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ORIGINAL RESEARCH

Efficacy and safety of upadacitinib in patients with rheumatoid arthritis and inadequate response or intolerance to biological treatments: results through 5 years from the SELECT-BEYOND study

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ABSTRACT

Objective To evaluate the efficacy and safety of upadacitinib over 5 years among patients with rheumatoid arthritis (RA) in a long-term extension (LTE) of the SELECT-BEYOND phase 3 trial.

Methods Patients refractory to ≥1 biological disease-modifying antirheumatic drug (DMARD) received upadacitinib 15 mg or 30 mg once daily or placebo, in combination with background conventional synthetic DMARD(s). At week 12, patients randomised to placebo were switched to upadacitinib 15 mg or 30 mg. All patients who completed the week 24 visit could enter the LTE for up to 5 years. Efficacy was analysed as observed and by non-responder imputation through week 260. Treatment-emergent adverse events per 100 patient-years were summarised over 5 years.

Results Of the 498 patients randomised, 418 (84%) completed week 24 and entered the LTE. Of those who remained in the trial (n=80, upadacitinib 15 mg; n=81, upadacitinib 30 mg), 36%/36% and 81%/77% randomised to upadacitinib 15/30 mg were in Clinical Disease Activity Index (CDAI) remission or low disease activity at week 260, respectively (as observed). Approximately 47% of all patients who began in high disease activity demonstrated a CDAI improvement >12 at week 260 with upadacitinib 15/30 mg. Functional and pain-related outcomes also showed comparable improvements with both doses. Numerically higher rates of anaemia, herpes zoster and creatine phosphokinase elevation were observed with upadacitinib 30 mg vs 15 mg. No new safety issues were identified.

Conclusions Upadacitinib 15/30 mg continued to be effective in treating clinical and functional outcomes in patients with RA. The safety profile observed over 5 years was consistent with earlier study-specific and integrated assessments of upadacitinib treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Janus kinase inhibitor upadacitinib has undergone safety and efficacy evaluations in approximately 4800 patients with rheumatoid arthritis (RA) across six global phase 3 studies in the SELECT programme.

⇒ In one of these trials, SELECT-BEYOND, treatment with upadacitinib 15 mg or 30 mg vs placebo, each with background conventional synthetic disease-modifying antirheumatic drug(s), led to significant improvements in clinical, functional and patient-reported outcomes over 12 weeks in patients with active RA and an inadequate response or intolerance to at least one biological treatment.

WHAT THIS STUDY ADDS

⇒ Clinical and functional disease characteristics could be effectively treated over 5 years with upadacitinib 15 mg or 30 mg; efficacy outcomes were also generally similar between both dose groups.

⇒ The safety profile observed over 5 years was consistent with earlier assessments of upadacitinib treatment in this population and compared with other studies in the upadacitinib development programme.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study suggest that upadacitinib continues to have a favourable benefit–risk profile and is a useful treatment choice for patients with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that can lead to impaired functional ability, chronic pain and higher mortality rates if not adequately treated. Methotrexate (MTX) is typically the first therapeutic choice for patients with RA, but other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) may be used.[1 2] In patients who are inadequate responders or are intolerant to these first-line

therapies, biological DMARDs (bDMARDs) are often an effective option. However, a significant unmet need remains as a proportion of patients still fail to achieve their desired treatment goal. Approximately one-third of patients receiving TNF inhibitors discontinue treatment within 1 year due to inadequate response or adverse events (AEs).[3] These patients may benefit from therapy with a different mechanism of action. Janus kinase (JAK) inhibitors, a class of oral targeted synthetic DMARDs, are an established alternative in patients who have failed prior csDMARD or bDMARD treatment.

The JAK inhibitor upadacitinib has been investigated in the SELECT phase 3 clinical programme for RA, composed of 6 trials of approximately 4800 patients in total, and was shown to be effective in a broad range of patients.[4–9] In SELECT-BEYOND, which was conducted in patients with RA with an inadequate response or intolerance to at least one or more bDMARDs (bDMARD-IR), treatment with upadacitinib 15 mg or 30 mg once daily, in combination with background csDMARD(s), led to significant improvements in clinical, functional and patient-reported outcomes over 24 weeks.[4] However, given the chronic nature of RA and the required continuation of therapy in most patients, it is critical to assess the long-term impact of any prescribed treatment(s). Here, we report the long-term efficacy and safety of upadacitinib over 5 years in the long-term extension (LTE) of SELECT-BEYOND.

METHODS

Patients

Study eligibility criteria and baseline demographics for SELECT-BEYOND have been described previously.[4] In brief, patients were ≥18 years old with a diagnosis of RA for ≥3 months and met the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for RA.[10] Eligibility criteria also included ≥6 swollen joints, ≥6 tender joints and high sensitivity C reactive protein (CRP) ≥3 mg/L. All enrolled patients received prior bDMARD therapy for RA and failed ≥1 bDMARD after receiving at least 3 months of treatment or having had to discontinue ≥1 bDMARD therapy due to intolerability, regardless of treatment duration. Patients were also required to be on csDMARD therapy (restricted to MTX, chloroquine, hydroxychloroquine, sulfasalazine or leflunomide) for ≥4 weeks before the first dose of study drug. A combination of up to two background csDMARDs was allowed except for the combination of MTX and leflunomide. Patients were excluded if they had prior exposure to any JAK inhibitor or a history of inflammatory joint disease other than RA.

Study design and treatment

SELECT-BEYOND (clinical trial number: NCT02706847) included a 24-week randomised, double-blind, treatment period (first 12 weeks were placebo-controlled), followed by a 236-week LTE (online supplemental figure 1). Patients were randomised 2:2:1:1 to one of the following four treatment groups, each receiving stable background csDMARD therapy: (1) upadacitinib 15 mg once daily, (2) upadacitinib 30 mg once daily, (3) placebo to upadacitinib 15 mg once daily and (4) placebo to upadacitinib 30 mg once daily. At week 12, patients randomised to placebo were switched to upadacitinib 15 mg or 30 mg in a prespecified manner. All patients who completed the week 24 visit could enter a double-blind LTE of up to 5 years. At week 24, if a patient failed to meet low disease Clinical Disease Activity Index criteria (CDAI ≤10), investigators were to adjust the patient's background RA therapies. Starting at week 24, initiation of or change in glucocorticoids, non-steroidal anti-inflammatory drugs, acetaminophen or adding or increasing doses in up to two csDMARDs (except the combination of MTX and leflunomide) was allowed as according to local label. Per protocol amendment following the approval of upadacitinib 15 mg for the treatment of RA, patients receiving upadacitinib 30 mg were transitioned to the 15 mg dose, with the earliest switch occurring at week 180.

Efficacy assessments

Efficacy assessments included the proportions of patients achieving low disease activity (LDA; defined by CDAI ≤10) or clinical remission (defined by CDAI ≤2.8),[11] 28-joint Disease Activity Score (DAS28[CRP]) ≤3.2 or <2.6,[12 13] ACR/EULAR Boolean-based remission,[14] ACR20/50/70 responses,[15] and minimal clinically important differences (MCID) in change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) of ≤−0.22. Additionally, the change from baseline in ACR components such as HAQ-DI[16] and patient's assessment of pain, as well as the severity and duration of morning stiffness were also examined. During the LTE, efficacy assessments were performed every 12 weeks. For patients who began in high disease activity, the proportions achieving an MCID in CDAI (improvement of CDAI >12, as previously defined in the literature[17]) were also evaluated.

Safety assessments

Safety outcomes included data from all patients receiving upadacitinib, with assignment based on drug doses at the time of the event. Treatment-emergent AEs (TEAEs) were defined as those that began after the first dose of the study drug but no more than 30 days after the last dose (cut-off date: 1 March 2022). However, mortality assessments also included non-treatment-emergent deaths beyond 30 days after the last dose of study drug.

Safety assessments were performed as previously described.[4] Major adverse cardiovascular events (MACE) and venous thromboembolism (VTE) events were adjudicated throughout the study by an independent Cardiovascular Adjudication Committee in a blinded manner. MACE were defined as cardiovascular (CV) death,

non-fatal myocardial infarction and non-fatal stroke. VTE included deep vein thrombosis (DVT) and pulmonary embolism (PE). Patients presenting with potential CV events were carefully monitored during further continuation of the study. Patients who developed symptoms of thrombosis were to be promptly evaluated and treated appropriately. If a diagnosis of DVT, PE or non-cardiac, non-neurological arterial thrombosis was confirmed, the patient was to be discontinued from study drug. Laboratory parameters were evaluated through week 260, including the proportion of patients meeting criteria for potentially clinically significant (grade 3 or 4) laboratory changes during the treatment period. The severity of TEAEs and laboratory changes were assessed by the investigator according to the Rheumatology Common Terminology Criteria (V.2.0) developed by the Outcome Measures in Rheumatology,[18] with the exception of creatine phosphokinase (CPK) and creatinine, for which the Common Toxicity Criteria developed by the National Cancer Institute was used.

Statistical analysis

Efficacy outcomes up to week 260 were examined separately in patients randomised to either upadacitinib 15 mg or 30 mg and in those who switched from placebo to upadacitinib 15 mg or upadacitinib 30 mg. CDAI responses before and after dose switch from upadacitinib 30 mg to the approved 15 mg dose were also evaluated. In addition to the complete analysis set, change from baseline in efficacy responses was separately assessed in patients who did not achieve CDAI LDA at week 260. Lastly, efficacy responses were evaluated in the subgroup of patients who failed ≥1 prior TNF inhibitor (TNF-IR). Data are reported as observed (AO); missing data for specified categorical endpoints were also imputed using non-responder imputation (NRI). Kaplan-Meier curves were used to examine background glucocorticoid use over time.

Safety assessments were based on available data up to week 260 for each patient. TEAEs, including AEs of special interest (AESIs), per 100 patient-years (PY), were summarised over 5 years for upadacitinib 15 mg and 30 mg groups, which includes exposure in patients randomised to upadacitinib as well as those who switched from placebo to upadacitinib at week 12. TEAEs are shown separately for patients who switched from upadacitinib 30 mg to the approved 15 mg dose, with exposure to upadacitinib 30 mg censored prior to the day of the switch to upadacitinib 15 mg; any event occurring after the switch was assigned to the upadacitinib 30 mg switched to upadacitinib 15 mg group. Rates of serious infections were also evaluated for patients receiving concomitant prednisone at the time of event (or up to 14 days after the last dose of prednisone) vs those who did not. All safety data are reported as exposure-adjusted event rates (EAERs), defined as events per 100 PY (E/100 PY).

RESULTS

Patients

As previously reported,[4] baseline demographics and disease characteristics were balanced across all treatment groups (summarised in online supplemental table 1). Of the 498 patients randomised and treated, 418 (84%) completed week 24 and entered the LTE (figure 1). During the LTE, 197 (47%) patients discontinued the study drug due to the following primary reasons: TEAEs (15%), withdrawal of study drug (8%), lack of efficacy (7%), lost to follow-up (4%) or other reasons (13%, many of which are related to lack of efficacy and are listed in online supplemental table 2). The proportion of patients who stopped study drug due to AEs or loss of efficacy from week 24 to week 260 was generally similar between groups (12%–18% due to AEs and 4%–9% due to loss of efficacy). Overall, 45% (n=74/164) and 47% (n=78/165) of patients randomised to upadacitinib 15 mg and 30 mg completed week 260, respectively. Approximately 10% of patients had discontinued background csDMARD treatment by study end. Additionally, ~20% of patients discontinued use of background glucocorticoids during the study, with approximately 55% of patients who received glucocorticoids discontinuing glucocorticoid use by 30 months (online supplemental figure 2).

Efficacy

Among the overall study population, achievement of disease activity targets through 5 years was similar in patients receiving either upadacitinib 15 mg or 30 mg. Of those who remained in the trial, approximately 80% achieved CDAI LDA, and 36% attained CDAI remission with either dose of upadacitinib at week 260 (AO) (figure 2). DAS28(CRP) ≤3.2/<2.6 was achieved by 81%/66% of patients in the upadacitinib 15 mg group who remained in the study vs 75%/60% of those in the upadacitinib 30 mg group at week 260; additionally, 28% of patients treated with upadacitinib 15 mg vs 23% on upadacitinib 30 mg achieved the ACR/EULAR Boolean-based remission definition (AO). The proportions of patients in CDAI remission or LDA were generally similar before and after dose switch from upadacitinib 30 mg to the approved 15 mg dose (online supplemental figure 3). Patients who switched from placebo to upadacitinib at week 12 also showed generally similar long-term efficacy responses from around week 16 to week 260 (figure 2). Consistent results with upadacitinib 15 mg and 30 mg for CDAI and DAS28(CRP) were also observed based on the more conservative NRI approach (figure 3). When evaluating the results by NRI, 36%/17% of patients achieved CDAI LDA/remission with either upadacitinib 15 mg or 30 mg, and DAS28(CRP) ≤3.2/<2.6 was attained by 37%/31% with upadacitinib 15 mg compared with 37%/29% with upadacitinib 30 mg at week 260. Of all patients who started the trial in high disease activity (defined as CDAI >22), approximately 45% remaining in the trial demonstrated a CDAI improvement >12 at week 260 (figure 4).

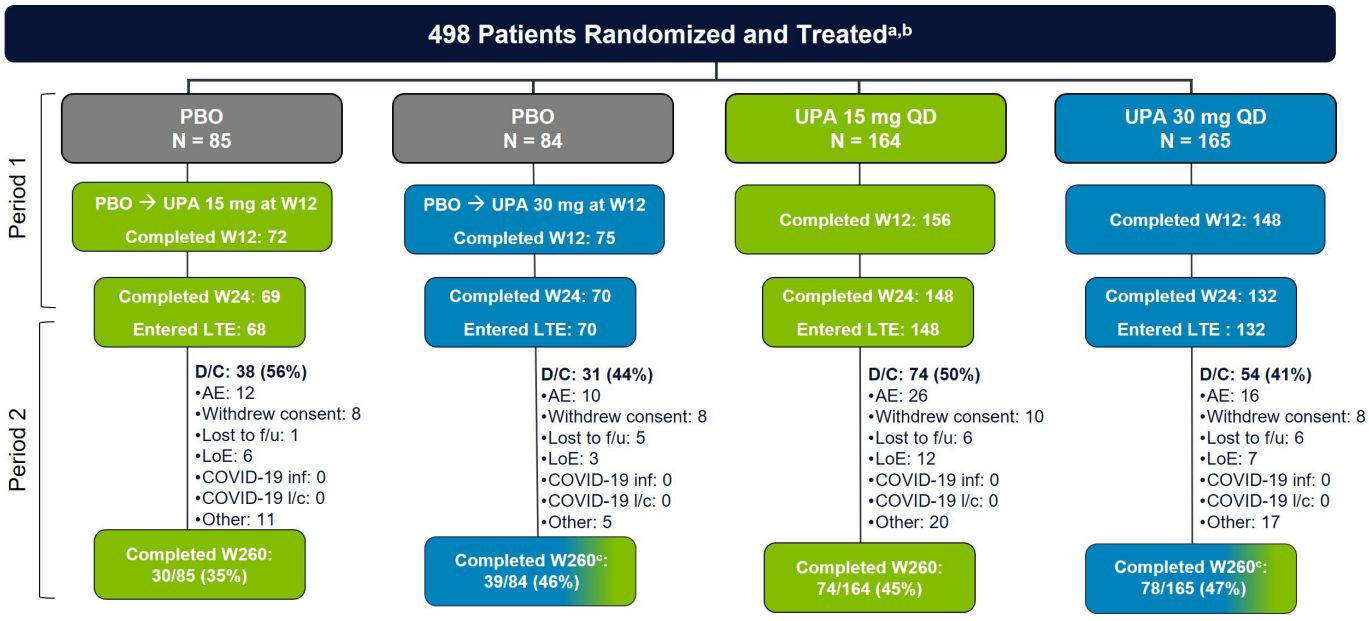


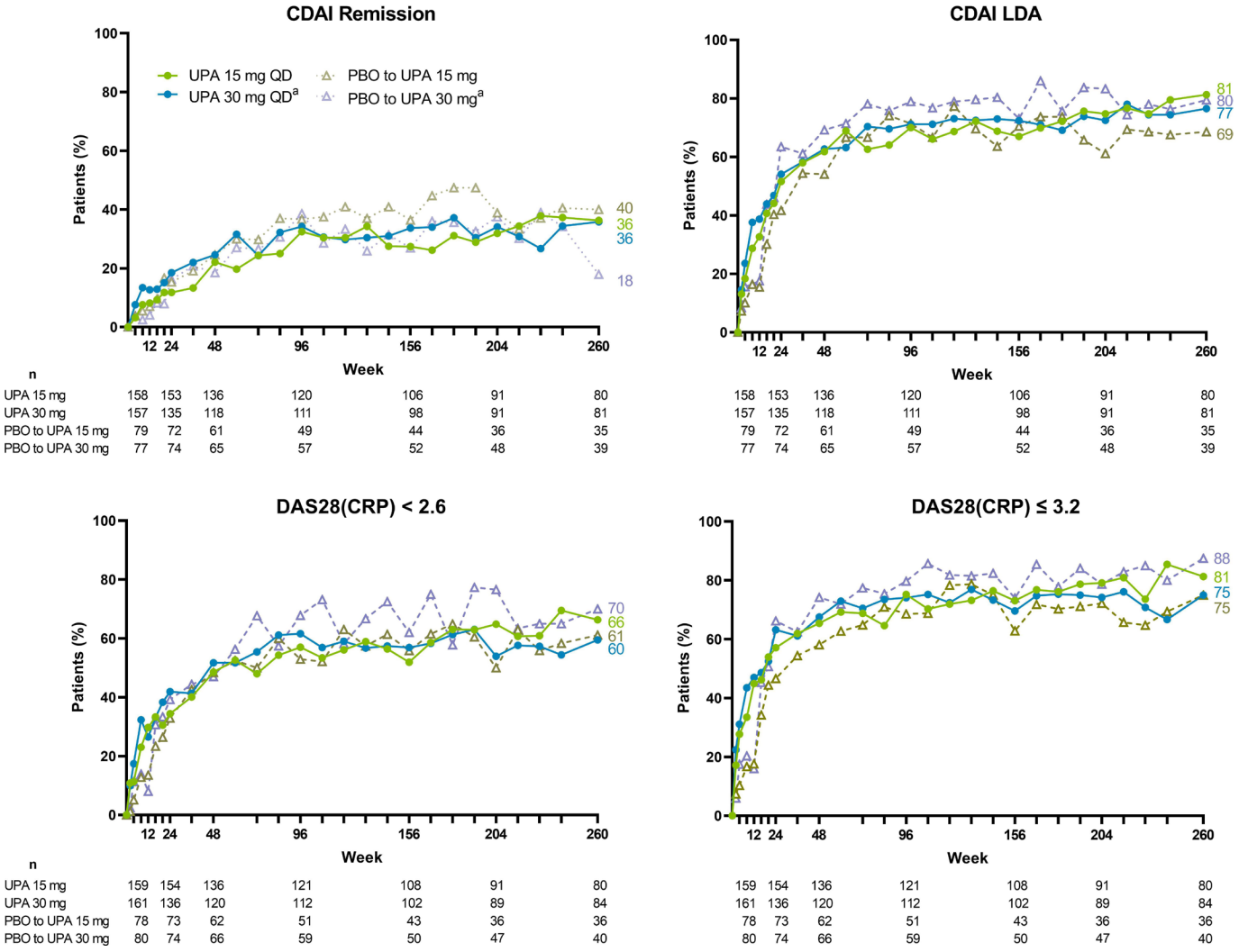
Figure 1 Disposition of patients through 5 years in SELECT-BEYOND. [a]The numbers of patients in each treatment group are shown, with the primary reason for discontinuation listed during the LTE through week 260. [b]A total of 499 patients were randomly assigned (n=165, UPA 15 mg; n=165, UPA 30 mg; n=85, PBO then UPA 15 mg; n=84, PBO then UPA 30 mg), but one patient withdrew from the UPA 15 mg group before the start of study treatment due to accidental randomisation. [c]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment. The switch occurred at different visits across the patient population, with the earliest switch occurring at the week 180 visit. AE, adverse event; D/C, discontinued; f/u, follow-up; inf, infection; l/c, logistical constraints; LoE, lack of efficacy; LTE, long-term extension; PBO, placebo; QD, once daily; UPA, upadacitinib; W, week.

As expected in an LTE trial in which patients who are not responding adequately to therapy or who develop intolerable AEs and discontinue the study, upadacitinib demonstrated improvements in ACR responses over 5 years in the patients remaining in the study (figure 5). By week 260, 88%/68%/51% of patients remaining in the trial achieved ACR20/50/70 responses with upadacitinib 15 mg and 88%/67%/46% with upadacitinib 30 mg (AO) (figure 5). Similar results were also achieved in those who switched from placebo to upadacitinib 15/30 mg. Taking into account patients who discontinued upadacitinib for the above reasons and for losing response over time, the NRI analysis showed ACR20/50/70 responses that were lower than in AO analyses but were similar for both doses (40%/32%/24% with upadacitinib 15 mg and 42%/32%/22% with upadacitinib 30 mg at week 260) (figure 6). Of the patients who remained in the study, functional and pain-related outcomes showed similar improvements with upadacitinib 15/30 mg, with a mean change from baseline of −0.6/−0.6 for HAQ-DI and −39/−37 mm for patient's assessment of pain at week 260 (AO). Additionally, 79% and 69% of patients randomised to upadacitinib 15 mg and 30 mg achieved a change in HAQ-DI of ≤−0.22 (AO). Sustained improvements in all other ACR components were observed over 5 years (online supplemental figure 4). Treatment with both doses also led to improvements in the severity and duration of morning stiffness (online supplemental figure 5). Of the approximately 20% of patients who did not meet CDAI LDA criteria at week 260, improvements in clinical and patient-reported outcomes were also observed. The mean change from baseline in these patients was −32.1/−25.0 with upadacitinib 15/30 mg for CDAI and −11.3/−11.3 for pain.

Consistent efficacy responses, including CDAI, DAS28(CRP) and ACR20/50/70, were observed in the subgroup of TNF-IR patients compared with the overall SELECT-BEYOND bDMARD-IR population (online supplemental figures 6–9). Boolean remission was achieved by 28% of TNF-IR patients randomised to upadacitinib 15 mg compared with 21% randomised to upadacitinib 30 mg at week 260 (AO). When analysed by NRI, 14% and 10% of patients attained Boolean remission with upadacitinib 15 mg and 30 mg at week 260, respectively. Functional and pain-related outcomes were also similar between the TNF-IR subgroup and the overall bDMARD-IR population and between those randomised to upadacitinib 15 mg or 30 mg. Among TNF-IR patients, the mean change from baseline in HAQ-DI and pain with upadacitinib 15/30 mg was −0.6/−0.6 and −38/−36 mm at week 260 (AO) (online supplemental figure 10). Additionally, 78% and 67% of TNF-IR patients randomised to upadacitinib 15 mg and 30 mg, respectively, achieved MCID in HAQ-DI of ≤−0.22 at week 260 (AO).

Safety

Through 5 years, the overall exposure time was similar for either dose of upadacitinib (759.5 PY with upadacitinib 15 mg and 621.9 PY with upadacitinib 30 mg). The total exposure time was shorter among patients who switched



n							
UPA 15 mg	158	153	136	120	106	91	80
UPA 30 mg	157	135	118	111	98	91	81
PBO to UPA 15 mg	79	72	61	49	44	36	35
PBO to UPA 30 mg	77	74	65	57	52	48	39

n							
UPA 15 mg	159	154	136	121	108	91	80
UPA 30 mg	161	136	120	112	102	89	84
PBO to UPA 15 mg	78	73	62	51	43	36	36
PBO to UPA 30 mg	80	74	66	59	50	47	40

Figure 2 Proportions of patients achieving CDAI or DAS28(CRP) disease activity states through 5 years (AO). Data are from patients who were initially randomised to UPA 15 mg or 30 mg and those who switched from PBO to either dose of UPA at week 12. The total number of patients (n) in each treatment group are shown at weeks 4, 24, 48, 96, 156, 204 and 260. Cut points for CDAI were ≤2.8 for remission and ≤10 for LDA. [a]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment. The switch occurred at different visits across the patient population, with the earliest switch occurring at the week 180 visit. AO, as observed; CDAI, Clinical Disease Activity Index; DAS28(CRP), 28-joint Disease Activity Score based on C reactive protein; LDA, low disease activity; PBO, placebo; QD, once daily; UPA, upadacitinib.

from upadacitinib 30 mg to 15 mg following protocol amendment (155.5 PY), which occurred after approval of upadacitinib 15 mg in RA (with the earliest switch occurring at week 180). The overall rate of AEs was numerically higher in patients on upadacitinib 30 mg (354.1 E/100 PY) than upadacitinib 15 mg (274.1 E/100 PY) (table 1). The majority (93%) of all AEs were mild to moderate in severity. The rates of serious TEAEs were similar in the upadacitinib 15 mg group and the 30 mg group (20.9 vs 23.3 E/100 PY) or among those who switched from upadacitinib 30 mg to 15 mg (21.9 E/100 PY). Rates of TEAEs leading to discontinuation of study drug were also generally similar with upadacitinib 15 mg compared with upadacitinib 30 mg (8.7 and 9.8 E/100 PY, respectively). Approximately 50% of AEs leading to discontinuation were mild to moderate in severity. Overall, upper respiratory and urinary tract infections were the most commonly reported TEAEs (≥10 events per 100 PY in any dose group) in patients receiving upadacitinib (online supplemental table 3).

No new safety issues were identified from the long-term observations of those continuing upadacitinib treatment (short-term results through week 24 are shown in online supplemental table 4). Through 5 years, the most commonly reported AESIs in patients receiving upadacitinib were serious infection, anaemia, hepatic disorder, herpes zoster and CPK elevation (online supplemental material text). Rates of serious infections and hepatic disorders were comparable between both upadacitinib doses. In contrast, numerically higher rates of anaemia, herpes zoster and CPK elevation were observed with upadacitinib 30 mg compared with 15 mg (table 1). The

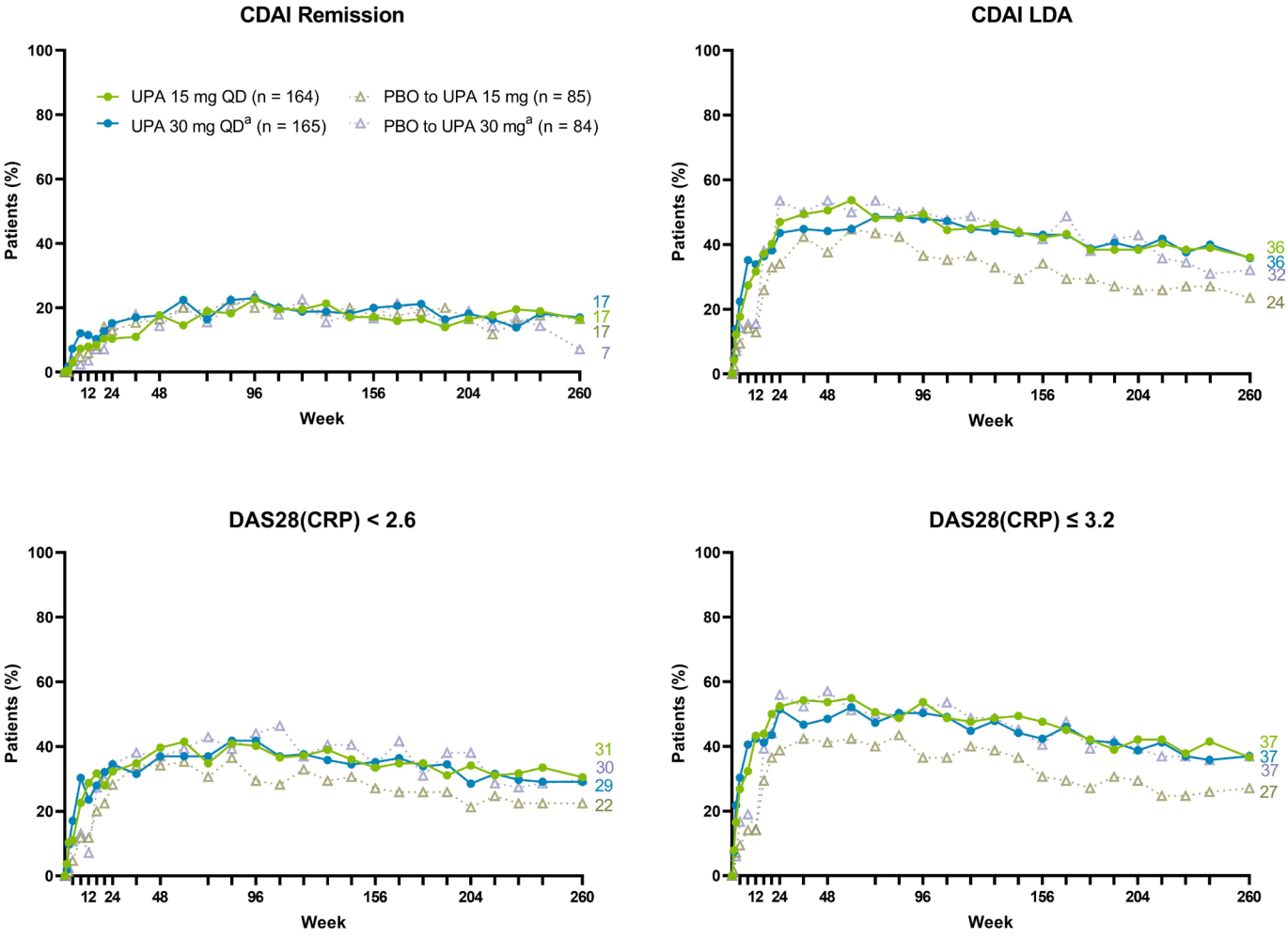


Figure 3 Proportions of patients achieving CDAI or DAS28(CRP) disease activity states through 5 years (NRI). Data are from patients who were initially randomised to UPA 15 mg or 30 mg and those who switched from PBO to either dose of UPA at week 12. Cut points for CDAI were ≤2.8 for remission and ≤10 for LDA. [a]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment. The switch occurred at different visits across the patient population, with the earliest switch occurring at the week 180 visit. CDAI, Clinical Disease Activity Index; DAS28(CRP), 28-joint Disease Activity Score based on C reactive protein; LDA, low disease activity; NRI, non-responder imputation; PBO, placebo; QD, once daily; UPA, upadacitinib.

most frequently reported types of serious infections included pneumonia and influenza (online supplemental materials text). Rates of infections were higher in patients receiving concomitant prednisone (90 and 117 E/100 PY with upadacitinib 15 mg and 30 mg, respectively) compared with those off prednisone (13 and 15 E/100 PY with upadacitinib 15 mg and 30 mg).

Most cases of herpes zoster were non-serious (upadacitinib 15 mg: n=28/29 (97%); upadacitinib 30 mg: n=43/46 (93%)) and involved a single dermatome (upadacitinib 15 mg: n=18/24 (75%); upadacitinib 30 mg: n=32/36 (89%)); no event showed meningoencephalopathic involvement. One serious herpes zoster event occurred in the upadacitinib 15 mg group (herpes zoster cutaneous disseminated), and three serious events occurred in the upadacitinib 30 mg group (two of which showed ophthalmic involvement). Most events of anaemia (~97%), hepatic disorder (~87%) and CPK elevation (~93%) were mild or moderate in severity in patients receiving upadacitinib 15 mg or 30 mg. The majority of hepatic disorders were hepatic enzyme elevations, with any potential Hy's law cases subjected to further medical review. One patient receiving upadacitinib 15 mg had an alanine transaminase (ALT) and aspartate transaminase (AST) ≥3×upper limit of normal (ULN), with bilirubin of >2×ULN. The patient showed signs of cholestasis, including yellowing of the skin and elevated levels of alkaline phosphatase (>1.5×ULN). They were admitted to the hospital for pancreatic cancer with compression of the bile duct; based on these characteristics, the event did not meet Hy's law criteria. One case of rhabdomyolysis was reported for elevated CPK (considered not related to study drug administration with an alternative aetiology of influenza), which resolved with appropriate treatment after 6 days. Two adjudicated gastrointestinal perforation events also occurred in patients receiving upadacitinib (online supplemental materials).

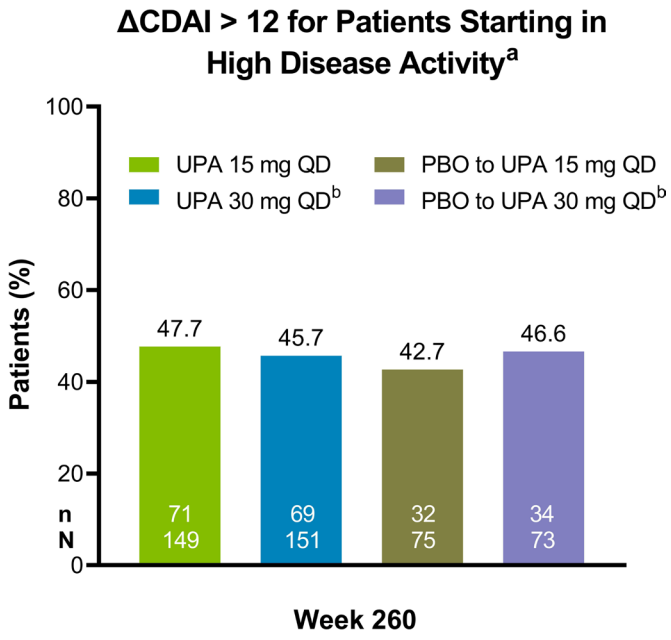


Figure 4 Proportions of patients starting in high disease activity with CDAI improvement >12 at week 260 (AO). Minimal clinically important differences in CDAI were previously defined as >12 for patients in high disease activity (Curtis *et al*,[17] 2015). The number of patients starting in high desease activity who achieved a CDAI improvement >12 (n) and the total number of patients in each treatment group (N) at week 260 are shown. [a]High disease activity was defined as CDAI >22. [b]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment. The switch occurred at different visits across the patient population, with the earliest switch occurring at the week 180 visit. AO, as observed; CDAI, Clinical Disease Activity Index; PBO, placebo; QD, once daily; UPA, upadacitinib.

EAERs of malignancy excluding non-melanoma skin cancer (NMSC) are reported in table 1. Ten malignancies excluding NMSC occurred in the upadacitinib 15 mg group, including two cases of bladder cancer and a single event each of breast cancer, colon cancer metastatic, endometrial adenocarcinoma, acute promyelocytic leukaemia, adenocarcinoma of the pancreas, malignant melanoma, non-small cell lung cancer metastatic and pancreatic carcinoma stage IV. In patients treated with upadacitinib 30 mg, four malignancies excluding NMSC were reported: two prostate cancer, one breast cancer and one rectal cancer metastatic. Among those who switched from upadacitinib 30 mg to 15 mg, one event of follicular thyroid cancer was also reported. Most (n=13/15, 87%) malignancies other than NMSC occurred in patients >50 years of age, and approximately half of events (n=8/15, 53%) occurred in former or current smokers. Per protocol amendment, all malignancies excluding NMSC led to the discontinuation of the study drug. Malignancies excluding NMSC were observed across the disease activity continuum, with 27% (n=4/15) in CDAI remission at the visit preceding malignancy occurrence (online supplemental figure 11). Rates of NMSC were similar for patients receiving either dose of upadacitinib (1.1 E/100PY and 0.8 E/100PY on upadacitinib 15 mg and 30 mg, respectively). Rates of basal cell carcinoma and squamous cell carcinoma were also comparable between doses (basal cell carcinoma: 0.5 E/100 PY for each dose; squamous cell carcinoma: 0.4 E/100 PY with upadacitinib 15 mg and 0.3 E/100 PY with upadacitinib 30 mg).

EAERs of adjudicated MACE and VTE are reported in table 1. MACE in patients on upadacitinib 15 mg included five non-fatal myocardial infarctions, three non-fatal strokes, one sudden cardiac death and one PE; on upadacitinib 30 mg, one non-fatal myocardial infarction and one sudden cardiac death were reported. Adjudicated VTEs in patients on upadacitinib 15 mg included three non-fatal PE, three non-fatal DVT, three concurrent DVT and PE (non-fatal), and one fatal concurrent DVT and PE; on upadacitinib 30 mg, one non-fatal PE, one non-fatal DVT, and one concurrent PE and DVT (non-fatal) were reported. Two VTE events (1.3 E/100 PY) also occurred in patients who switched from upadacitinib 30 mg to 15 mg, including one non-fatal DVT and one non-fatal event of concurrent PE and DVT. All MACE and the majority (n=15/16, 94%) of VTE events occurred in patients aged ≥50 years. Additionally, all patients who experienced MACE or VTE had at least one associated CV risk factor in addition to RA, such as hypertension or congestive heart failure, obesity, smoking, immobility or prior history of DVT. Of those who experienced MACE or VTE, CDAI scores at the visit preceding event occurrence were distributed across the disease activity spectrum (online supplemental figures 12 and 13).

The rate of COVID-19 events was numerically lower in patients receiving upadacitinib 30 mg (0.6 E/100 PY) than in patients receiving upadacitinib 15 mg (2.4 E/100 PY), or in patients receiving upadacitinib 15 mg switched from upadacitinib 30 mg (8.4 E/100 PY). The lower rate for patients in the 30 mg group may be due to differences in the timing of the study, with most patients who initially received upadacitinib 30 mg having been switched to the approved 15 mg dose by the beginning of the COVID-19 pandemic. Upadacitinib treatment was interrupted or discontinued in approximately 60% of patients with COVID-19 events. For the two treatment-emergent COVID-19-related deaths (ie, involving complications from COVID-19 infection and resulting death due to another AE) that occurred during the trial, upadacitinib treatment was withdrawn on diagnosis of COVID-19 infection. Of 30 treatment-emergent COVID-19 infections, 38% (n=6/16), 25% (n=1/4) and 30% (n=3/10) of events were serious in patients in the upadacitinib 15 mg, upadacitinib 30 mg and upadacitinib 15 mg switched from 30 mg groups, respectively; similarly, all except for one of these events (in the upadacitinib 15 mg switched from 30 mg group) required hospitalisation (online supplemental table 5). None of the treatment-emergent COVID-19 infections were fatal.

The rates of treatment-emergent death were generally similar across groups (0.9, 0.8 and 1.3 E/100 PY in the upadacitinib 15 mg, upadacitinib 30 mg and upadacitinib

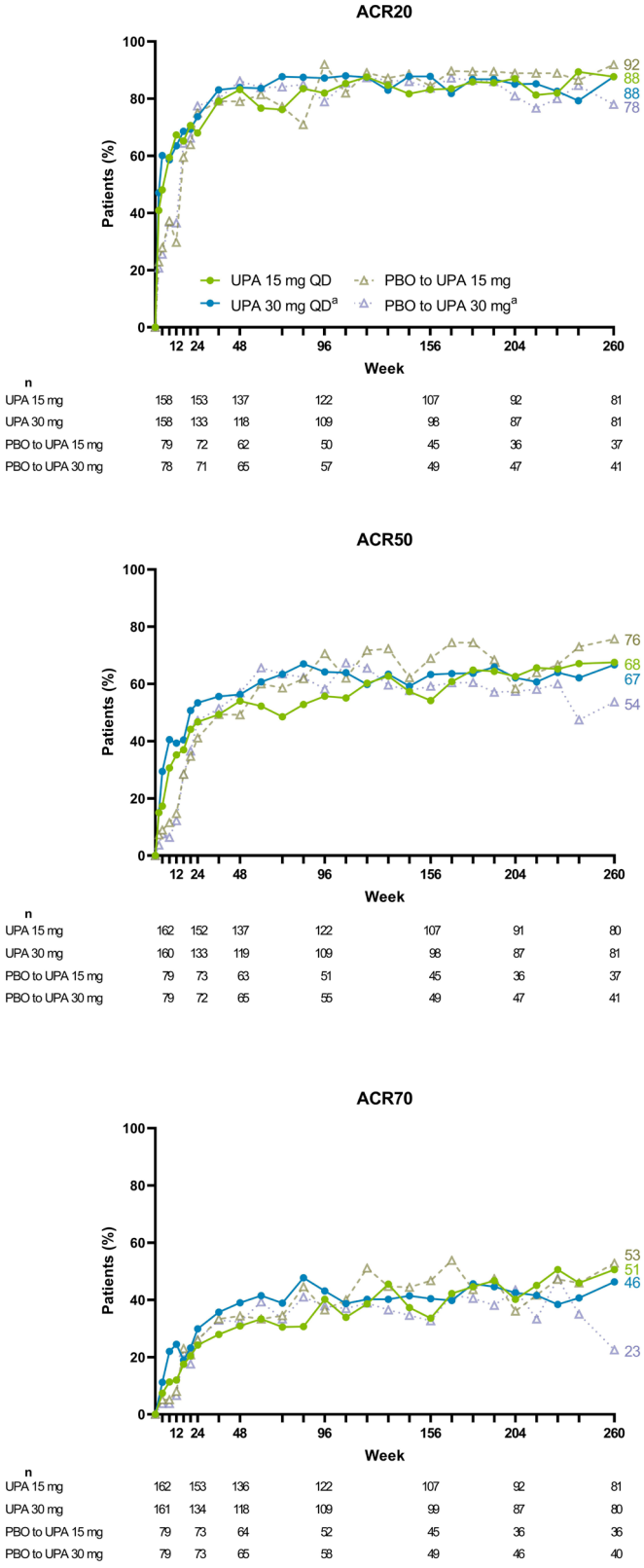


Figure 5 Proportions of patients achieving ACR20/50/70 responses through 5 years (AO). Data are from patients who were initially randomised to UPA 15 mg or 30 mg and those who switched from PBO to either dose of UPA at week 12. A total number of patients (n) in each treatment group are shown at weeks 4, 24, 48, 96, 156, 204 and 260. [a]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment. The switch occurred at different visits across the patient population, with the earliest switch occurring at the week 180 visit. ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology response criteria; AO, as observed; PBO, placebo; QD, once daily; UPA, upadacitinib.

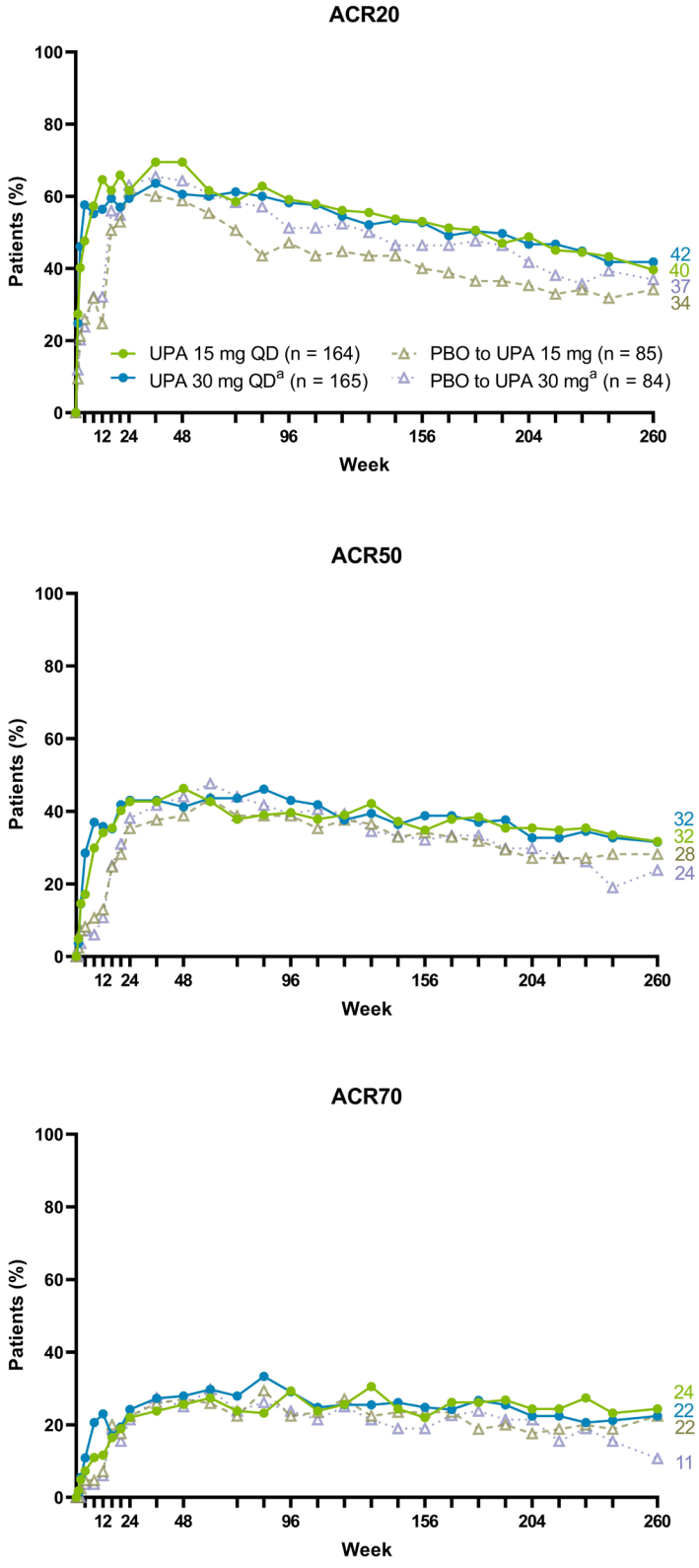


Figure 6 Proportions of patients achieving ACR20/50/70 responses through 5 years (NRI). Data are from patients who were initially randomised to UPA 15 mg or 30 mg and those who switched from PBO to either dose of UPA at week 12. [a]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment. The switch occurred at different visits across the patient population, with the earliest switch occurring at the week 180 visit. ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology response criteria; NRI, non-responder imputation; PBO, placebo; QD, once daily; UPA, upadacitinib.

Table 1 Adverse events of interest through 5 years

Events (E/100 PY) (95% CI)*	UPA 15 mg QD (n=236; PY=759.5)	UPA 30 mg QD (n=240; PY=621.9)	UPA 30 mg QD switched to UPA 15 mg QD (n=138; PY=155.5)
Any TEAE	2082 (274.1) (262.5, 286.2)	2202 (354.1) (339.4, 369.2)	269 (173.0) (152.9, 195.0)
Serious TEAEs	159 (20.9) (17.8, 24.5)	145 (23.3) (19.7, 27.4)	34 (21.9) (15.1, 30.6)
Any TEAE leading to discontinuation of study drug	66 (8.7) (6.7, 11.1)	61 (9.8) (7.5, 12.6)	14 (9.0) (4.9, 15.1)
Any infection	656 (86.4) (79.9, 93.2)	725 (116.6) (108.2, 125.4)	63 (40.5) (31.1, 51.8)
Serious infection	38 (5.0) (3.5, 6.9)	39 (6.3) (4.5, 8.6)	7 (4.5) (1.8, 9.3)
Opportunistic infection†	4 (0.5) (0.1, 1.3)	0	1 (0.6) (0, 3.6)
Herpes zoster	29 (3.8) (2.6, 5.5)	46 (7.4) (5.4, 9.9)	9 (5.8) (2.6, 11.0)
Malignancy (excluding NMSC)	10 (1.3) (0.6, 2.4)	4 (0.6) (0.2, 1.6)	1 (0.6) (0, 3.6)
NMSC	8 (1.1) (0.5, 2.1)	5 (0.8) (0.3, 1.9)	3 (1.9) (0.4, 5.6)
Hepatic disorder	54 (7.1) (5.3, 9.3)	43 (6.9) (5.0, 9.3)	4 (2.6) (0.7, 6.6)
Anaemia	27 (3.6) (2.3, 5.2)	32 (5.1) (3.5, 7.3)	5 (3.2) (1.0, 7.5)
Neutropaenia	10 (1.3) (0.6, 2.4)	21 (3.4) (2.1, 5.2)	1 (0.6) (0, 3.6)
Lymphopaenia	5 (0.7) (0.2, 1.5)	15 (2.4) (1.3, 4.0)	4 (2.6) (0.7, 6.6)
CPK elevation‡	21 (2.8) (1.7, 4.2)	33 (5.3) (3.7, 7.5)	4 (2.6) (0.7, 6.6)
MACE (adjudicated)	10 (1.3) (0.6, 2.4)	2 (0.3) (0, 1.2)	0
VTE (adjudicated)§	11 (1.4) (0.7, 2.6)	3 (0.5) (0.1, 1.4)	2 (1.3) (0.2, 4.6)
GI perforation (adjudicated)	0	2 (0.3) (0, 1.2)	0
COVID-19	18 (2.4) (1.4, 3.7)	4 (0.6) (0.2, 1.6)	13 (8.4) (4.5, 14.3)
All deaths¶	9 (1.2) (0.5, 2.2)	5 (0.8) (0.3, 1.9)	2 (1.3) (0.2, 4.6)
Deaths ≤30 days after last dose	7 (0.9) (0.4, 1.9)	5 (0.8) (0.3, 1.9)	2 (1.3) (0.2, 4.6)
Deaths >30 days after last dose	2 (0.3) (0, 1.0)	0	0

Safety data are reported as exposure-adjusted event rates.
*Data include all patients receiving upadacitinib, with assignment based on drug dose at the time of event. TEAEs are reported separately (last column) for patients who switched from UPA 30 mg to the approved 15 mg dose, with the earliest switch occurring at week 180. For those patients, exposure to upadacitinib 30 mg was censored prior to the day of the switch to upadacitinib 15 mg; any event occurring after the switch was assigned to the upadacitinib 30 mg switched to upadacitinib 15 mg group.
†Opportunistic infections exclude oral candidiasis and herpes zoster. No cases of TB were reported during the study.
‡One case of rhabdomyolysis (with an alternative aetiology of influenza) was reported on UPA 30 mg.
§VTE is defined as pulmonary embolism and deep vein thrombosis.
¶Includes treatment-emergent and non-treatment-emergent deaths.
AE, adverse event; CPK, creatine phosphokinase; GI, gastrointestinal; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; PBO, placebo; PY, patient-years; QD, once daily; TB, tuberculosis; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolism.

from 30 mg to 15 mg groups, respectively). The most common AEs leading to death were CV in nature (additional details in online supplemental materials text). Numerically higher proportions of patients treated with upadacitinib 30 mg vs 15 mg had grade 3/4 haemoglobin disorders (table 2) at some point during their treatment; however, no dose-dependency was observed in the rates of ALT and AST disorders or other common laboratory parameters. In general, haematology, clinical chemistry and urinalysis values that were normal at baseline rarely shifted to outside the standard range at the final clinic assessment, and grade 3 or 4 laboratory abnormalities newly observed at any time point during the study generally resolved without discontinuation of study drug. The group mean values for key haematology variables (haemoglobin, lymphocytes, neutrophils and platelets) were generally within normal range at baseline and at subsequent treatment visits.

DISCUSSION

SELECT-BEYOND included treatment-refractory RA patients who had an inadequate response or intolerance to ≥1 prior bDMARD therapy and continued to show high disease activity on background csDMARDs. Approximately one-fourth of enrolled patients had received previous treatment with ≥3 bDMARDs. In this report, we expand the clinical knowledge base of continuing JAK inhibitor treatment in refractory patients, providing long-term efficacy and safety data for upadacitinib therapy.

Table 2 Grade 3/4 laboratory abnormalities observed at any point during the 5-year study

Parameter*	UPA 15 mg QD (N=236)		UPA 30 mg QD (N=240)		UPA 30 mg QD switched to UPA 15 mg QD (N=138)	
	n/N_obs † (%)	Mean change from BL‡±SD	n/N_obs† (%)	Mean change from BL‡±SD	n/N_obs† (%)	Mean change from BL‡±SD
Haemoglobin (g/dL)						
Grade 3 (decreased 2.1 to <3.0§ or Hb ≥7.0 to <8.0)	27/234 (11.5)	−2.3±0.2	38/240 (15.8)	−2.4±0.2	16/137 (11.7)	−2.3±0.2
Grade 4 (decreased ≥3.0§ or Hb <7.0)	19/234 (8.1)	−4.2±1.1	23/240 (9.6)	−3.7±0.5	4/137 (2.9)	−4.4±2.3
Lymphocytes (×10^9/L)						
Grade 3 (0.5 to <1.0)	89/234 (38.0)	−0.82±0.59	94/240 (39.2)	−0.87±0.57	54/136 (39.7)	−0.96±0.64
Grade 4 (<0.5)	12/234 (5.1)	−1.14±0.57	13/240 (5.4)	−0.94±0.60	6/136 (4.4)	−1.00±0.67
Neutrophils (×10^9/L)						
Grade 3 (0.5 to <1.0)	4/234 (1.7)	−1.6±0.9	7/240 (2.9)	−3.9±5.6	1/136 (0.7)	−16.4
Grade 4 (<0.5)	3/234 (1.3)	−3.3±1.4	0/240	0	1/136 (0.7)	−1.9
ALT (U/L)						
Grade 3 (3.0 to <8.0×ULN)	13/234 (5.6)	119.3±48.5	10/240 (4.2)	93.4±51.8	1/137 (0.7)	52.0
Grade 4 (>8.0×ULN)	4/234 (1.7)	463.3±289.8	1/240 (0.4)	844.0	1/137 (0.7)	2746.0
AST (U/L)						
Grade 3 (3.0 to 8.0×ULN)	11/234 (4.7)	134.0±59.0	6/240 (2.5)	112.5±25.8	2/137 (1.5)	84.5±24.8
Grade 4 (>8.0×ULN)	2/234 (0.9)	1228.0±1412.8	1/240 (0.4)	534.0	1/137 (0.7)	6627.0
Creatine kinase (U/L)						
Grade 3 (>5.0×ULN to 10.0×ULN)	3/234 (1.3)	1304.0±222.6	7/240 (2.9)	1161.6±383.7	0/136	0
Grade 4 (>10.0×ULN)	1/234 (0.4)	1838.0	3/240 (1.3)	4259.3±2459.7	1/136 (0.7)	6677.0
Creatinine (µMol/L)						
Grade 3 (>3.0 to 6.0×ULN)	0/234	0	0/240	0	0/137	0
Grade 4 (>6.0×ULN)	0/234	0	0/240	0	1/137 (0.7)	813.3

Safety data are reported as exposure-adjusted event rates.
*Data are for patients with worsening in grade severity for laboratory parameters. Grading was based on Outcome Measures in Rheumatology criteria, except for creatine kinase and creatinine, where the National Cancer Institute's standard common terminology criteria was used. Data include all patients receiving upadacitinib, with assignment based on drug dose at the time of event. TEAEs are reported separately (last column) for patients who switched from UPA 30 mg to the approved 15 mg dose, with the earliest switch occurring at week 180. For those patients, exposure to upadacitinib 30 mg was censored prior to the day of the switch to upadacitinib 15 mg; any event occurring after the switch was assigned to the upadacitinib 30 mg switched to upadacitinib 15 mg group.
†N_obs indicates the number of patients with both baseline and postbaseline values for the respective parameter.
‡Changes from baseline to worst reported value for laboratory variables are shown for patients with grade 3 or grade laboratory abnormalities.
§Decrease from baseline. Baseline is defined as the last observation on or before the date of the first dose of study drug in the corresponding treatment group.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, haemoglobin; PBO, placebo; QD, once daily; TEAEs, treatment-emergent adverse events; ULN, upper limit of the normal range; UPA, upadacitinib.

Through 5 years, upadacitinib continued to be effective in treating the signs and symptoms of RA. Additionally, no new safety issues emerged from the long-term study, and our findings are consistent with the known safety profile of upadacitinib.[4 19 20]

Both upadacitinib 15 mg and 30 mg treatment demonstrated sustained improvements in clinical, functional and patient-reported outcomes through 5 years. At week 260, over three-quarters of patients remaining in the study attained CDAI LDA, and clinical remission was seen in approximately one-third of patients. Moreover, nearly half of all patients who started the trial in high disease activity had a CDAI improvement >12 at week 260. Significant mean improvements from baseline in physical function, as assessed by HAQ-DI, and pain were also observed over 5 years. Morning stiffness, a hallmark characteristic of RA that can significantly affect a patient's quality of life and ability to work,[21] showed sustained improvements in mean severity and duration compared with baseline values. Overall, long-term efficacy responses were similar between patients initially randomised to either upadacitinib 15 mg or 30 mg. Moreover, no apparent loss of benefit was observed in patients who switched from upadacitinib 30 mg to the approved 15 mg dose following protocol amendment. Patients who switched from placebo to upadacitinib 15/30 mg at week 12 generally showed comparable efficacy throughout the LTE relative to those initially randomised to upadacitinib. Of the approximately 20% of patients who remained in the study but did not meet CDAI LDA criteria by week 260, improvements in clinical and patient-reported outcomes were also observed, although typically to a lower extent than in the overall SELECT-BEYOND population.

The safety profile observed over 5 years was consistent with earlier analyses from SELECT-BEYOND and an integrated safety analysis of upadacitinib across five trials.[4 19] Compared with short-term safety results (up to week 24), the rates of most AEs and AESIs remained generally similar or decreased over time, and no change in the safety profile of upadacitinib was identified after prolonged exposure. As observed previously, higher frequencies of some AEs were noted in the upadacitinib 30 mg group compared with the 15 mg group, including increased rates of CPK elevation, lymphopaenia, anaemia and neutropaenia. Dose-dependent increases in herpes zoster were observed with upadacitinib 30 mg vs 15 mg, consistent with the known association for elevated herpes zoster risk with JAK inhibition.[19 22 23] Rates of COVID-19 were highest in patients who switched from upadacitinib 30 mg to 15 mg, but this is possibly due to the timing of the treatment switch and the short exposure to the 15 mg dose in conjunction with the onset of the pandemic.

This study was not designed to evaluate the relative safety of upadacitinib versus an active comparator. Notably, however, there was no detectable dose-dependent effect for malignancy excluding NMSC, MACE or VTE, with overlapping confidence intervals between upadacitinib 15 mg and 30 mg. The vast majority of patients who experienced MACE or VTE were ≥50 years of age, and all had at least 1 CV risk factor at baseline. Additionally, there was no increase in MACE and VTE rates observed here compared with those reported at earlier time points in SELECT-BEYOND.[4] Rates of malignancy (excluding NMSC), MACE and VTE were also generally comparable between upadacitinib 15 mg and 30 mg in an integrated analysis of upadacitinib safety.[19] The rates of malignancy (excluding NMSC) identified here during the 5-year study are similar to analyses based on real-world data.[24–26] Disease activity around the time of malignancy excluding NMSC, MACE and VTE was also assessed at the visit preceding event occurrence; however, perhaps due to the limited number of events, no clear pattern emerged between disease activity and occurrence of these AEs.

Limitations of this study include potential biases that may arise due to the inherent nature of LTEs, which only include patients who met the original inclusion criteria necessary to enter the study. Consequently, the results may not fully capture the real-world experience of the treatment in a more diverse patient population with comorbidities or specific characteristics that were excluded during the original trial, such as a history of inflammatory joint disorders other than RA. Moreover, approximately 54% of patients randomised to upadacitinib did not complete the trial on study drug, which could potentially lead to differences in the characteristics of the final study population compared with those of the overall population at study entry. Additionally, the results based on AO data may overestimate treatment efficacy, as those who remain in a trial long-term are often those who respond to and are tolerant of the treatment. To address this issue, more conservative estimates based on NRI were also included. Another limitation is the lack of a placebo control beyond week 12 of the study and the absence of any active comparators. More generally, it should be emphasised that this was not a dedicated safety study to assess long-term safety versus a comparator, but instead, is the LTE of a study that was designed to inform long-term treatment results. Comparisons between short-term and long-term safety results should also be treated with caution due to a significant proportion of patients not completing the trial; moreover, those who remained may have been more likely to have responded to and tolerated the treatment. Lastly, the patient population of SELECT-BEYOND lacked geographic diversity, with the majority (~86%) of patients included from North America and Western Europe. Despite these limitations, the 5-year data from this study expand our understanding of the long-term benefit–risk profile of upadacitinib in a clinically controlled setting.

In summary, the safety profile observed over 5 years was consistent with earlier assessments of upadacitinib treatment in this population and compared with other studies in the upadacitinib development programme. Clinical and functional outcomes of bDMARD-IR patients who were treated with upadacitinib 15 mg or 30 mg were maintained over 5 years. Notably, by week 260, over

three-quarters of patients remaining in the trial on upadacitinib 15 mg or 30 mg were in CDAI LDA and almost 50% of all patients who began in high disease activity and stayed in the trial had a CDAI improvement >12.

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Patient consent for publication Not applicable.

Ethics approval SELECT-BEYOND was conducted in accordance with International Council for Harmonisation guidelines, applicable regulations and the Declaration of Helsinki. Independent ethics committees and institutional review boards approved all study-related documents. Patients provided written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual and trial-level data (analysis data sets), as well as other information (eg, 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 (SAP) and execution of a Data Sharing Agreement (DSA). 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, visit the following link: https://vivli.org/ourmember/abbvie/ then select 'Home'.

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