 ± 187.6	142.4 ± 169.8	146.1 ± 184.9
AM stiffness severity	6.3 ± 2.3	6.3 ± 2.3	6.3 ± 2.1
FACIT-F	26.9 ± 11.1	27.0 ± 11.1	26.2 ± 11.4
RA-WIS[c]	14.5 ± 6.1	14.8 ± 6.0	14.6 ± 5.9
SF-36 summary scores			
PCS	32.5 ± 7.3	32.5 ± 6.8	32.2 ± 7.0
MCS	43.0 ± 10.6	43.0 ± 11.1	42.7 ± 10.6
SF-36 domains			
Physical functioning	31.8 ± 8.9	31.4 ± 8.9	31.2 ± 8.7
Role-physical	33.5 ± 7.9	33.4 ± 7.7	33.0 ± 7.4
Bodily pain	34.2 ± 6.7	34.4 ± 6.7	34.4 ± 6.5
General health	37.7 ± 8.0	37.9 ± 8.3	37.9 ± 8.1
Vitality	40.9 ± 8.9	41.1 ± 9.1	40.8 ± 8.9
Social functioning	38.1 ± 9.8	38.1 ± 9.8	37.8 ± 10.6
Role-emotional	38.2 ± 11.4	37.8 ± 11.5	37.2 ± 11.2
Mental health	40.7 ± 10.2	40.8 ± 10.7	40.8 ± 10.0

[a]Percentages calculated on non-missing values. [b]Duration in min. [c]Only calculated for patients who are employed. ADA: adalimumab; AM: morning; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; DAS, disease activity score; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; MCS: Mental Component Summary; MTX, methotrexate; PBO, placebo; PCS: Physical Component Summary; PRO: patient-reported outcome; PtGA: Patient's Global Assessment of Disease Activity; RA, rheumatoid arthritis; RA-WIS: Work Instability Scale for RA; RF, rheumatoid factor; SD, standard deviation; SF-36: 36-Item Short Form Health Survey; UPA: upadacitinib; VAS: visual analogue scale.

Scores ≥ normative values. Less than one-third of patients in any treatment group reported PRO scores ≥ normative values at baseline (Fig. 3A and B). At week 12, the proportion of UPA- *vs* ADA-treated patients reporting scores ≥ normative values was significantly greater ($P < 0.05$) in HAQ-DI (21% *vs* 14%), and SF-36 PCS (16% *vs* 11%) (Fig. 3A). Similarly, comparing UPA to ADA, the percentage of patients reporting scores ≥ normative values at 12 weeks across SF-36 domains were statistically significant in bodily pain ($P < 0.01$) and vitality domains ($P < 0.05$) (Fig. 3B).

Patient-reported outcomes at week 2

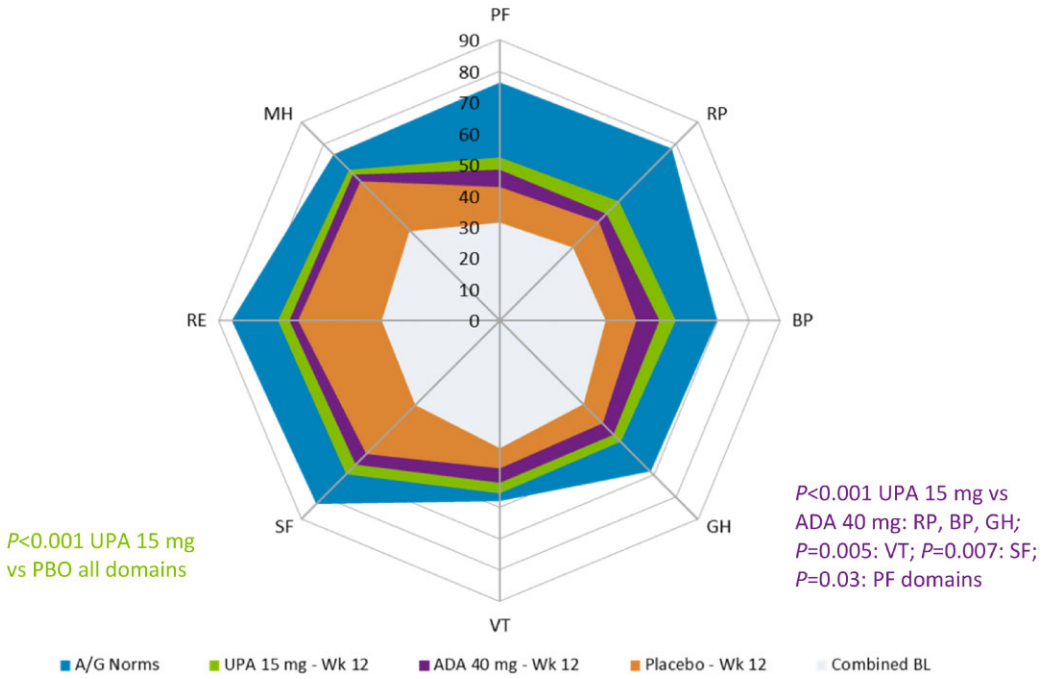
Improvements in patient-reported pain, and duration and severity of AM stiffness were reported as early as week 2, the first post- baseline visit. At week 2, treatment with UPA resulted in statistically significant LSM changes from baseline in pain, and severity and duration of AM stiffness compared with PBO (Table 2). At week 2, LSM changes from baseline were clinically meaningful and similar between UPA and ADA in pain and AM stiffness severity and duration (Table 2).

Sixty-eight percent each of UPA- and ADA-treated patients reported improvements ≥ MCID in AM stiffness severity compared with 48% with PBO (UPA *vs* PBO; $P < 0.001$). Similarly, 60% and 59% of patients receiving UPA or ADA, respectively, reported improvements ≥ MCID in pain compared with 40% receiving PBO (UPA *vs* PBO; $P < 0.001$). In both UPA and ADA groups, the median time to response was 2 weeks for pain VAS and severity of AM stiffness compared with 4 weeks with PBO.

Patient-reported outcomes at weeks 26 and 48

LSM changes from baseline at weeks 26 and 48. At weeks 26 and 48, comparisons are between UPA and ADA only. At week 26, UPA treatment resulted in statistically significant LSM changes from baseline *vs* ADA in

Fig. 1 SF-36 domain scores at baseline and week 12 for all treatment groups relative to age- and gender-matched normative values



ADA, adalimumab; A/G norms, age- and gender-matched normative values; BL, baseline; BP, bodily pain; GH, general health; MH, mental health; PBO, placebo; PF, physical functioning; RE, role-emotional; RP, role-physical; SF-36, 36-Item Short-Form Health Survey; SF, social functioning; UPA, upadacitinib; VT, vitality.

PtGA, pain, HAQ-DI, AM stiffness severity, FACIT-F, SF-36 PCS and four of eight domain scores (Table 3). At week 48, UPA resulted in significantly better changes from baseline *vs* ADA in PtGA (−35.3 *vs* −30.2), pain (−36.7 *vs* −32.1), HAQ-DI (–0.7 *vs* –0.6), FACIT-F (10.2 *vs* 8.9) and SF-36 PCS scores (9.8 *vs* 8.1) (Table 3).

Maintenance of improvements ≥ MCID at weeks 26 and 48. Significantly (all $P < 0.05$), more UPA- than ADA-treated patients continued to report clinically meaningful improvements in PROs from weeks 12 through 26 in PtGA, pain, HAQ-DI, AM stiffness severity, SF-36 PCS, MCS and five of eight domains (Supplementary Fig. 1A and B, available at *Rheumatology* online). Significantly (all $P < 0.05$), greater percentages of patients treated with UPA *vs* ADA continued to report clinically meaningful improvements from weeks 12 to 48 in PtGA, pain, HAQ-DI, FACIT-F, severity and duration of AM stiffness, SF-36 PCS and MCS, and all eight domain scores (Supplementary Fig. 1C and D, available at *Rheumatology* online).

Discussion

Treatment with tumor necrosis factor inhibitors (TNFis) represent an established standard of care for patients with RA [7, 8, 10], with well-known clinical benefits and safety profiles, while, JAK inhibitors, which include UPA, are an emerging class [7, 8]. SELECT-COMPARE offered the unique opportunity to analyse the impact of UPA treatment on HRQOL in patients with MTX-IR RA *vs* PBO and, more importantly, *vs* standard- of- care active comparator, ADA. At week 12, improvements reported by the UPA treatment group significantly outperformed PBO and met or exceeded ADA based on the percentages of patients reporting improvements ≥ MCID and scores ≥ normative values. The proportions of patients reporting short-term improvements ≥ MCID were similar to those receiving UPAD 15 mg treatment in SELECT-NEXT, another csDMARD-IR patient population and in a bDMARD-IR population in SELECT-BEYOND [19, 20]. In the current analysis, improvements in pain and AM stiffness occurred as early as week 2 with UPA and ADA. Rapid improvements with UPAD *vs* PBO occurred as early as week 1 in SELECT-NEXT in PtGA, pain, HAQ-DI, and AM stiffness.[19] The proportion of patients maintaining clinically meaningful improvements was significantly greater with UPA *vs* ADA in PtGA, pain, fatigue, HAQ-DI, and severity and duration of AM stiffness over 26 and 48 weeks.

The SELECT-COMPARE trial is the only head-to-head trial demonstrating superiority of a JAK inhibitor (UPA) *vs* a TNFi (ADA) for prespecified, multiplicity-adjusted ranked end points related to signs and symptoms (ACR20/50), pain, and function (HAQ-DI) at week 12 [21, 34–37]. Pain and physical functioning are key domains for patients that must improve due to their impact on HRQOL and daily activities [6, 38]. In RCTs, tofacitinib

Table 2 LSM changes from baseline at weeks 12 and 2 following UPAD initiation

PRO measures	LSM change (95% CI)		
	UPAD 15 mg ($n = 651$)	PBO ($n = 651$)	ADA 40 mg ($n = 327$)
Week 12			
PtGA	–30.39 (–32.62, –28.16)[a,b]	–15.24 (–17.44, –13.04)	–23.55 (–26.43, –20.67)[c]
Pain VAS	–31.76 (–33.96, –29.56)[a,b]	–15.46 (–17.63, –13.29)	–25.31 (–28.16, –22.47)[c]
HAQ–DI	–0.61 (–0.66, –0.56)[a,b]	–0.30 (–0.35, –0.25)	–0.51 (–0.57, –0.44)[c]
AM stiffness duration	–92.63 (–103.03, –82.23)[a]	–48.59 (–58.84, –38.34)	–82.71 (–95.80, –69.62)[c]
AM stiffness severity	–3.37 (–3.59, –3.15)[a,b]	–1.83 (–2.05, –1.61)	–2.86 (–3.14, –2.57)[c]
FACIT-F	8.95 (7.98, 9.93)[a,b]	4.81 (3.85, 5.77)	7.44 (6.25, 8.64)[c]
RA-WIS (among employed patients)	–5.16 (–6.10, –4.23)[a]	–1.98 (–2.87, –1.10)	–4.45 (–5.61, –3.28)[c]
SF-36 Summary Scores			
PCS	7.89 (7.11, 8.68)[a,b]	3.56 (2.79, 4.33)	6.27 (5.31, 7.23)[c]
MCS	6.39 (5.50, 7.29)[a]	3.67 (2.78, 4.55)	5.39 (4.29, 6.49)[c]
SF-36 domains			
Physical functioning	7.31 (6.45, 8.18)[a,b]	3.59 (2.74, 4.45)	6.18 (5.12, 7.25)[c]
Role-physical	6.85 (6.06, 7.65)[a,b]	3.63 (2.85, 4.41)	5.16 (4.19, 6.14)[c]
Bodily pain	9.85 (9.02, 10.68)[a,b]	4.61 (3.80, 5.43)	8.03 (7.02, 9.05)[c]
General health	7.27 (6.49, 8.05)[a,b]	3.12 (2.35, 3.89)	5.67 (4.72, 6.63)[c]
Vitality	8.24 (7.38, 9.10)[a,b]	4.26 (3.41, 5.10)	6.79 (5.74, 7.84)[c]
Social functioning	7.19 (6.32, 8.06)[a,b]	3.40 (2.54, 4.25)	5.75 (4.69, 6.82)[c]
Role-emotional	6.24 (5.31, 7.18)[a]	3.60 (2.68, 4.53)	5.21 (4.05, 6.36)[c]
Mental health	6.99 (6.11, 7.87)[a]	4.02 (3.15, 4.88)	5.91 (4.83, 6.99)[c]
Week 2			
Pain VAS	–17.57 (–19.53, –15.60)[a]	–7.10 (–9.04, –5.17)	–17.94 (–20.41, –15.46)[c]
AM stiffness duration	–49.09 (–61.46, –36.71)[a]	–16.73 (–28.98, –4.47)	–41.79 (–57.98, –25.61)[c]
AM stiffness severity	–1.62 (–1.82, –1.42)[a]	–0.65 (–0.85, –0.45)	–1.65 (–1.90, –1.39)[c]

[a]$P < 0.05$ for UPA *vs* PBO. LSM change from baseline P values represents statistical significance between groups. [b]$P < 0.05$ for UPA *vs* ADA. LSM change from baseline P values represents statistical significance between groups. [c]$P < 0.05$ for ADA *vs* PBO. LSM change from baseline P values represents statistical significance between groups. ADA: adalimumab; AM: morning; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ-DI: HAQ-Disability Index; LSM: least squares mean; MCS: Mental Component Summary; PBO: placebo; PCS: Physical Component Summary; PRO: patient-reported outcome; PtGA: Patient's Global Assessment of Disease Activity; RA-WIS: Work Instability Scale for RA; SF-36: 36-Item Short Form Health Survey; UPAD: upadacitinib; VAS: visual analogue scale.

(tofa) was non-inferior to ADA by ACR50 at 6 months and baricitinib (bari) 4 mg superior to ADA by ACR20 and significantly better than ADA in HAQ-DI at week 12 [34, 37, 39]. A significantly greater reduction in pain was also reported in bari- *vs* ADA-treated patients [40]. In ORAL Strategy, similar percentages of patients reported improvements $\geq$ MCID in pain with tofa + MTX and ADA + MTX (75% *vs* 76%) [36]. Additionally, rapid clinically meaningful improvements in pain and AM stiffness occurred as early as week 2 with UPA and ADA. In ORAL Strategy, clinically meaningful improvements in pain were reported as early as 6 weeks with tofa + MTX and ADA + MTX, and in pain and PtGA in ORAL Solo as early as week 2 with tofa monotherapy [36, 41]. In RA-BEAM, significantly greater improvements in the non-ranked end point, worst joint pain for bari (4 mg)- *vs* ADA-treated patients were observed as early as week 2 [37]. However, whether UPA is equivalent to, worse than, or superior to tofa and/or bari, can only be assessed in a well-controlled, randomized, properly powered head-to-head clinical trial.

Key domains of RA disease activity that must improve from patients' perspectives include fatigue, pain, and independence (i.e. restoration of social and professional daily activities) [42]. Fatigue is associated with disease burden and negative impacts on HRQOL [3, 4, 43, 44], including reductions in patients' ability to perform daily activities and maintain employment [45, 46]. The importance of treating fatigue is evident, as fatigue was recently included in the UPA RA treatment label for the first time [11]. In the current study, the percentages of patients maintaining improvements in fatigue and work instability through 48 weeks were greater in patients treated with UPA *vs* ADA. These results indicate that treatment with UPA improves the key symptoms of fatigue and may improve patients' ability to remain gainfully employed.

Consistent with published primary efficacy results from SELECT-COMPARE [13, 21], improvements in PROs were seen as early as 2 weeks after treatment initiation with UPA. Greater proportions of UPA- *vs* ADA-treated patients reported scores $\geq$ normative values in

Table 3 LSM changes from baseline at weeks 26 and 48

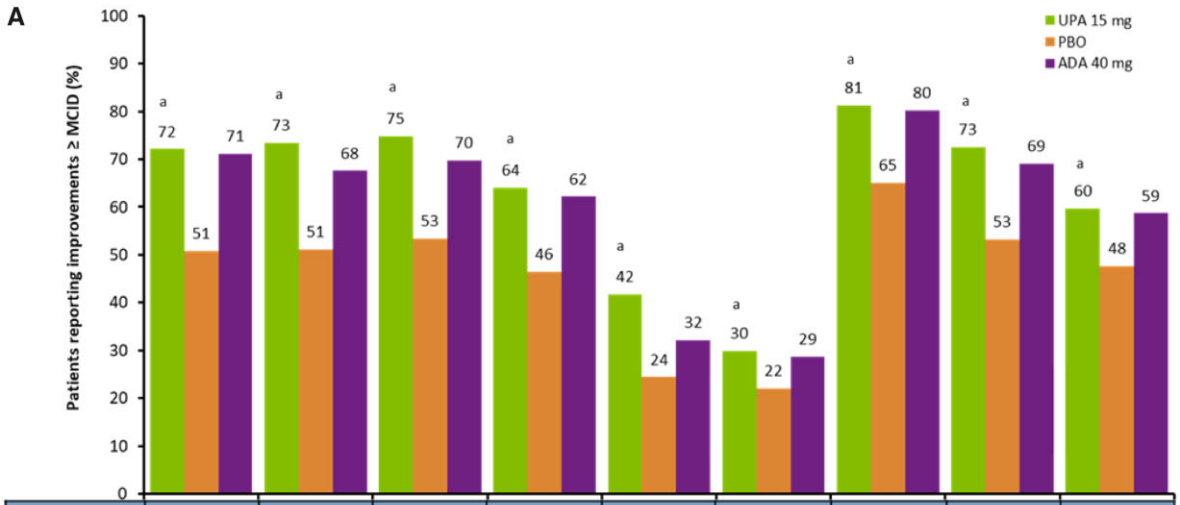
PRO	UPAD 15 mg		ADA 40 mg	
	n	LSM mean change (95% CI)	*n*	LSM mean change (95% CI)
Week 26				
PtGA	600	–35.71 (–38.37, –33.05)[a]	287	–29.99 (–33.32, –26.66)
Pain VAS	600	–36.75 (–39.42, –34.08)[a]	287	–31.87 (–35.20, –28.54)
HAQ–DI	599	–0.69 (–0.76, –0.63)[a]	287	–0.57 (–0.65, –0.50)
AM stiffness duration	603	–100.21 (–111.12, –89.30)	285	–91.30 (–105.00, –77.60)
AM stiffness severity	602	–3.87 (–4.14, –3.61)[a]	284	–3.38 (–3.71, –3.05)
FACIT-F	596	9.67 (8.66, 10.68)[a]	285	8.24 (6.98, 9.50)
RA-WIS (among employed patients)	227	–5.89 (–6.94, –4.85)	97	–4.62 (–5.96, –3.28)
PCS	598	9.51 (8.65, 10.37)[a]	286	7.84 (6.77, 8.92)
MCS	598	6.17 (5.22, 7.13)	286	5.48 (4.29, 6.67)
SF-36 domains				
Physical functioning	598	8.81 (7.87, 9.74)[a]	286	7.49 (6.32, 8.66)
Role-physical	598	8.31 (7.46, 9.16)[a]	286	6.30 (5.24, 7.36)
Bodily pain	598	11.26 (10.35, 12.17)	286	10.31 (9.18, 11.45)
General health	598	7.82 (7.00, 8.65)[a]	286	6.11 (5.08, 7.14)
Vitality	598	8.65 (7.74, 9.56)[a]	286	6.72 (5.59, 7.85)
Social functioning	598	7.47 (6.54, 8.41)	286	6.85 (5.67, 8.02)
Role-emotional	598	7.08 (6.10, 8.05)	286	6.30 (5.09, 7.52)
Mental health	598	6.81 (5.86, 7.75)	286	5.90 (4.72, 7.09)
Week 48				
PtGA	574	–35.33 (–38.58, –32.09)[a]	272	–30.17 (–34.01, –26.34)
Pain VAS	574	–36.68 (–39.89, –33.47)[a]	272	–32.07 (–35.86, –28.28)
HAQ–DI	573	–0.73 (–0.81, –0.65)[a]	272	–0.60 (–0.69, –0.51)
AM stiffness duration	579	–101.65 (–113.12, –90.19)	270	–95.50 (–109.08, –81.92)
AM stiffness severity	577	–3.82 (–4.12, –3.52)	269	–3.51 (–3.86, –3.15)
FACIT-F	568	10.23 (9.06, 11.41)[a]	274	8.93 (7.57, 10.30)
RA-WIS (among employed patients)	206	–5.26 (–6.78, –3.75)	95	–4.77 (–6.47, –3.07)
PCS	573	9.75 (8.71, 10.80)[a]	276	8.06 (6.82, 9.29)
MCS	573	6.31 (5.21, 7.41)	276	5.97 (4.68, 7.26)
SF-36 domains				
Physical functioning	573	9.46 (8.35, 10.57)[a]	276	7.79 (6.48, 9.10)
Role-physical	573	8.34 (7.31, 9.37)[a]	276	6.83 (5.62, 8.04)
Bodily pain	573	11.31 (10.21, 12.41)[a]	276	9.96 (8.67, 11.26)
General health	573	7.79 (6.78, 8.79)[a]	276	6.62 (5.44, 7.81)
Vitality	573	9.07 (7.97, 10.18)	276	7.84 (6.54, 9.14)
Social functioning	573	7.60 (6.50, 8.71)	276	6.83 (5.53, 8.13)
Role-emotional	573	6.94 (5.81, 8.07)	276	6.46 (5.13, 7.80)
Mental health	573	7.28 (6.19, 8.38)	276	6.50 (5.21, 7.79)

[a]$P < 0.05$ for UPA *vs* ADA. LSM change from baseline *P* values represents statistical significance between groups. ADA: adalimumab; AM: morning; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ-DI: HAQ-Disability Index; LSM: least squares mean; MCS: Mental Component Summary; PBO: placebo; PCS: Physical Component Summary; PRO: patient-reported outcome; PtGA: Patient's Global Assessment of Disease Activity; RA-WIS: Work Instability Scale for RA; SF-36: 36-Item Short Form Health Survey; UPAD: upadacitinib; VAS: visual analogue scale.

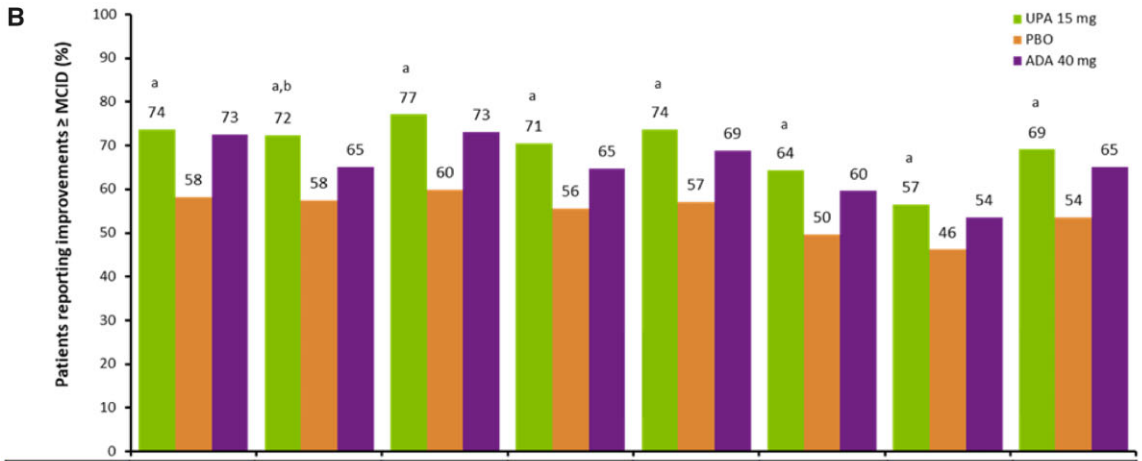
physical functioning, bodily pain, and vitality at week 12. The percentage of patients reporting clinically meaningful improvements was similar between patients treated with UPA and ADA at week 12; however, a greater percentage of patients treated with UPA *vs* ADA maintained those improvements at weeks 26 and 48, including in key domains of PtGA, pain, physical functioning, AM stiffness severity and duration, fatigue, and SF-36 PCS and MCS. The improvements in PROs support the primary results from SELECT-COMPARE, which demonstrated the superiority of UPAD to ADA in key measures of pain and physical function [21].

There are several strengths in this analysis. Data were collected during a phase 3 RCT, which ensures patients were closely followed for a significant period and PROs were consistently measured. The PBO- and active comparator-controlled double-blind randomized trial design implemented for this trial mitigates bias that may arise due to unobservable differences between treatment groups. The blinded design also mitigates biased reporting from the patient's perspective. The validated

FIG. 2 Patients reporting PRO score improvements ≥ MCID at week 12



	HAQ-DI (n); NNT	PtGA (n); NNT	Pain VAS (n); NNT	FACIT-F (n); NNT	RA-WIS (n); NNT	AM stiffness duration (n); NNT	AM stiffness severity (n); NNT	SF-36 PCS (n); NNT	SF-36 MCS (n); NNT
UPA 15 mg	(465); **4.7**	(474); **4.5**	(483); **4.7**	(413); **5.7**	(120); **5.8**	(194); **12.7**	(526); **6.1**	(469); **5.2**	(386); **8.4**
PBO	(330)	(332)	(347)	(299)	(64)	(144)	(424)	(345)	(309)
ADA 40 mg	(231); **4.9**	(219); **6.1**	(227); **6.1**	(202); **6.3**	(42); **13.1**	(93); **15.1**	(260); **6.6**	(226); **6.3**	(192); **9.1**

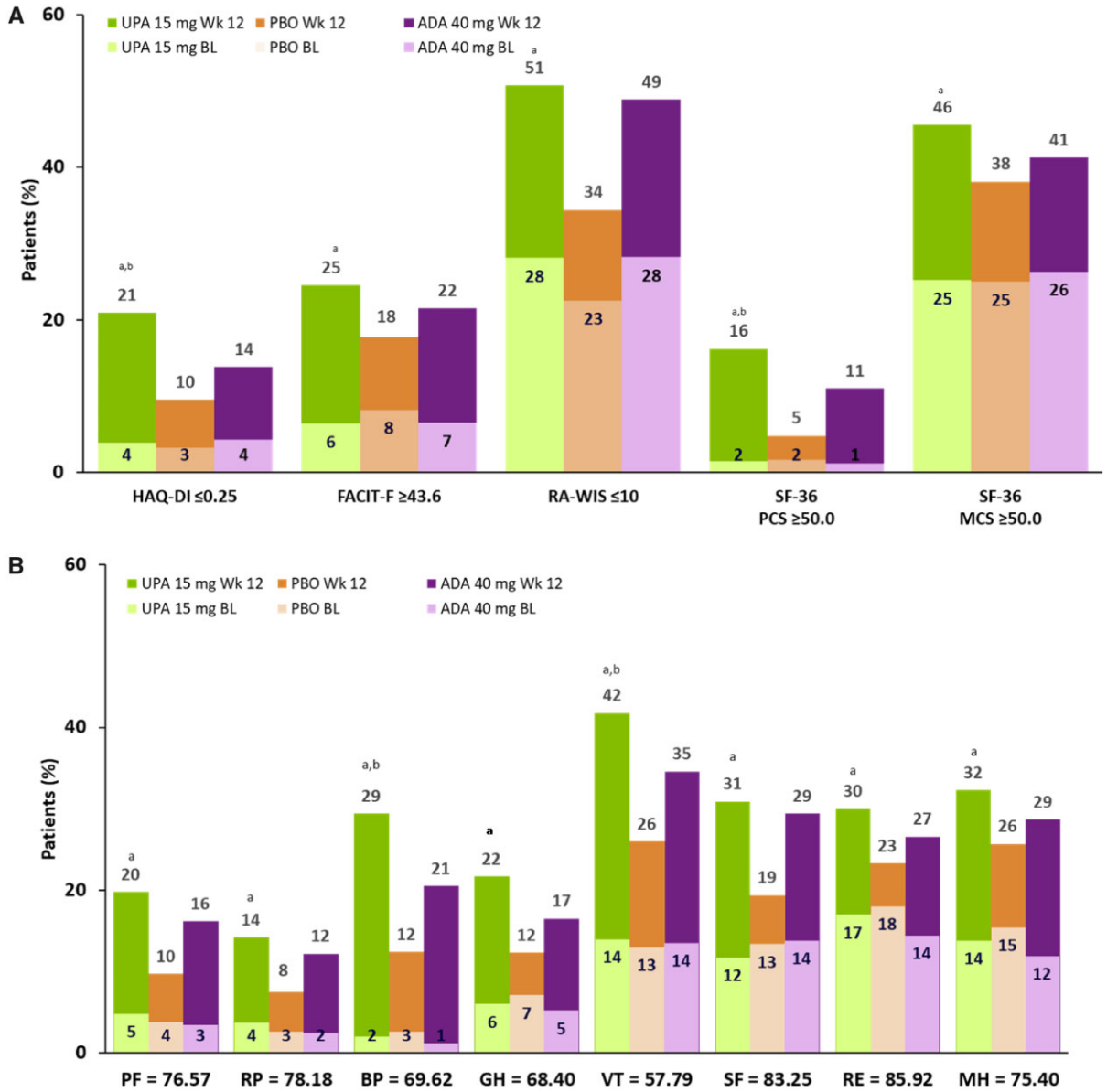


	PF (n); NNT	RP (n); NNT	BP (n); NNT	GH (n); NNT	VT (n); NNT	SF (n); NNT	RE (n); NNT	MH (n); NNT
UPA 15 mg	(479); **6.5**	(470); **6.7**	(501); **5.8**	(458); 6.7	(479); **6.0**	(418); **6.8**	(368); **9.6**	(449); **6.5**
PBO	(379)	(374)	(390)	(362)	(372)	(323)	(301)	(349)
ADA 40 mg	(237); **7.0**	(213); **13.0**	(239); **7.6**	(212); **10.8**	(225); **8.6**	(195); **10.0**	(175); **13.7**	(213); **8.7**

[a]*P*<0.05 for UPA vs PBO; [b]*P*<0.05 for UPA vs ADA.

[a]$P < 0.05$ for UPA vs PBO; [b]$P < 0.05$ for UPA vs ADA.ADA, adalimumab; AM, morning; BP, bodily pain; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; GH, general health; HAQ-DI, HAQ-Disability Index; MCID, minimal clinically important difference; MCS, Mental Component Summary; MH, mental health; NNT, number needed to treat; PBO, placebo; PCS, Physical Component Summary; PF, physical functioning; PRO, patient-reported outcome; PtGA, Patient's Global Assessment of Disease Activity; RA-WIS; Work Instability Scale for RA; RE, role-emotional; RP, role-physical; SF, social functioning; SF-36, 36-Item Short-Form Health Survey; UPAD, upadacitinib; VAS, visual analog scale; VT, vitality.

FIG. 3 Patients reporting PRO scores ≥ normative values at baseline and week 12



[a]$P < 0.01$ for UPAD vs PBO; [b]$P < 0.05$ for UPA vs ADA. ADA, adalimumab; BL, baseline; BP, bodily pain; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; GH, general health; HAQ-DI, HAQ-Disability Index; MCS, Mental Component Summary; MH, mental health; PBO, placebo; PCS, Physical Component Summary; PF, physical functioning; PRO, patient-reported outcome; RA-WIS, Work Instability Scale for RA; RE, role-emotional; RP, role-physical; SF, social functioning; SF-36, 36-Item Short-Form Health Survey; UPA, upadacitinib; VT, vitality.

PROs used in this analysis measure various aspects of the patient's experience, such as pain, fatigue, impact on daily activities, and mental health. Use of MCID definitions and normative values to assess responses make these data interpretable in terms of clinically relevant improvements from the patient's perspective.

These analyses also had limitations. The study population evaluated in the SELECT-COMPARE trial had active and severe RA as it was enriched to assess radiographic progression by including patients who had 1–3 erosions at study entry. Thus, outcomes obtained in this population may not be applicable to other RA populations. In addition, high proportions of patients in the PBO group reported improvements ≥ MCID at week 12. Reasons for an elevated response in the PBO group are not clear; however, an elevated PBO response has been observed in recent clinical trials in RA [19, 20, 47]. PROs were collected at fixed visits; therefore, responses can only be assessed at these predefined visits and not during time intervals between visits. Generalizability of these

results may be limited, as patients enrolled in RCTs are selected based on certain exclusion/inclusion criteria and may differ from patients in the general RA population. Methods used to impute missing data (NRI) assume that missing PRO scores are associated with non-response, and since patients were able to switch rescue therapy, may underestimate the true rate of response. The present analysis examined PROs over 48 weeks; it is important to see whether these changes remain stable, continue to improve, or disappear over time in patients with a chronic disease.

In summary, among patients with active RA, treatment with UPA 15 mg daily with background MTX therapy resulted in statistically significant and clinically meaningful improvements in PROs compared with PBO. Treatment with UPA resulted in reductions in pain and severity of AM stiffness reported as early as 2 weeks post treatment initiation and maintained over 48 weeks. Overall, PRO improvements with UPA treatment met or exceeded treatment with ADA, especially in key domains of pain, function, and vitality/fatigue; this was most evident in the greater proportions of UPA- *vs* ADA-treated patients reporting scores $\geq$ normative values. UPAD may offer an effective treatment option for MTX-IR patients with RA with better effects than a mainstay of current standard of care, ADA.

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Data availability statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. Access is provided to anonymized, patient and trial-level data (analysis data sets), as well as other information (e.g. protocols and Clinical Study Reports) from AbbVie-sponsored Phase II–IV global interventional clinical trials conducted in patients (completed as of May 2004, for products and indications approved in either the USA or the European Union), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

Access to this clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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