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Achievement of treatment targets and maintenance of response with upadacitinib in patients with moderate-to-severe rheumatoid arthritis in real-world practice: 1-year outcomes from the UPHOLD observational study

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Abstract

Background Upadacitinib (UPA), an oral Janus kinase inhibitor, has shown efficacy with an acceptable safety profile in rheumatoid arthritis (RA) clinical trials.

Objective To assess the real-world effectiveness and safety of UPA in adults with moderate-to-severe RA in the UPHOLD observational study.

Methods Co-primary endpoints were: (i) proportion of patients achieving disease activity score in 28 joints using C-reactive protein (DAS28[CRP]) remission (< 2.6) at 6 months; and (ii) proportion of those patients maintaining remission at 12 months. Additional analyses included proportions of patients achieving and maintaining DAS28(CRP) low disease activity (LDA; ≤ 3.2), other composite measures of disease activity, and subgroup analyses by therapy strategy and prior treatment. Treatment-emergent adverse events (TEAEs) in the full analysis set (FAS; patients receiving ≥ 1 UPA dose) were reported through August 10, 2023. Co-primary and selected secondary endpoints were analyzed by modified non-responder imputation (mNRI) in modified (m)FAS1 (FAS patients who completed 6 months of treatment and had DAS28[CRP] data available, and those who discontinued before 6 months) and mFAS2 (mFAS1 patients who achieved remission at 6 months, completed 12 months of treatment, and had DAS28[CRP] data available, and those who discontinued between 6 and 12 months); and as observed (AO) in patients with non-missing data.

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Results Of 1719 participants, 1717 were enrolled; 1701 comprised the FAS. Overall, 400/1719 (23.3%) patients discontinued before 12 months. Of mFAS1 patients, 499 (mNRI: 499/1074 [46.5%]; AO: 499/902 [55.3%]) achieved DAS28(CRP) remission at 6 months; of mFAS2 patients, 269 (mNRI: 269/340 [79.1%]; AO: 269/317 [84.9%]) maintained remission at 12 months. DAS28(CRP) remission or LDA rates were consistent regardless of whether UPA was initiated and maintained as monotherapy or combination therapy. Similar responses were observed across prior treatment subgroups. Among selected TEAEs of special interest, herpes zoster and serious infection occurred at 3.12 and 2.62 events/100 patient-years, respectively. No new safety signals were identified.

Conclusions UPA demonstrated real-world effectiveness in moderate-to-severe RA, with approximately half of patients achieving DAS28(CRP) remission at 6 months and most maintaining remission through 12 months. The real-world benefit–risk profile of UPA remains favorable and is consistent with phase 3 clinical trial data.

Trial registration NCT04497597

Keywords Effectiveness, Real-world, Rheumatoid arthritis, Safety, Upadacitinib

Introduction

Rheumatoid arthritis (RA), a chronic, systemic, inflammatory disease that primarily affects the joints, can be associated with significant disability, pain, and reduced quality of life. Treatment for RA is aimed at limiting and controlling disease activity, as prolonged high levels of disease activity increase the risk of progressive joint damage, irreversible functional impairment, and even mortality [1–3]. Despite advances in the management of RA, only 20–40% of patients treated with biologic disease-modifying antirheumatic drugs (bDMARDs) and/or conventional synthetic (cs)DMARDs, such as methotrexate (MTX), achieve sustained clinical remission, and many patients remain suboptimally managed [3–8]. International guidelines encourage a treat-to-target approach, with remission or low disease activity (LDA) as the optimal targets of therapy [9, 10].

A number of Janus kinase (JAK) inhibitors are now approved for the treatment of RA. Treatment with these agents in appropriate patients is recommended by current guidelines and may enable more patients to achieve disease control targets [2, 9, 11–13].

Upadacitinib (UPA), an oral, selective, and reversible JAK inhibitor, has demonstrated efficacy and safety, alone or in combination with csDMARDs, across a range of patient populations and rheumatologic/immune diseases, including in the phase 3 SELECT RA clinical trial program [12, 14–21]. Although the efficacy of UPA in achieving remission and LDA has been extensively demonstrated in randomized controlled trials (RCTs), data on whether the response rates observed in RCTs can be achieved and maintained in a real-world population are limited. Such data are important, as there may be differences in patient characteristics between clinical trials and clinical practice, and the efficacy seen in clinical trials may not accurately reflect real-world effectiveness [22]. Further characterization of UPA use (with or without background MTX), evaluation of its effectiveness, and long-term maintenance of effect in real-world populations, including those with previous exposure and/or inadequate response/intolerance to bDMARDs or other targeted synthetic (ts)DMARDs, will be of considerable value for treatment decision-making in clinical practice.

The aim of the present interim analysis was to assess the effectiveness and safety of UPA, including achievement and maintenance of defined stringent disease control targets, as well as outcomes with different treatment strategies and patient characteristics, after 1 year of therapy in a real-world setting.

Methods

Study design and patient population

Upadacitinib treatment patterns, achievement of treatment targets and maintenance of response in moderate-to-severe rheumatoid arthritis patients in real-world practice (UPHOLD; NCT04497597) is a non-interventional, prospective, open label, multi-country, multi-center, post-marketing observational cohort study aimed at assessing the achievement and maintenance of remission with UPA over 12 months following initiation of therapy. Primary, interim analyses were performed at 6 and 12 months, with a total follow-up time of up to 24 months (Supplementary Fig. 1). This 12-month interim analysis reports data between the start date of October 16, 2020 and data cutoff of August 10, 2023 (including all patients within the 12-month visit window).

Adult patients (aged ≥ 18 years) with moderate-to-severe RA, in whom the treating physician decided to initiate treatment with UPA as per label [23], prior to and independent of study enrollment, were considered as eligible. The patients were treated with UPA, either in combination with csDMARDs or as monotherapy. The use of concomitant antirheumatic treatments, such as corticosteroids, non-steroidal anti-inflammatory drugs, and other analgesics, was at the discretion of the treating physician. Prior use of tsDMARDs and/or bDMARDs was permitted. Patients were excluded if they had

participated in a clinical trial of an investigational drug concurrently or within the last 30 days, had received prior treatment with UPA, or could not be treated with UPA according to the locally approved label.

The present study complied with the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) statement for observational studies [24]. The study was conducted according to the International Council for Harmonisation guidelines, local regulations and guidelines governing clinical study conduct, and the Declaration of Helsinki. All patients provided written informed consent, and the study protocol and consent forms were approved by an institutional review board or independent ethics committee at each study site.

Effectiveness

The co-primary efficacy endpoints were: (i) the proportion of patients receiving UPA who achieved disease activity score in 28 joints using C-reactive protein (DAS28[CRP]) of < 2.6 (defined in this study as DAS28[CRP] remission) at 6 months; and (ii) the proportion of patients achieving DAS28(CRP) remission at 6 months who continued to receive UPA and maintained remission (or had no more than a 0.6-point increase in DAS28[CRP]) at 12 months. Secondary and exploratory effectiveness endpoints included the proportion of patients achieving DAS28(CRP) ≤ 3.2 (defined in this study as DAS28[CRP] LDA) at 6 months; the proportion of patients achieving DAS28(CRP) LDA at 6 months who maintained LDA (or had no more than a 0.6-point increase in their DAS28[CRP]) at 12 months; disease activity status by analysis visit, defined as the proportion of patients with remission, LDA, moderate disease activity (MDA), and high disease activity (HDA) per DAS28(CRP), clinical disease activity index (CDAI), and simplified disease activity index (SDAI) cutoff values; and proportion of patients among those achieving remission/LDA at 6 months who maintained remission/LDA at 12 months (or had no more than a 0.6-point increase in DAS28[CRP]) while remaining on their initial treatment strategy (UPA monotherapy or combined with csDMARDs).

Subgroup analyses by prior treatment exposure were also performed for selected effectiveness endpoints. The subgroups were defined as follows: ts/bDMARD-naïve: no prior use of tumor necrosis factor (TNF) inhibitors (TNFis), other bDMARDs, or tsDMARDs at baseline; ts/bDMARD-experienced: prior use of any tsDMARD (JAK inhibitor) or bDMARD (TNFi or other bDMARD); TNFi-experienced: prior use of only a TNFi (infliximab, adalimumab, etanercept, golimumab, certolizumab); and tsDMARD-experienced: prior use of a tsDMARD (JAK inhibitor).

Safety

All treatment-emergent adverse events (TEAEs; AEs occurring after the first dose of study drug and up to 30 days after the last dose of study drug) by the cutoff date of August 10, 2023 were recorded, including serious TEAEs and selected TEAEs of special interest, including herpes zoster, serious infection, hepatic disorder, malignancy, major adverse cardiovascular events (MACE), and thrombotic events. Laboratory test results were categorized as either normal or abnormal, and abnormal values were categorized as clinically significant or non-significant. Clinical significance was determined by the investigator and was defined as a newly observed unfavorable and unintended laboratory abnormality.

Statistical analysis

Baseline interim analyses were performed in the enrolled analysis set (EAS; all patients who signed the informed consent form and met all eligibility criteria for the study). All safety analyses and baseline effectiveness evaluations were performed in the full analysis set (FAS; all patients who received at least one dose of UPA during the study). The first co-primary endpoint was evaluated in a modified (m)FAS (mFAS1; all patients within the FAS who completed 6 months of treatment with UPA and had DAS28[CRP] data available at the 6-month visit, or who discontinued the study prematurely before 6 months). The second co-primary endpoint was evaluated in the mFAS2 (all patients within the mFAS1 who achieved remission at 6 months, completed 12 months of treatment with UPA, and had DAS28[CRP] data available at the 12-month visit, or who discontinued the study prematurely between 6 and 12 months) (Fig. 1). Similar mFASs were adopted for the analysis of secondary and exploratory endpoints, depending on the timepoint and the outcome in question.

For the co-primary and selected secondary endpoints, modified non-responder imputation (mNRI; discontinuations for any reason before pre-specified timepoints were treated as non-responders) was employed using the mFAS1 and mFAS2. Effectiveness data were also analyzed as observed (AO) using pre-specified analysis sets without imputation of missing data.

Safety data were assessed for all patients in the FAS. All AEs were investigator-reported and coded using the Medical Dictionary for Regulatory Activities (version 26.0) preferred terminology [25]. TEAEs were recorded up to the data cutoff date of August 10, 2023 and reported as exposure-adjusted event rates (EAERs; events per 100 patient-years [E/100 PY]) and exposure-adjusted incidence rates (EAIRs; n/100 PY). Laboratory parameters were summarized using descriptive statistics and reported as the number of patients with clinically significantly abnormal laboratory values.

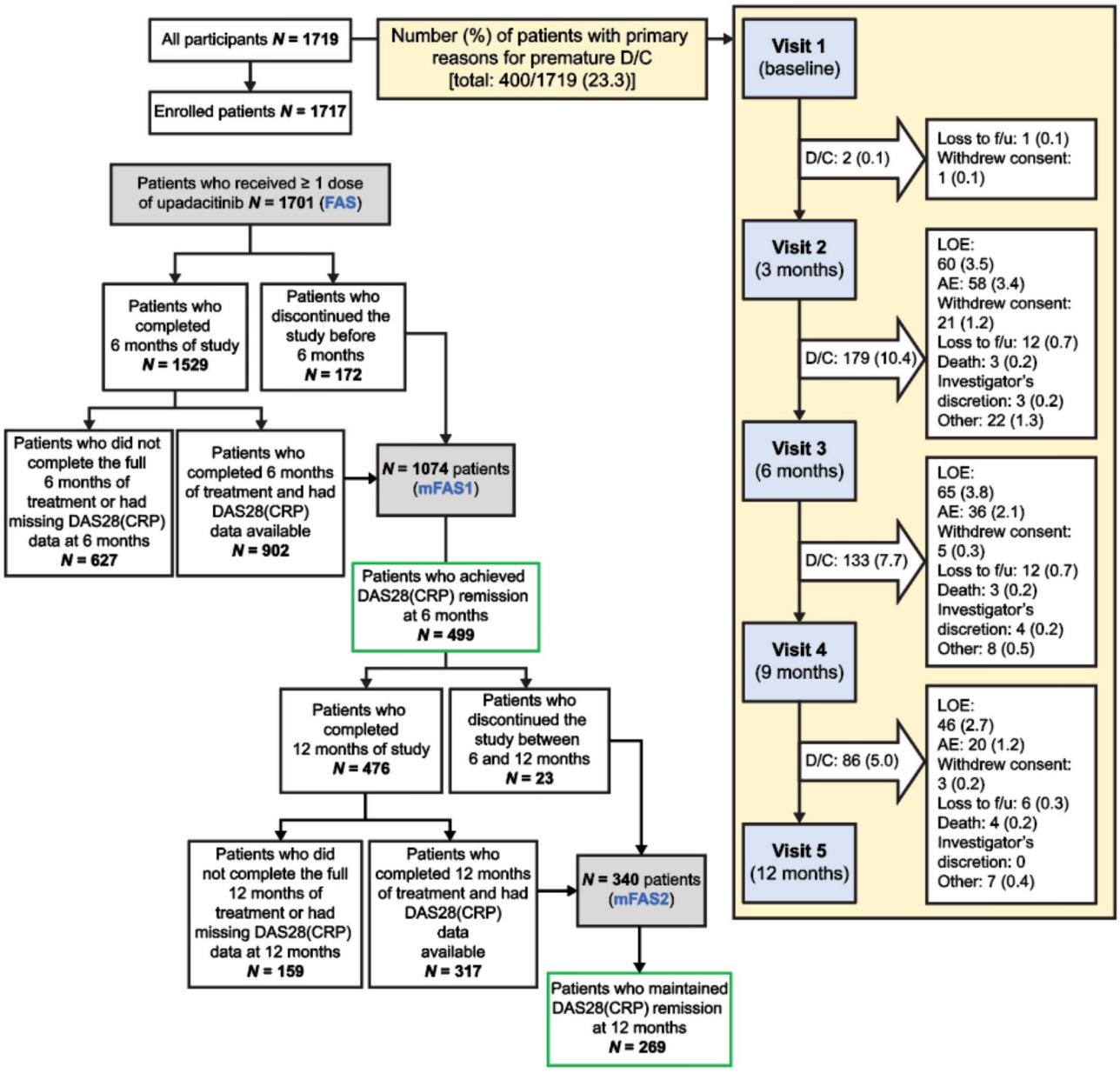


Fig. 1 Patient disposition

Note: Some patients may have discontinued the study treatment but remained in the study and completed the 6- or 12-month follow-up for baseline and safety assessments. Premature discontinuation refers to patients who discontinued the study before the specified timepoint

AE adverse event, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *D/C* discontinuation, *FAS* full analysis set, *f/u* follow-up, *LOE* lack of efficacy, *mFAS* modified FAS

Sample size calculations assumed that 37% of enrolled patients would achieve DAS28(CRP) < 2.6 at 6 months and, of these, 80% would maintain this response at 12 months. Assuming a 20% dropout rate from baseline to month 6 and a 15% dropout rate from month 6 to month 12, a sample size of 1660 was considered as appropriate to provide a 95% confidence interval (CI) of half-width equal to 2.6% (CI: 37% ± 2.6%) and 3.8% (CI: 80% ± 3.8%) for the first and second co-primary endpoints, respectively.

Results

Patient disposition and characteristics

Of the 1719 participants, 1717 were included in the EAS and 1701 were included in the FAS. Of the 1719 participants, 400 (23.3%) prematurely discontinued; 171 (9.9%) discontinued with a primary reason of lack of efficacy, and 114 (6.6%) with a primary reason of AEs (Fig. 1).

Patient demographics and disease characteristics at baseline are summarized in Table 1. In summary, the mean age of the patients was 56.9 years, 79.9% of the

Table 1 Patient demographics and disease characteristics at UPA initiation

Parameter	FAS (*N* = 1701)
Age (years), mean (SD)	56.9 (12.4)
Sex, female, *n* (%)	1359 (79.9)
Race, *n* (%)	
White	1184 (69.6)
Asian	85 (5.0)
Arabic	75 (4.4)
Other[a]	40 (2.4)
BMI (kg/m^2), mean (SD)[b]	26.9 (5.5)
RA duration from diagnosis, years, mean (SD)[c]	10.1 (9.1)
Smoking status, *n* (%)[d]	
Current	316 (18.6)
Former	354 (20.8)
Never	1028 (60.5)
Vaccination status, *n* (%)	
SARS-CoV-2	836 (49.1)
BCG[e]	616 (37.5)
Streptococcus pneumoniae	353 (20.8)
Seasonal influenza	350 (20.6)
Varicella zoster	99 (5.8)
Erosions on X-ray, *n* (%)	710 (41.7)
RF and/or ACPA positive, *n* (%)[f]	545 (77.6)
Disease activity, mean (SD)	
Swollen joint count	5.7 (5.20)
Tender joint count	8.1 (6.4)
DAS28(CRP)	4.6 (1.2)
CDAI	26.5 (12.6)
SDAI	28.2 (14.1)
Presence of ≥ 1 cardiovascular risk factor, *n* (%)[g]	1058 (62.2)
Patients initiating UPA in combination with csDMARDs, *n* (%)	878 (51.6)
Any concomitant medication, *n* (%)[h]	1312 (77.1)
Corticosteroids[i]	734 (43.2)
NSAIDs	351 (20.6)
Any prior therapies[j], *n* (%)[k]	1523 (90.0)
≥ 1 csDMARD[l]	1203 (79.0)
≥ 1 biologic DMARD[l]	979 (64.3)
≥ 1 targeted synthetic DMARD[l]	276 (18.1)

[a]Including Black or African American, Indian, American Indian, or Alaska Native, and multiple. [b]Of 1646 patients with available data, 43 (2.6%) were underweight (BMI < 18.5), 617 (37.5%) were normoweight (BMI 18.5–24.9), 577 (35.1%) were overweight (BMI 25.0–29.9), and 409 (24.8%) were obese (BMI ≥ 30). [c]*n* = 1687. [d]*n* = 1698. [e]*n* = 1644. [f]Patients with ≥ 1 positive result for either RF or ACPA; *n* = 702. [g]History of hypertension, diabetes mellitus, high-density lipoprotein cholesterol ≤ 40 mg/dL in ≥ 1 measurement before enrollment, low-density lipoprotein cholesterol ≥ 130 mg/dL in ≥ 1 measurement before enrollment, and current/former tobacco/nicotine use. [h]Methotrexate: *n* = 706 (41.5%) patients. [i]The mean equivalent dose of prednisone during the first week was 8 mg/day (*n* = 461), and 393 patients (85.2%) received ≥ 5 mg/day. Not ongoing. [k]*n* = 1692. [l]Patients may be counted multiple times between type of RA therapies

ACPA anti-citrullinated protein antibody, *BCG* bacillus Calmette-Guérin, *BMI* body mass index, *CDAI* clinical disease activity index, *csDMARD* conventional synthetic DMARD, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *DMARD* disease-modifying antirheumatic drug, *FAS* full analysis set, *NSAID* non-steroidal anti-inflammatory drug, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *SD* standard deviation, *SDAI* simplified disease activity index, *UPA* upadacitinib

patients were female, and the mean disease duration was 10.1 years. UPA was initiated in 48.4% of patients in the FAS as monotherapy; the remaining patients received UPA in combination with csDMARDs. Of 1523 patients in the FAS receiving prior RA therapy, 64.3% had received ≥ 1 bDMARD and 18.1% had received ≥ 1 tsDMARD, while 43.2% were receiving concomitant corticosteroids (Table 1). A total of 162 (9.5%) and 131 (7.7%) among FAS patients had received prior therapy with tofacitinib and baricitinib, respectively.

Effectiveness

Disease activity outcomes

The co-primary endpoints were assessed in mFAS1 and mFAS2 (Fig. 1). A total of 499 patients in mFAS1 (mNRI: 499/1074 [46.5%]; AO: 499/902 [55.3%]) achieved the first co-primary endpoint of DAS28(CRP) remission

(< 2.6) at 6 months. A total of 269 patients in mFAS2 (mNRI: 269/340 [79.1%]; AO: 269/317 [84.9%]) achieved the second co-primary endpoint of maintenance of DAS28(CRP) remission at 12 months (Fig. 2).

The achievement and maintenance of DAS28(CRP) LDA (≤ 3.2) followed a similar trend: LDA was achieved by 638 (mNRI: 638/1074 [59.4%]; AO: 638/902 [70.7%]) mFAS1 patients at 6 months and was maintained by 361 (mNRI: 361/436 [82.8%]; AO: 361/395 [91.4%]) patients at the 12-month visit (Fig. 2).

The proportions of patients who met the criteria for remission according to DAS28(CRP) (< 2.6), CDAI (≤ 2.8), or SDAI (≤ 3.3) cutoffs increased from 5.3%, 0.6%, and 0.6% at baseline to 59.8%, 28.0%, and 28.3% at 12 months, respectively. The proportions of patients who met the criteria for LDA according to DAS28(CRP) (≤ 3.2), CDAI (≤ 10.0), or SDAI (≤ 11.0) cutoffs increased from 13.0%, 5.6%, and 5.9% at baseline to 77.2%, 68.5%, and 69.7% at 12 months, respectively (AO data; Fig. 3 and Supplementary Fig. 2). The proportions of patients meeting the criteria for MDA and HDA per respective DAS28(CRP), CDAI, and SDAI cutoff values at baseline, 6 months, and 12 months (AO data) are presented in Fig. 3.

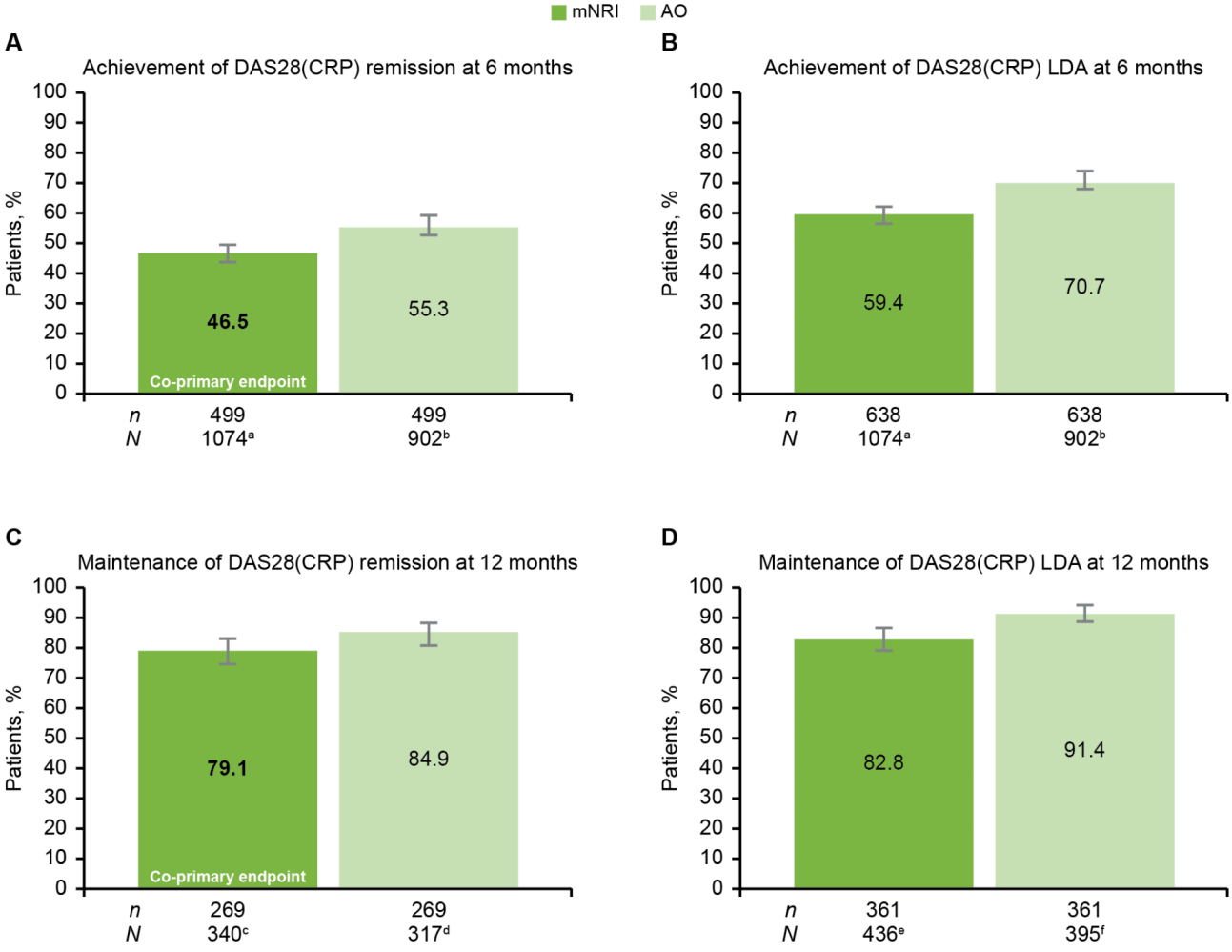
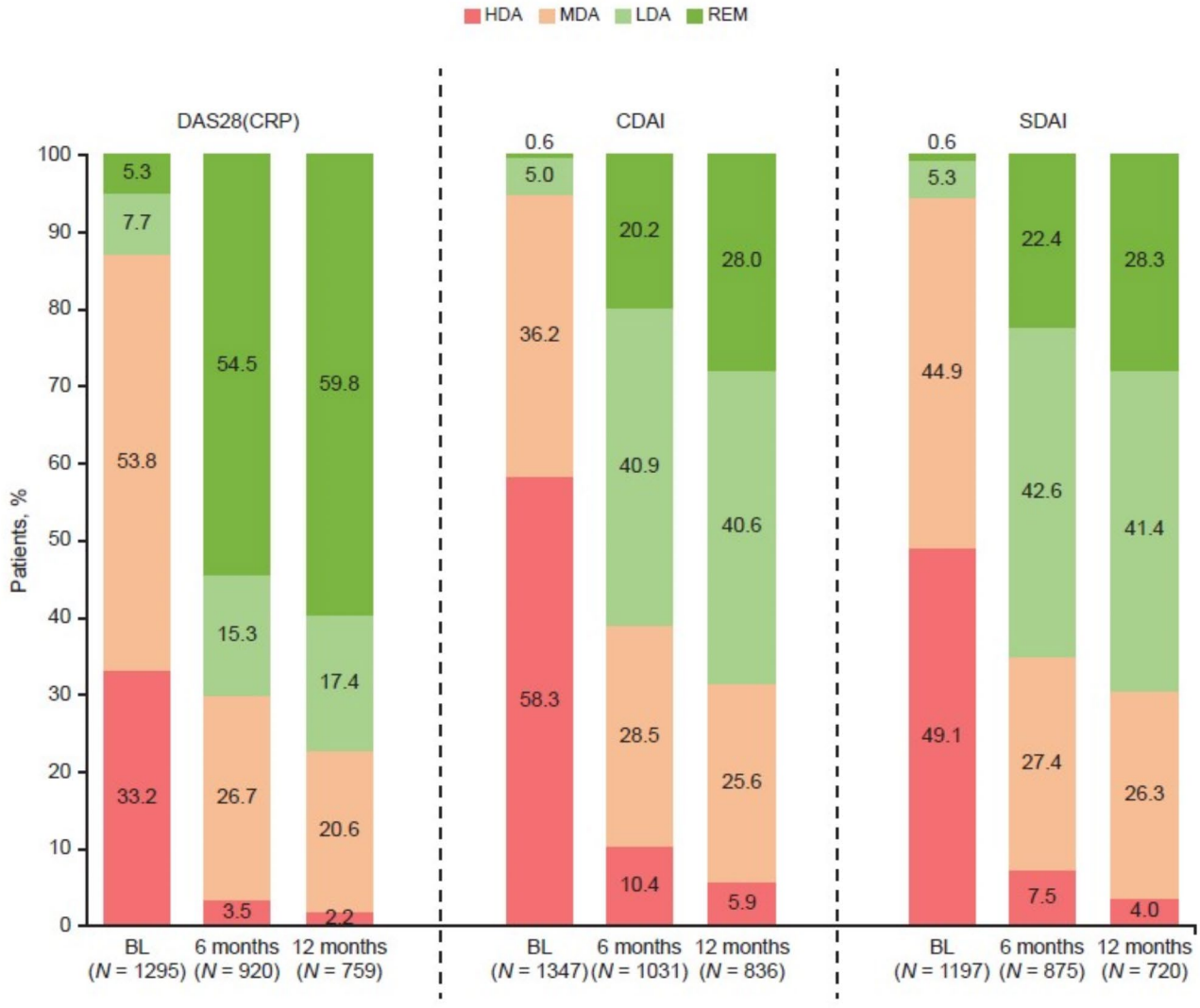


Fig. 2 Achievement (**A**, **B**) and maintenance (**C**, **D**) of DAS28(CRP) remission (< 2.6) and LDA (≤ 3.2) (mNRI and AO)
Error bars represent 95% confidence intervals
[a]mFAS1: All patients within the FAS who completed 6 months of UPA 15 mg treatment and had DAS28(CRP) data available ($n = 902$) or who discontinued treatment for any reason before month 6 ($n = 172$). [b]Number of patients in mFAS1 with non-missing data. [c]mFAS2: All patients within mFAS1 who achieved remission at 6 months and completed 12 months of UPA 15 mg treatment and had DAS28(CRP) data available ($n = 317$), or who discontinued treatment for any reason between 6 and 12 months ($n = 23$). [d]Number of patients in mFAS2 with non-missing data. [e]All patients within mFAS1 who achieved LDA at 6 months and completed 12 months of UPA 15 mg treatment and had DAS28(CRP) data available ($n = 395$), or who discontinued the study between 6 and 12 months ($n = 41$). [f]Number of patients within mFAS1 who achieved LDA at 6 months and completed 12 months of UPA 15 mg treatment and had DAS28(CRP) data available, or who discontinued the study between 6 and 12 months with non-missing data
AO as observed, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *FAS* full analysis set, *LDA* low disease activity, *mFAS* modified FAS, *mNRI* modified non-responder imputation, *RA* rheumatoid arthritis, *UPA* upadacitinib



REM, *n*	68	501	454	8	208	234	7	196	204
LDA, *n*	100	141	132	67	422	339	64	373	298
MDA, *n*	697	246	156	487	294	214	538	240	189
HDA, *n*	430	32	17	785	107	49	588	66	29

Fig. 3 Disease activity by DAS28(CRP), CDAI, and SDAI at baseline, 6 months, and 12 months (AO)
Note: The proportion of patients who achieved each level of disease activity was calculated using the number of patients with non-missing data for the disease activity score as the denominator. The sum of the proportions may not total 100.0% due to rounding
DAS28(CRP) remission: < 2.6; LDA: 2.6 ≤ DAS28(CRP) ≤ 3.2; MDA: 3.2 < DAS28(CRP) ≤ 5.1; HDA: > 5.1. CDAI remission: ≤ 2.8; LDA: 2.8 < CDAI ≤ 10.0; MDA: 10.0 < CDAI ≤ 22.0; HDA: > 22.0. SDAI remission: ≤ 3.3; LDA: 3.3 < SDAI ≤ 11.0; MDA: 11.0 < SDAI ≤ 26.0; HDA: > 26.0
AO as observed, *BL* baseline, *CDAI* clinical disease activity index, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *HDA* high disease activity, *LDA* low disease activity, *MDA* moderate disease activity, *REM* remission, *SDAI* simplified disease activity index

Outcomes by prior treatment exposure

When evaluating the subgroups per prior treatment exposure (ts/bDMARD-naïve, ts/bDMARD-experienced, TNFi-experienced, and tsDMARD-experienced) by number of prior bDMARDs, 67.0% of the patients in the TNFi-experienced group had received one prior bDMARD, while 24.9% had received two, and 8.1% had received ≥ 3 prior bDMARDs. In contrast, 37.5% and 23.9% of patients in the ts/bDMARD- and tsDMARD-experienced groups, respectively, had received one prior

bDMARD, while 57.8% and 58.3%, respectively, had received > 1 prior advanced therapy (Supplementary Table 1).

When the co-primary endpoints were assessed in the prior treatment exposure subgroups (ts/bDMARD-naïve, ts/bDMARD-experienced, TNFi-experienced, and tsDMARD-experienced), 35.0–52.3% of patients achieved DAS28(CRP) remission (< 2.6) at 6 months, and 67.6–84.0% maintained remission at 12 months (mNRI; Supplementary Fig. 3). A similar trend was observed on subgroup analysis for DAS28(CRP) LDA (≤ 3.2), with 47.9–66.7% of patients achieving DAS28(CRP) LDA at 6 months, and 74.5–87.3% maintaining LDA at 12 months (mNRI; Supplementary Fig. 3). Of note, the lowest proportions of patients achieving DAS28(CRP) remission and LDA were observed in the tsDMARD-experienced subgroup. The proportions of ts/bDMARD-experienced, TNFi-experienced, tsDMARD-experienced, and ts/bDMARD-naïve patients achieving and maintaining remission and LDA by DAS28(CRP), CDAI, and SDAI followed a similar response pattern, although the tsDMARD- and ts/bDMARD-experienced patient subgroups had numerically lower response rates at 6 and 12 months compared with the other subgroups (AO; Supplementary Fig. 4).

Outcomes by treatment strategy

Outcomes by baseline monotherapy or combination therapy. Of patients who had DAS28(CRP) remission at 6 months and available DAS28(CRP) data at 6 and 12 months, who stayed on UPA (or discontinued between 6 and 12 months), 80.5% (136/169) of those who initiated UPA as monotherapy maintained DAS28(CRP) remission at 12 months while remaining on monotherapy, and 79.4% (104/131) of those who initiated UPA in combination with csDMARDs maintained DAS28(CRP) remission at 12 months while remaining on combination therapy (mNRI; Supplementary Fig. 5). Similar results were observed for patients initiating UPA at baseline as monotherapy or combination therapy who achieved DAS28(CRP) LDA at 6 months, with 82.9% (175/211) and 84.2% (149/177), respectively, maintaining LDA at 12 months while staying on their initial therapy scheme (mNRI; Supplementary Fig. 5).

Of patients who initiated UPA as combination therapy and switched to monotherapy, 73.0% (27/37) maintained remission and 80.0% (36/45) maintained LDA at 12 months (Supplementary Fig. 5). Of patients who initiated UPA as monotherapy and switched to combination therapy, two out of four maintained remission and three out of six maintained LDA at 12 months.

Outcomes by monotherapy or combination therapy by analysis visit. A total of 49.6% of patients receiving UPA monotherapy and 43.8% of patients receiving combination therapy were in DAS28(CRP) remission at 6 months; the respective proportions were 41.2% and 37.5% at 12 months. A similar trend was observed for DAS28(CRP) LDA, with 61.7% and 51.6% of patients receiving monotherapy, and 57.9% and 49.1% of patients receiving combination therapy achieving this endpoint at 6 and 12 months, respectively. The proportions of patients achieving DAS28(CRP) remission and LDA by analysis visit grouped by therapy strategy are summarized in Supplementary Table 2.

Safety

There were a total of 2436 TEAEs (101.45 E/100 PY) reported through the data cutoff date of August 10, 2023 (Fig. 4). Among selected TEAEs of special interest, the most common were herpes zoster (75 [3.12 E/100 PY]), serious infection (63 [2.62 E/100 PY]), and hepatic disorder (59 [2.46 E/100 PY]). There were 20 events of malignancy, excluding non-melanoma skin cancer (NMSC) (0.83 E/100 PY), and nine of NMSC (0.37 E/100 PY) (Supplementary Table 3). A total of six MACE (0.25 E/100 PY) and 15 thrombotic events (0.62 E/100 PY) were reported; the thrombotic events included 12 venous thromboembolic events (VTE; eight events of pulmonary embolism and four events of deep vein thrombosis), two events of portal vein thrombosis, and one event of arterial thrombosis. There were no reported events of gastrointestinal perforation. Details on MACE and VTE, including presence of cardiovascular risk factors, are provided in Supplementary Table 4. A total of 199 patients (11.7%) had 263 TEAEs resulting in drug discontinuation (10.95 E/100 PY). A total of 14 TEAEs (0.58 E/100 PY) resulted in death: COVID-19 ($n = 3$); myocardial infarction ($n = 2$); multi-organ failure ($n = 2$); septic shock ($n = 1$); pneumonia ($n = 1$); domestic accident ($n = 1$); metastatic renal cancer ($n = 1$); gastrointestinal bleeding ($n = 1$); sudden death ($n = 1$); and unknown ($n = 1$). Of those, only one case of pneumonia and one case of multi-organ failure were considered by the investigator to have a reasonable possibility of being related to the study drug. The respective EAIRs of TEAEs in this patient population are presented in Supplementary Fig. 6.

The proportions of patients with investigator-determined clinically significantly abnormal laboratory test results are summarized in Supplementary Table 5. The most commonly reported clinically significant abnormalities at 12 months were elevated serum creatine phosphokinase (CPK) levels (1.5%) and blood lipid abnormalities (elevated total cholesterol, 4.0%; elevated low-density lipoprotein, 5.8%; and elevated triglyceride levels, 2.8%). Among treatment-emergent laboratory abnormalities, two events of decreased hemoglobin concentration, four of increased serum CPK levels, and six of hepatic enzyme elevation led to permanent drug discontinuation.

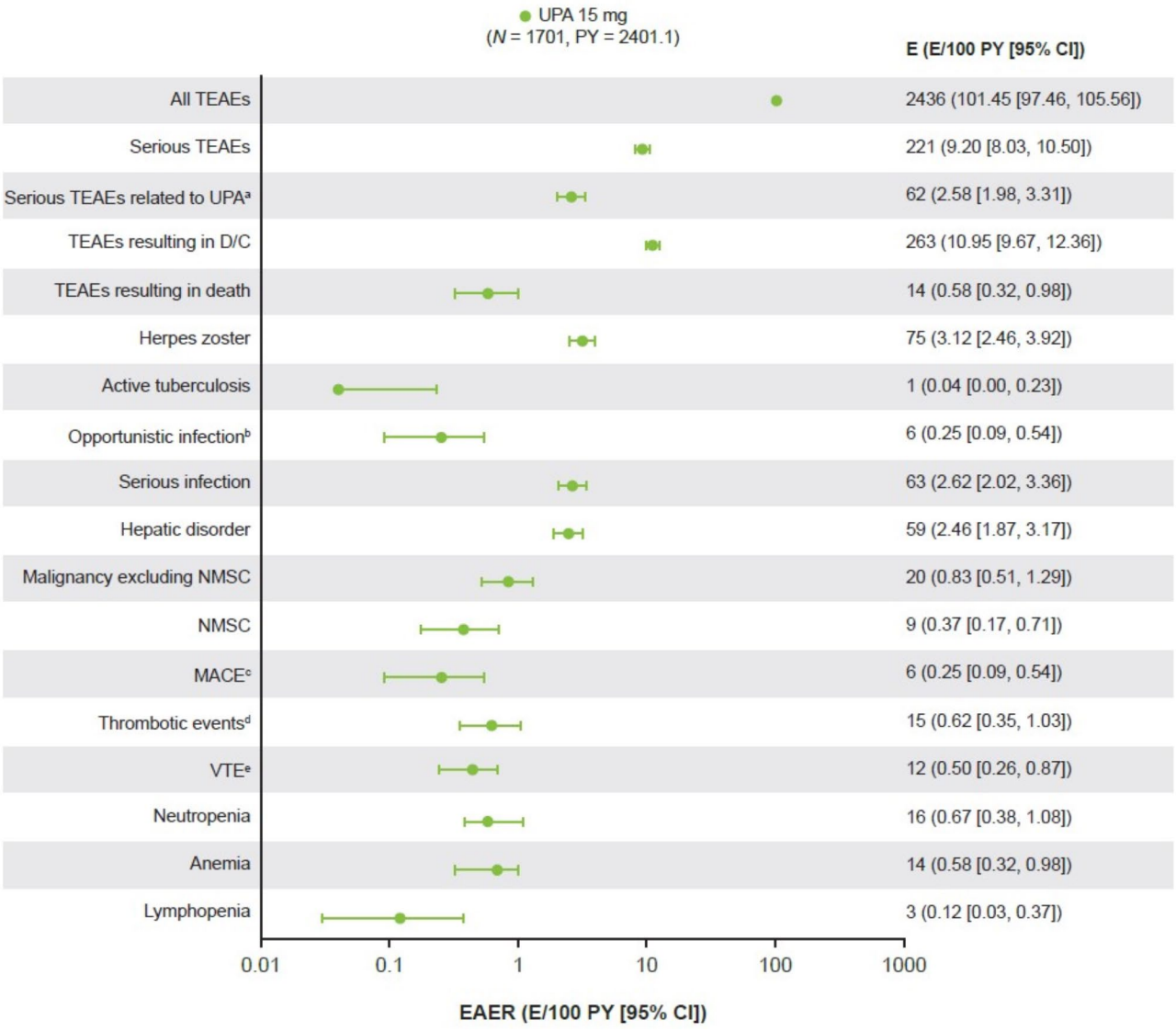


Fig. 4 EAERs of TEAEs in patients with moderate-to-severe RA treated with UPA 15 mg

Note: Safety was evaluated by assessing all TEAEs (AEs occurring after the first dose of study drug and up to 30 days after the last dose of study drug) occurring in the FAS up to the data cutoff date of August 10, 2023. There were no reported events of gastrointestinal perforation

[a]Reasonable possibility. [b]Excluding herpes zoster and active tuberculosis. [c]Includes cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. [d]Includes VTE, other venous thrombosis, and arterial thromboembolic events (VTE: $n=12$; arterial occlusive disease: $n=1$; PVT: $n=2$). [e]Includes DVT ($n=4$) and PE ($n=8$)

AE adverse event, *CI* confidence interval, *D/C* discontinuation, *DVT* deep vein thrombosis, *E* event, *EAER* exposure-adjusted event rate, *FAS* full analysis set, *MACE* major adverse cardiovascular events, *NMSC* non-melanoma skin cancer, *PE* pulmonary embolism, *PVT* portal vein thrombosis, *PY* patient-years, *RA* rheumatoid arthritis, *TEAE* treatment-emergent adverse event, *UPA* upadacitinib, *VTE* venous thromboembolic events

Discussion

Although a small number of studies have examined the real-world effectiveness of JAK inhibitors in patients with RA [26–29], data on the maintenance of remission for patients with RA receiving JAK inhibitors in real-world clinical practice are limited. To the best of our knowledge, this study represents the first systematic evaluation of attainment and maintenance of remission among patients initiating therapy with a JAK inhibitor, in this case, UPA, in a real-world setting to date.

In this interim analysis of a non-interventional study, patients with RA who initiated UPA treatment in a real-world setting generally had long disease duration and moderate-to-high disease activity, and over half the patients in this analysis had a history of bDMARD exposure. UPA 15 mg was effective for the treatment of RA, with 46.5% (mNRI)/55.3% (AO) of patients achieving DAS28(CRP) remission by 6 months, and 79.1% (mNRI)/84.9% (AO) of those patients maintaining remission through 12 months of treatment. Achievement

of remission and LDA at 6 months and maintenance of effect through 12 months was observed regardless of prior therapy exposure, as improvements in disease activity were observed in all subgroups with prior exposure to bDMARD and/or tsDMARD treatment, as well as in ts/bDMARD-naïve patients. Although similar responses and maintenance of effect were observed across all subgroups, the highest rates of remission/LDA were observed in ts/bDMARD-naïve and TNFi-experienced patients and were numerically similar between these two groups; this may be partly explained by the fact that the TNFi-experienced group included patients previously treated with TNFi only and, therefore, fewer patients had been more heavily treated with ≥ 2 bDMARDs (i.e., were treatment-refractory). As expected, patients with prior exposure to tsDMARD and ts/bDMARD therapy had numerically lower response rates at 6 and 12 months compared with the other subgroups; however, improvements in disease activity were also observed in the tsDMARD-experienced and ts/bDMARD-experienced subgroups, with > 50% achieving remission/LDA at 12 months. These observations may further support the use of UPA irrespective of prior line of therapy, and the benefits of switching to a drug with a different mechanism of action for patients who may be refractory to previous treatments [30–32]. Furthermore, this study indicated that UPA was effective in a patient population who had previously received JAK inhibitor treatment, as 18.1% of patients had prior exposure to ≥ 1 tsDMARD. In addition, most patients were able to maintain remission/LDA at 12 months, regardless of whether they had initiated UPA as monotherapy or combination therapy. When assessing remission and LDA by therapy visit, UPA, either as monotherapy or in combination with csDMARDs, was consistently effective at inducing clinical response through 12 months, although the monotherapy groups trended toward a slight numeric increase in response rates over time compared with the combination therapy groups. These results are consistent with previous findings on the real-world effectiveness of UPA [28, 33–35].

The efficacy results were consistent with data reported for UPA in RA in the SELECT phase 3 clinical trial program, in which UPA achieved the primary endpoints for efficacy in different RA populations (e.g., MTX-naïve, csDMARD- and bDMARD-refractory), and achieved high remission/LDA rates regardless of the applied criteria (e.g., DAS28[CRP], CDAI, SDAI, or Boolean criteria) or therapy strategy (in combination with MTX or other csDMARDs, or as monotherapy) [36, 37].

In two previous single-center real-world studies including 115 and 98 patients with RA treated with JAK inhibitors (tofacitinib and baricitinib), 33–64% of patients had achieved remission or LDA at 6 months [26, 27]. Similar effectiveness and drug retention rates between bDMARDs and JAK inhibitors were reported among elderly Japanese patients with RA in a real-world setting, suggesting JAK inhibitors as a potential therapeutic option for patients with possible comorbidities who are refractory to csDMARDs [38]. The outcomes in the present study were in line with previous real-world data reporting improvements in disease activity with UPA, regardless of previous ts/bDMARD exposure [33, 39, 40], baseline CRP levels [34], or treatment strategy [33].

The safety profile of UPA in this real-world cohort of patients was consistent with that reported in long-term clinical trial programs of UPA in rheumatologic diseases, including RA, psoriatic arthritis, and axial spondyloarthritis [20, 36].

Although the rate of TEAEs leading to drug discontinuation in this study was higher than previously reported phase 3 study data for RA (10.95 vs. 4.9, respectively) [20], this may be partly due to the real-world setting and the overlap with the recent pandemic, as data were collected between October 2020 and August 2023. In addition, the present findings (TEAEs leading to drug discontinuation in 11.7% of patients) are in line with recent real-world studies reporting TEAEs leading to UPA discontinuation in 11.5% of patients at 6 months, and discontinuation due to safety concerns in 9.6% of patients at 6 months and in 11.4% of patients at 12 months [35, 41]. Regarding the discontinuation of other JAK inhibitors due to AEs, a previous review of real-world studies of tofacitinib in RA reported discontinuation rates of < 10% [42], with the exception of one study in which ~ 25% of patients discontinued treatment in the first year due to safety concerns [43]. A more recent study reported overall JAK inhibitor (tofacitinib, baricitinib, UPA, or filgotinib) discontinuation rates of 20.6% at 12 months due to AEs (14.4% among patients aged < 65 years and 26.3% among patients aged ≥ 65 years; $p = 0.019$) [44]. The proportions of patients remaining on treatment and discontinuing treatment were not found to differ significantly among different JAK inhibitors in the ANSWER real-world study [45]; however, other data suggest that patients with RA initiating UPA were significantly less likely to discontinue therapy compared with other JAK inhibitors, or compared with the TNF inhibitor adalimumab, in the first 12 months of treatment [46].

Patients with RA have been reported to carry a twofold increased risk of cardiovascular morbidity and mortality, and a threefold increased risk of VTE; up to 70% of MACE risk can be explained by known risk factors in the medical history or disease-specific factors (e.g., inflammation and disease activity), and the majority of VTE cases are associated with pre-existing risk factors [47]. Although the ORAL Surveillance study [11] raised concerns regarding increased risk of cardiovascular events and malignancy with tofacitinib (later expanded to

include other JAK inhibitors), further investigations dedicated to determining the cardiovascular risk associated with tofacitinib use compared with TNF inhibitors have been inconclusive [48]. In addition, recent real-world safety data indicate that JAK inhibitors overall carry an acceptable risk of AEs of special interest, including cardiovascular events, without marked differences between different JAK inhibitors [49], or between JAK inhibitors and bDMARDs [50]. However, treatment recommendations for RA advise healthcare providers to consider pertinent risk factors when evaluating the use of JAK inhibitors to optimize treatment selection [47]. There was no statistically significantly increased risk of first primary cancer in patients with RA treated with JAK inhibitors compared with bDMARDs, although the risk estimates in some analyses were elevated for JAK inhibitors [51]. A recent real-world study suggested an increased risk for NMSC with JAK inhibitors compared with TNF inhibitors (fully adjusted hazard ratio = 1.39 [95% CI: 1.01–1.91]) [52]. However, a causative biologic mechanism remains to be determined, and the risks must be viewed in light of the increased risks for several other comorbidities and adverse outcomes in patients with active RA [52]. In the current study, the EAERs for MACE (0.3), VTE (0.5), malignancy excluding NMSC (0.8), and NMSC (0.4) were low, consistent with previous phase 3 results for UPA in RA [20, 21, 36, 53]. There were no reported events of gastrointestinal perforation. The proportion of patients with reported laboratory abnormalities at baseline in hemoglobin concentration and markers of inflammation had decreased notably at 12 months; there were no notable changes from baseline through 12 months in the proportions of patients with reported abnormalities in other laboratory test results, including white blood cell counts, liver function tests, or blood lipid levels.

Limitations of the present study include its observational nature, which is associated with inherent biases. Such studies, rather than being dictated by a strict protocol, evaluate outcomes in a real-life setting based on routine clinical practice and the physician's judgment. Therefore, as the clinical significance of some reported data is determined by the investigator, objective interpretation may be difficult. Furthermore, DAS28(CRP) data were not available for all patients at the 12-month visit. Patient availability and interference of external factors (such as the recent pandemic) with regular visits may also lead to unequal treatment duration and follow-up when assessments are required at defined time intervals. In addition, although the DAS is a well-established and validated measure of disease activity, it has been criticized for allowing a high swollen joint count while meeting the definition of remission, due to calculation effects [54]. Furthermore, the use of DAS28(CRP) with therapies that may heavily influence CRP levels via the interleukin-6 pathway, such as JAK inhibitors, has also been challenged. As a result, CRP decreases may not always reflect a parallel improvement in disease activity and affected joint counts, and patients with RA classified as being in clinical remission based on disease activity scores containing CRP may still exhibit active synovitis [55]. However, despite these limitations, real-world studies provide valuable evidence on how a therapy performs outside the narrow confines of the research setting, providing essential information on the long-term safety and effectiveness of a drug in clinical practice.

Conclusion

UPA was effective in achieving and maintaining stringent disease control targets in patients with moderate-to-severe RA in real-world clinical practice, with almost half of patients achieving remission and over half of patients achieving LDA at 6 months, and the majority of those patients demonstrating maintenance of treatment response through 12 months. The effectiveness and maintenance of effect of UPA were consistent across patient populations with different treatment strategies and prior treatment experience. The effectiveness and safety profile of UPA remains favorable in real-world patient populations and is consistent with data from phase 3 clinical trials, with no newly identified safety signals.

Abbreviations

ACPA	Anti-citrullinated protein antibody
AE	Adverse event
AO	As observed
BCG	Bacillus Calmette-Guérin
bDMARD	Biologic DMARD
BL	Baseline
BMI	Body mass index
CDAI	Clinical disease activity index
CI	Confidence interval
CPK	Creatine phosphokinase
CRP	C-reactive protein
csDMARD	Conventional synthetic DMARD
DAS28(CRP)	Disease activity score in 28 joints using CRP
D/C	Discontinuation
DMARD	Disease-modifying antirheumatic drug
DVT	Deep vein thrombosis
E	Event
EAER	Exposure-adjusted event rate
EAIR	Exposure-adjusted incidence rate
EAS	Enrolled analysis set
FAS	Full analysis set
f/u	Follow-up
HDA	High disease activity
JAK	Janus kinase
LDA	Low disease activity
LOE	Lack of efficacy
MACE	Major adverse cardiovascular events
MDA	Moderate disease activity
MTX	Methotrexate
mFAS	Modified FAS
mNRI	Modified non-responder imputation
NMSC	Non-melanoma skin cancer
NSAID	Non-steroidal anti-inflammatory drug
PE	Pulmonary embolism
PVT	Portal vein thrombosis

PY	Patient-years
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
REM	Remission
RF	Rheumatoid factor
SD	Standard deviation
SDAI	Simplified disease activity index
TEAE	Treatment-emergent AE
TNF	Tumor necrosis factor
TNFi	TNF inhibitor
tsDMARD	Targeted synthetic DMARD
UPA	Upadacitinib
VTE	Venous thromboembolic events

Supplementary Information

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Supplementary Material 1

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Author contributions

AO contributed to the study design and was an investigator in the study. AO, EF, PS, JA, MR, RN, DZ, and SA were investigators in the study. TG conducted the statistical analyses. AO, EF, PS, JA, MR, RN, EMB, TG, ILG, SS, DZ, and SA analyzed and interpreted the data and contributed to the critical revision of the manuscript. All named authors met the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Data availability

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), 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. These 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, statistical analysis plan, and execution of a data sharing agreement. Data requests can be submitted at any time after approval in the USA and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, please visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing.

Declarations

Ethics approval and consent to participate

The study was conducted according to the International Council on Harmonisation guidelines and the Declaration of Helsinki. The trial protocol was approved by independent ethics committees and institutional review boards. Written informed consent was provided by patients ahead of study screening.

Consent for publication

Not applicable.

Competing interests

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