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# Safety and Efficacy of Upadacitinib in Patients With Active Ankylosing Spondylitis and an Inadequate Response to Nonsteroidal Antiinflammatory Drug Therapy: One-Year Results of a Double-Blind, Placebo-Controlled Study and Open-Label Extension

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**Objective.** To report the efficacy and safety of upadacitinib through 1 year in patients with ankylosing spondylitis (AS).

**Methods.** In the SELECT-AXIS 1 study, adults with active AS and an inadequate response to nonsteroidal antiinflammatory drugs were randomized to receive upadacitinib 15 mg once daily or placebo. At week 14, patients who had been randomized to receive placebo were switched to upadacitinib, and all patients continued in the open-label extension and received upadacitinib up to week 104; interim data up to week 64 are reported herein.

**Results.** Of 187 patients, 178 completed week 14 on study drug and entered the open-label extension. Similar proportions of patients in either group (continuous upadacitinib or placebo-to-upadacitinib) achieved Assessment of SpondyloArthritis international Society 40% response (ASAS40) or Ankylosing Spondylitis Disease Activity Score (ASDAS) showing low disease activity at week 64: ≥70% of patients achieved these end points based on nonresponder imputation (NRI) and ≥81% based on as-observed analyses. Furthermore, ≥34% (NRI) and ≥39% (as-observed analysis) achieved ASDAS showing inactive disease or ASAS showing partial remission at week 64. Mean changes from baseline (week 0) to week 64 in pain, function, and inflammation showed consistent improvement or sustained maintenance through the study. Among 182 patients receiving upadacitinib (237.6 patient-years), 618 adverse events (260.1 per 100 patient-years) were reported. No serious infections, major adverse cardiovascular events, venous thromboembolic events, gastrointestinal perforation, or deaths were reported.

**Conclusion.** Upadacitinib 15 mg once daily showed sustained and consistent efficacy over 1 year. Patients who switched from placebo to upadacitinib at week 14 showed similar efficacy versus those who received continuous upadacitinib.

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## INTRODUCTION

Ankylosing spondylitis (AS), also known as radiographic axial spondyloarthritis, is a chronic, inflammatory rheumatic disease affecting the axial skeleton, mainly characterized by back pain (including nocturnal back pain) and morning stiffness, and peripheral pain due to arthritis, enthesitis, and extraarticular manifestations (1,2). Irreversible structural damage often occurs, negatively impacting patients' lives (3). To maximize patients' quality of life, therapeutic intervention is necessary to control the signs and symptoms of disease, prevent structural damage, and maintain physical function (4). To achieve these goals, a treatment target for AS should be set at achieving sustained inactive disease or low disease activity (4,5). In recent years, JAK inhibitors have emerged for the treatment of several immune-mediated inflammatory diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn's disease, and ulcerative colitis (6–8), and are under investigation as a treatment for AS (9–13).

Upadacitinib, a JAK inhibitor engineered for increased selectivity for JAK1 over JAK2, JAK3, and tyrosine kinase 2 (14), was investigated for the treatment of patients with AS who had an inadequate response to nonsteroidal antiinflammatory drugs (NSAIDs) in the randomized, placebo-controlled phase II/III SELECT-AXIS 1 study (15). The study met its primary end point, with a significantly greater proportion of patients receiving upadacitinib achieving Assessment of SpondyloArthritis international Society 40% response (ASAS40) (16) at week 14 versus placebo (51.6% for upadacitinib 15 mg once daily versus 25.5% for placebo; $P < 0.001$), as well as several multiplicity-controlled secondary end points reflecting significant improvement in disease activity, function, and magnetic resonance imaging outcomes for upadacitinib versus placebo. Upadacitinib was well tolerated, and no serious infections, herpes zoster, malignancy, venous thromboembolic events, or deaths were reported during the first 14 weeks. The objective of this interim analysis of the SELECT-AXIS 1 extension study is to report safety and efficacy, including extraspinal outcomes, in patients with AS receiving upadacitinib 15 mg once daily through 1 year.

## PATIENTS AND METHODS

**Study design.** SELECT-AXIS 1 (ClinicalTrials.gov identifier: NCT03178487) is a randomized, multicenter (62 centers in 20 countries), phase II/III study consisting of a 14-week double-blind, placebo-controlled period 1 and an ongoing 90-week open-label extension period 2 to evaluate the safety and efficacy of upadacitinib 15 mg (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract). The methods and results of period 1 have been published previously (15). Briefly, patients were randomized 1:1 to receive upadacitinib 15 mg once daily or placebo for 14 weeks. Patients who completed period 1 were eligible to enter period 2 and receive open-label upadacitinib 15 mg once daily for 90 weeks, up to week 104. Reported herein are efficacy results at week 64, when all patients continuing in the study had at least 1 year of upadacitinib exposure, including in the placebo-to-upadacitinib switch group. Of note, patients and investigators remained blinded with regard to the patients' period 1 assignment throughout the study.

This study was conducted in accordance with International Council for Harmonisation guidelines and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent, and the study protocol was approved by an institutional review board or independent ethics committee at each study site.

**Participants.** The study enrolled adult patients (age ≥18 years) with AS who met the modified New York criteria (17) based on independent central reading of radiographs of the sacroiliac joints and who had active disease at baseline (i.e., week 0), defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (18) score of ≥4 and patient's assessment of back pain score of ≥4 (on a numerical rating scale [NRS] of 0–10) at screening and baseline visit, and had an inadequate response to ≥2 NSAIDs or intolerance to or contraindication for NSAIDs. Patients receiving a stable dose of concomitant conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), oral glucocorticoids, NSAIDs, and analgesics were eligible; patients with prior exposure to JAK inhibitors or biologic DMARDs (such as tumor necrosis factor [TNF] inhibitors and interleukin-17A [IL-17A] inhibitors) were excluded.

**Patient and public involvement.** This research was done without any formal patient/patient organization involvement in the study design, development of patient-relevant outcomes, interpretation of results, or the writing or editing of the manuscript.

**Efficacy end points.** Efficacy was assessed based on the percentage of patients achieving ASAS20, ASAS40, ASAS showing partial remission, BASDAI50, and Ankylosing Spondylitis Disease Activity Score (ASDAS) (19) showing inactive disease (ASDAS ID; defined as an ASDAS <1.3), ASDAS showing low disease activity (ASDAS LDA; <2.1), ADSAS showing major improvement (ASDAS MI; decrease from baseline ≥2.0), and ASDAS showing clinically important improvement (ASDAS CII; decrease from baseline ≥1.1) through 64 weeks (20,21). In addition, change from baseline in the ASDAS using the C-reactive protein level (ASDAS-CRP) (22), Bath Ankylosing Spondylitis Functional Index (BASFI) (23), and linear Bath Ankylosing Spondylitis Metrology Index (BASMI) (24) through 64 weeks and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) (25), Work Productivity and Activity Impairment (WPAI; on a scale of 0–100) (26), ASAS health index, and AS quality of life (ASQoL) (27) through 52 weeks were assessed. Pain end points included back pain, nocturnal back pain, BASDAI question 2 (back pain), and BASDAI question

3 (peripheral pain/swelling). The proportions of patients achieving BASDAI <4 and normalization of high-sensitivity CRP (hsCRP ≤2.87) were evaluated in exploratory analyses.

**Safety assessment.** One-year safety reports are based on data available on the cutoff date of January 31, 2020, and were assessed as rate of treatment-emergent adverse events (AEs) reported as events per 100 patient-years. Treatment-emergent AEs were defined as AEs that began or worsened in severity after the first dose and through 30 days after the last dose of study medication.

**Statistical analysis.** One-year efficacy analysis was performed by randomized treatment group sequence in patients receiving upadacitinib 15 mg once daily from baseline throughout periods 1 and 2 (continuous upadacitinib group) and in patients switching from randomized placebo at week 14 (period 1) to open-label upadacitinib 15 mg once daily (period 2). For binary efficacy end points, response rate and 95% confidence interval (95% CI) were reported as-observed and by using nonresponder imputation (NRI) for missing data (patients who prematurely discontinued the study drug were considered as nonresponders for all subsequent visits after discontinuation, and any patient with any missing

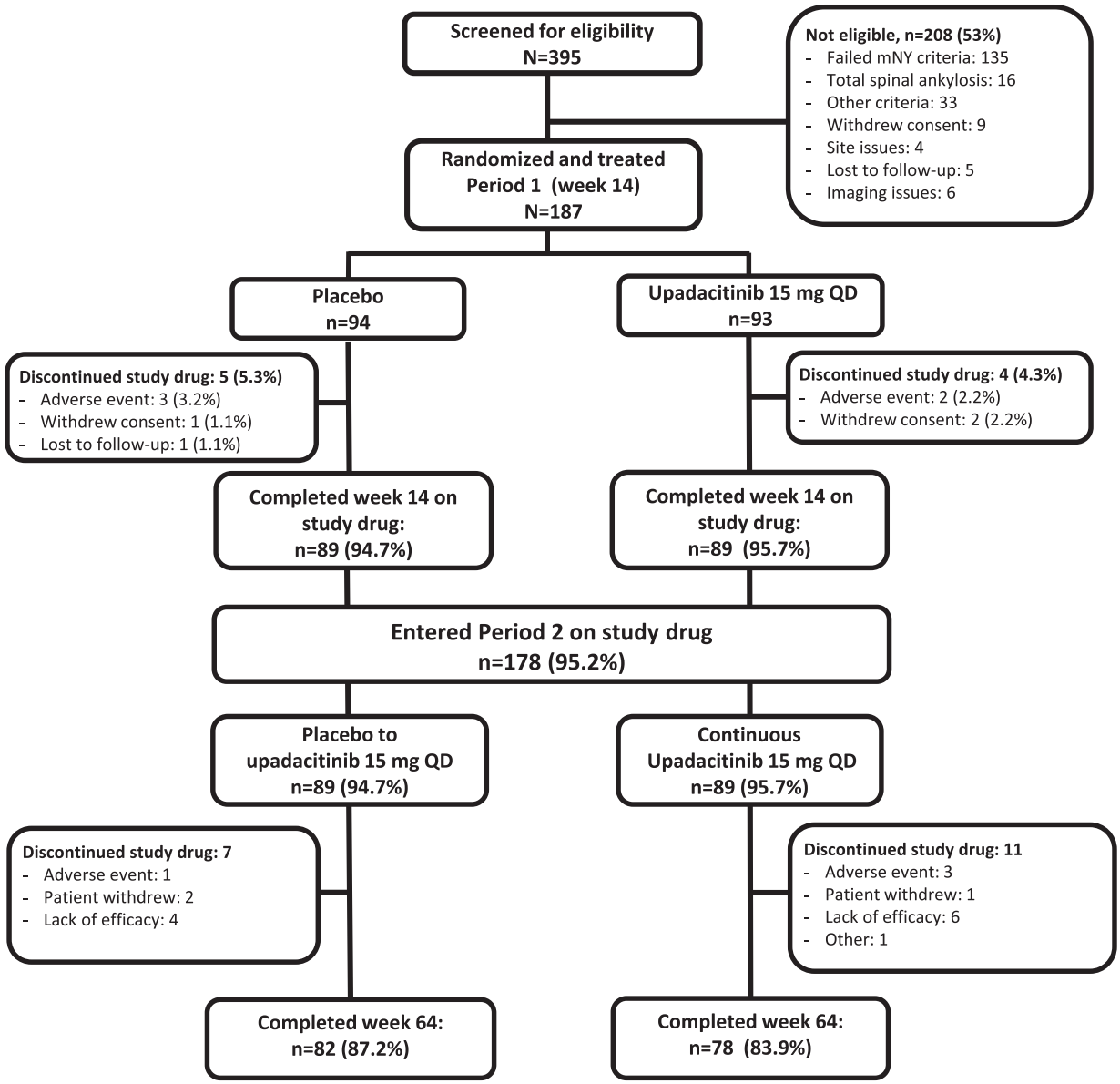


**Figure 1.** Patient disposition through week 64. Among the reasons for study drug discontinuation in period 2, adverse events included diarrhea, headache, and vertigo in 1 patient; squamous cell carcinoma of the tongue in 1 patient; and headache in 1 patient in the continuous upadacitinib group; and hemiparesthesia (right side) and intervertebral disc protrusion in 1 patient in the placebo-to-upadacitinib group; patient withdrawals included 1 patient who did not wish to administer the medication (lost to follow-up) and 1 patient who did not want to continue the study procedure or the study treatment in the placebo-to-upadacitinib group, and 1 patient who had challenges with transportation to the clinic in the continuous upadacitinib group; the "other" category included 1 patient who moved to a different country. mNY = modified New York; QD = once daily.

value at a specific visit was treated as a nonresponder for that visit). For continuous efficacy end points, descriptive statistics on as-observed data and estimated change from baseline with 95% CI from mixed-effects model repeated measures (MMRM) were reported. MMRM included the categorical fixed effects of treatment, visit, treatment-by-visit interaction, and stratification factor of hsCRP level at screening visit, premature discontinuation flag, and the continuous fixed covariate of baseline value using unstructured variance–covariance matrix. No statistical comparison was performed between the 2 treatment group sequences.

## RESULTS

Of the 187 patients randomized to period 1, 178 (89 in the continuous upadacitinib group and 89 in the placebo-to-upadacitinib switch group) completed week 14 on study drug and entered the open-label extension; 160 patients (78 [84%] in the continuous upadacitinib group and 82 [87%] in the placebo-to-upadacitinib switch group) completed week 64 (Figure 1). Lack of efficacy (n = 10) and AEs (n = 4) were the most common reasons for discontinuation of study drug between weeks 14 and 64.

Up to the data cutoff date, 88% of the patients (160 of 182) who received ≥1 dose of upadacitinib 15 mg once daily had at least 52 weeks of exposure to upadacitinib; 34% (62 of 182) had ≥18 months of exposure.

Patient demographic and baseline disease characteristics have been reported previously (15). Treatment arms were well balanced; in the upadacitinib and placebo arms, respectively, the majority of patients were male (68% and 73%) and HLA–B27 positive (75% and 78%), the mean age was 47.0 and 43.7 years, and most patients were from Europe (71% and 71%) and White (85% and 81%) (15). The mean duration since AS symptom onset was 14.8 years and 14.0 years, the mean duration since diagnosis was 7.8 years and 6.0 years, the mean ASDAS was 3.5 and 3.7, and the mean hsCRP level was 9.6 mg/liter and 11.7 mg/liter in the upadacitinib and placebo groups, respectively. Concomitant medications in the upadacitinib and placebo arms included NSAIDs (76% and 86%, respectively), csDMARDs (14% and 18%, respectively), and glucocorticoids (6% and 13%, respectively).

**Efficacy.** The percentage of patients achieving the primary efficacy end point of ASAS40 (52% in the NRI analysis and 54% in the as-observed analysis at week 14) continued to increase throughout the study in the continuous upadacitinib group: 72% and 85% of patients (in the NRI analysis and as-observed analysis, respectively) achieved ASAS40 at week 64 (Figure 2 and Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract). An analogous pattern of improvement was observed in ASDAS LDA (70% in the NRI analysis and 84% in the as-observed analysis), ASDAS ID (34% in the NRI analysis and 42% in the as-observed analysis), and ASAS showing partial remission (40% in the NRI analysis and 46% in the as-observed analysis) (Figures 2 and 3). Patients who switched from placebo to upadacitinib at week 14 showed a speed of onset and magnitude of response comparable to those in patients who were initially randomized to receive upadacitinib (responses in the switched group at week 64 were 70% in the NRI analysis and 81% in the as-observed analysis for ASAS40; 71% in the NRI analysis and 86% in the as-observed analysis for ASAS LDA; 36% in the NRI analysis and 44% in the as-observed analysis for ASAS ID; and 34% in the NRI analysis and 39% in the as-observed analysis for ASAS showing partial remission) (Figures 2 and 3).

Likewise, the percentage of patients achieving ASAS20 and BASDAI50 (Supplementary Figure 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract) and ASDAS CII and ASDAS MI (Supplementary Figure 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract) improved throughout the study in the continuous upadacitinib group; patients who switched to upadacitinib from placebo at week 14 showed a rapid onset of response for these end points, with responses at week 64 similar to those observed in patients receiving continuous upadacitinib (Supplementary Figures 2 and 3). At week 64, 88% of patients had a BASDAI <4 (90% [72 of 80] in the continuous upadacitinib group and 87% [71 of 82] in the placebo-to-upadacitinib switch group).

Mean changes from baseline to 1 year in disease activity, as measured by the ASDAS and pain, including back pain and nocturnal back pain, showed consistent improvement or sustained maintenance throughout the study in the continuous upadacitinib group; a similar magnitude of improvement was seen in the placebo-to-upadacitinib switch group after initiation of upadacitinib at week 14 (Figures 4 and 5 and Supplementary Table 2 and Supplementary Figure 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract). Improvements in function (BASFI) and inflammation, based on both clinical (mean of BASDAI questions 5 and 6) and laboratory (hsCRP) end points were also sustained through week 64 (Figure 4 and Supplementary Figure 5 and Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract). Analogous patterns of improvement over time were shown in assessments of quality of life (ASQoL and ASAS health index), spinal mobility (BASMI), enthesitis (MASES), and patient global assessment of disease activity (Supplementary Table 2 and Supplementary Figures 6 and 7, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract).

Among patients who were employed at baseline, the mean WPAI overall work impairment score continued to improve throughout the study in the continuous upadacitinib group (from –20.5 at week 14 [95% CI –27.1, –14.0] to –35.6 at week 52 [95% CI –43.2, –28.0]; as-observed analysis) and placebo-to-upadacitinib switch group (from –12.3 at week 14 [95% CI –19.8, –4.8] to –27.7 at week 52 [95% CI

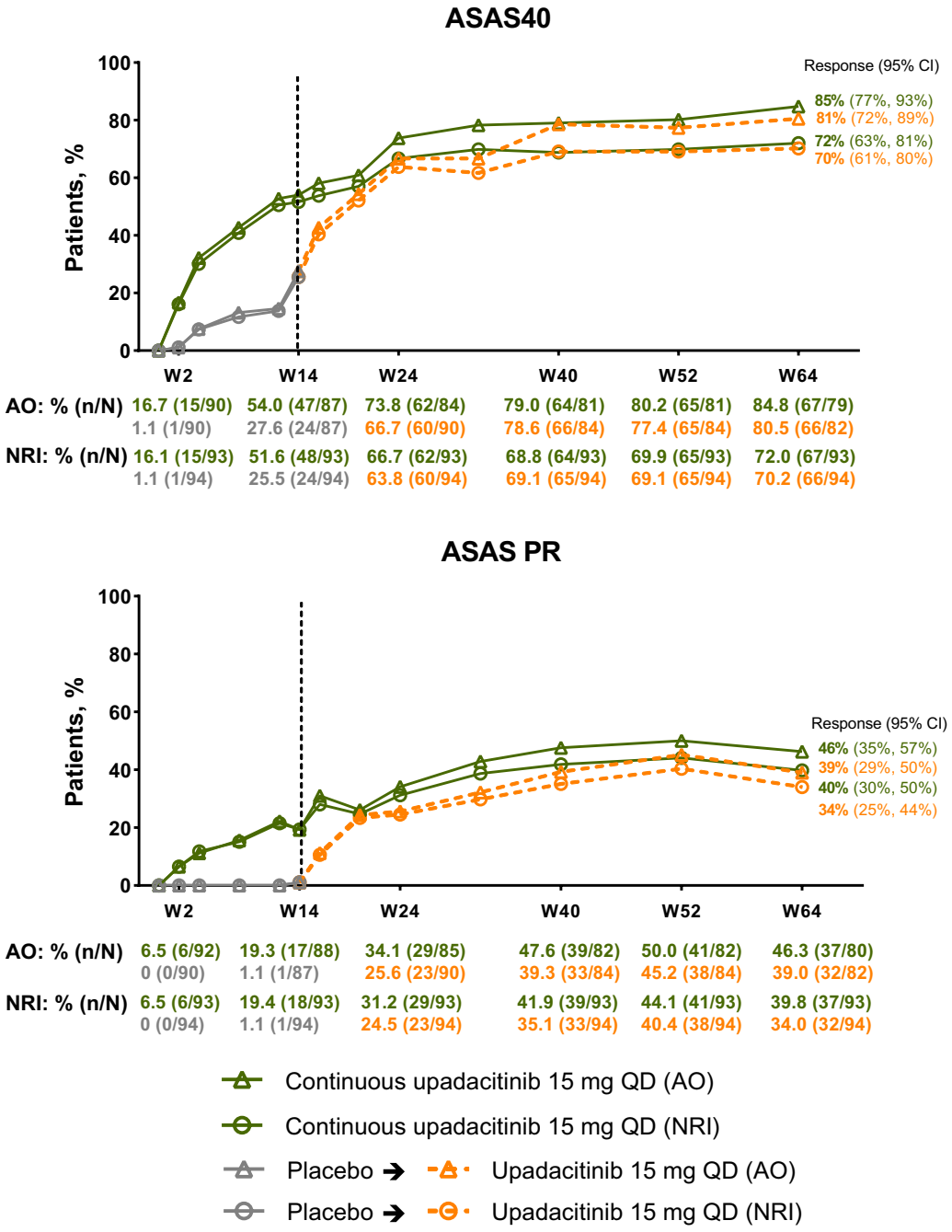


**Figure 2.** Percentage of patients achieving Assessment of SpondyloArthritis international Society 40% response (ASAS40) and ASAS showing partial remission (ASAS PR) over time. All patients randomized to receive placebo received open-label upadacitinib beginning at week 14. 95% CI = 95% confidence interval; AO = as-observed; NRI = nonresponder imputation; QD = once daily.

–35.4, –20.0]; as-observed analysis). Results were similar in the MMRM analysis (Supplementary Table 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract).

**Safety.** Safety through the January 31, 2020 data cutoff date was assessed in 182 patients (237.6 patient-years) receiving upadacitinib 15 mg once daily during period 1 or 2; a total of 618 AEs (260.1 per 100 patient-years) were reported (Table 1).

The most common AEs were nasopharyngitis (37 events [15.6 per 100 patient-years]), increased blood creatine phosphokinase (28 events [11.8 per 100 patient-years]), and upper respiratory tract infection (26 events [10.9 per 100 patient-years]). The creatine phosphokinase elevation events were all nonserious, none led to study drug discontinuation, and all except 2 were asymptomatic. The 2 symptomatic AEs were based on muscle pain with alternative explanations of increased exercise or physical activity, mild, and resolved with continued study drug treatment. The

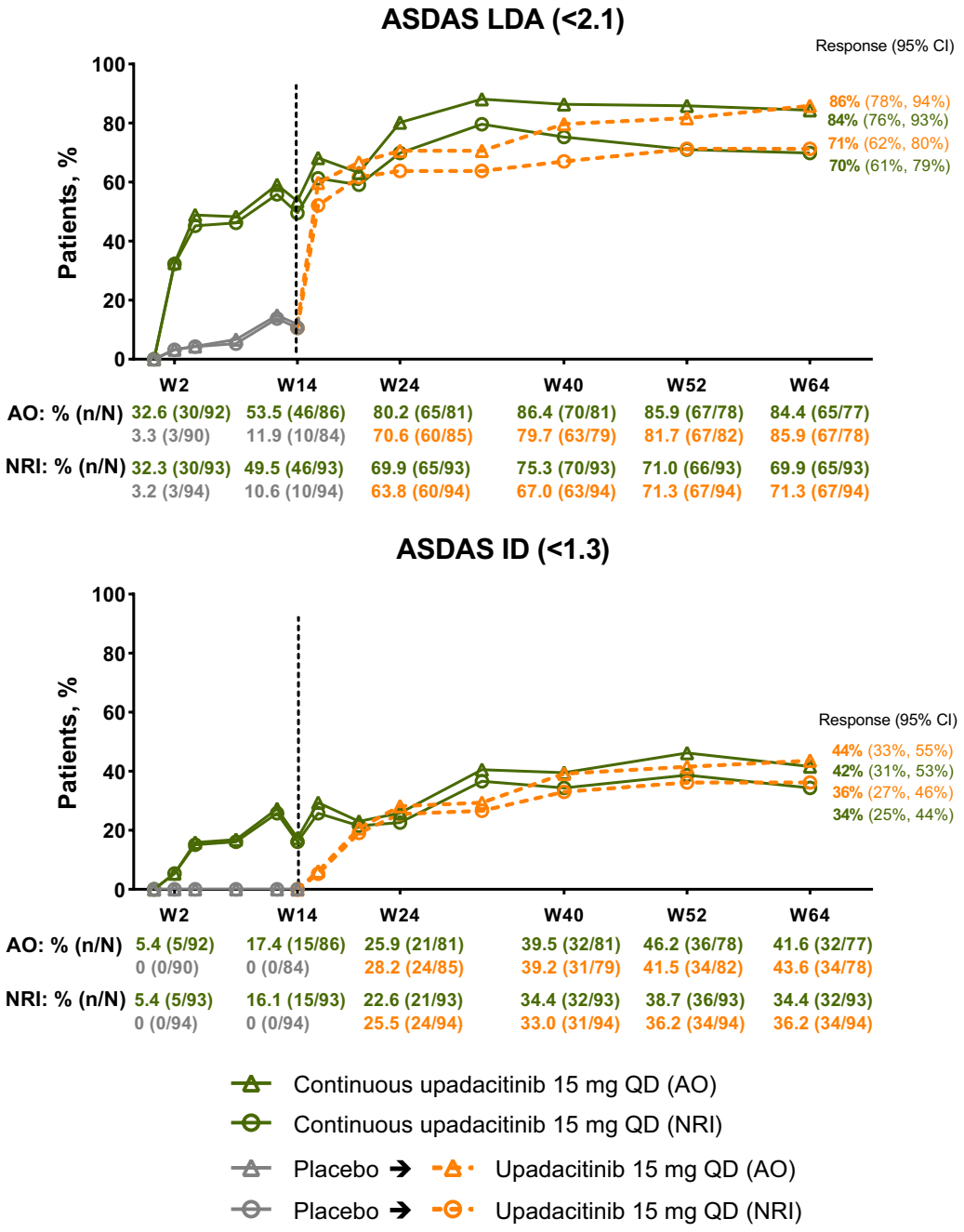


**Figure 3.** Percentage of patients achieving Ankylosing Spondylitis Disease Activity Score showing low disease activity (ASDAS LDA; <2.1) and ASDAS showing inactive disease (ASDAS ID; <1.3) over time. All patients randomized to receive placebo received open-label upadacitinib beginning at week 14. 95% CI = 95% confidence interval; AO = as-observed; NRI = nonresponder imputation; QD = once daily.

rates of serious AEs (5.9 per 100 patient-years) and AEs leading to discontinuation (6.3 per 100 patient-years) were low (Supplementary Table 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract).

No serious infections, active tuberculosis, major adverse cardiovascular events, venous thromboembolic events, gastrointestinal perforation, inflammatory bowel disease (IBD), renal dysfunction, or deaths were reported with upadacitinib treatment; of note, 4 patients (2 in each group) had a history of IBD at baseline. Rates of other events of interest were also low. The only malignancy reported was a stage IVa squamous cell carcinoma of the tongue in a 61-year-old man (former smoker) after the week 20 visit; per investigator, the event had no reasonable possibility to be related to the study drug but did lead to discontinuation of the study drug as required by the study protocol. Five events of herpes zoster (2.1 per 100 patient-years) in 4 patients were reported; all were nonserious and limited to 1 dermatome, and 1 led to discontinuation of the study drug. Two opportunistic infections (0.8 per 100 patient-years) were reported; both were nonserious events

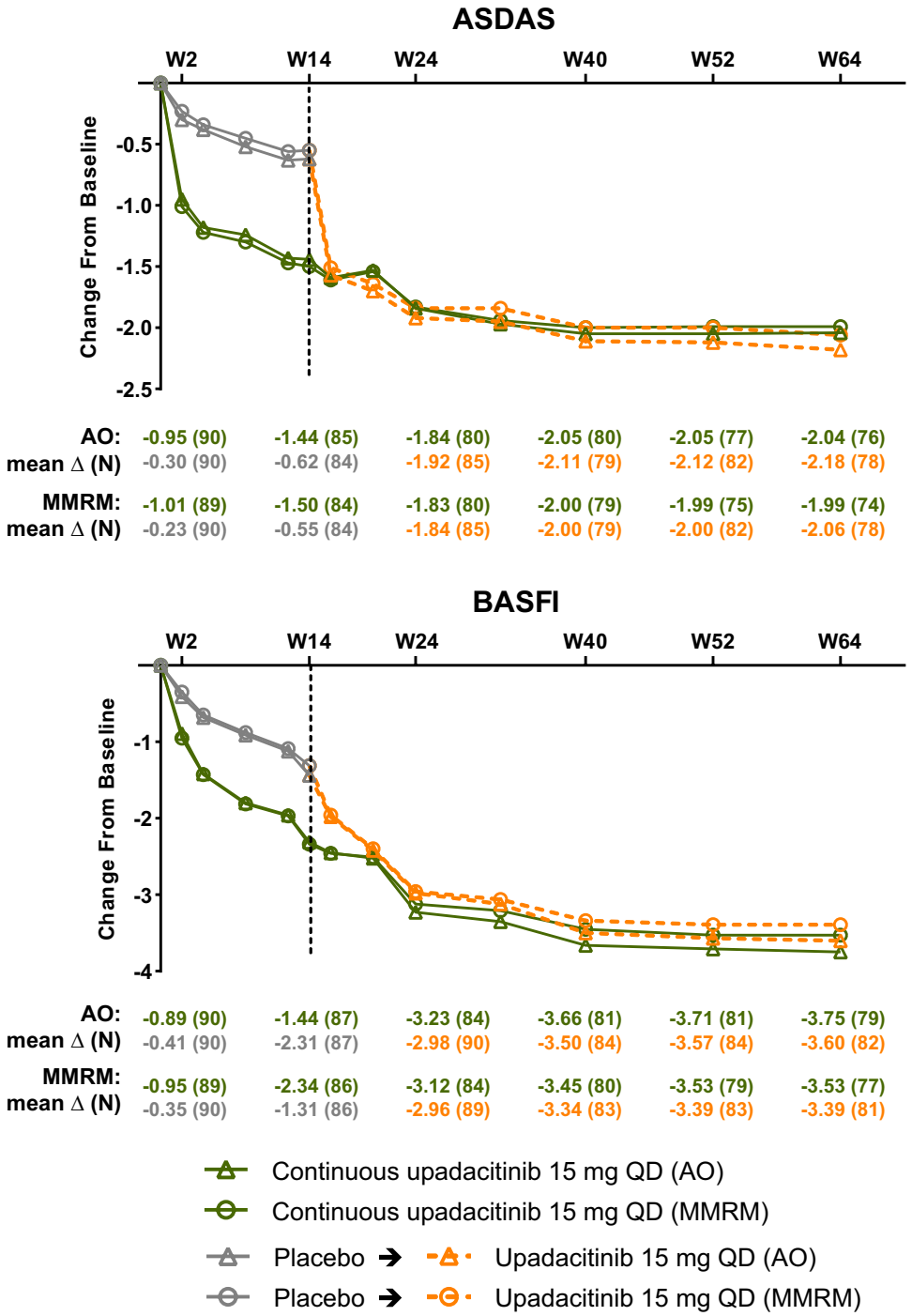


**Figure 4.** Change from baseline (Δ) in Ankylosing Spondylitis Disease Activity Score using the C-reactive protein level (ASDAS-CRP) and Bath Ankylosing Spondylitis Functional Index (BASFI) over time. All patients randomized to receive placebo received open-label upadacitinib beginning at week 14. AO = as-observed; MMRM = mixed-effects model repeated measures; QD = once daily.

of esophageal candidiasis of moderate severity in the same patient, and neither event led to discontinuation of study drug. Thirteen uveitis events in 8 patients (5.5 per 100 patient-years) were reported; all events occurred in patients with a history of uveitis (Supplementary Table 6, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract). The mean time to onset of uveitis among these patients was 343 days, and the median was 295 days (range 115–721 days).

All events of neutropenia, anemia, and lymphopenia were nonserious, and none led to study drug discontinuation. The majority of events related to hepatic disorders were based on transient asymptomatic alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations, all were nonserious and mild to moderate in

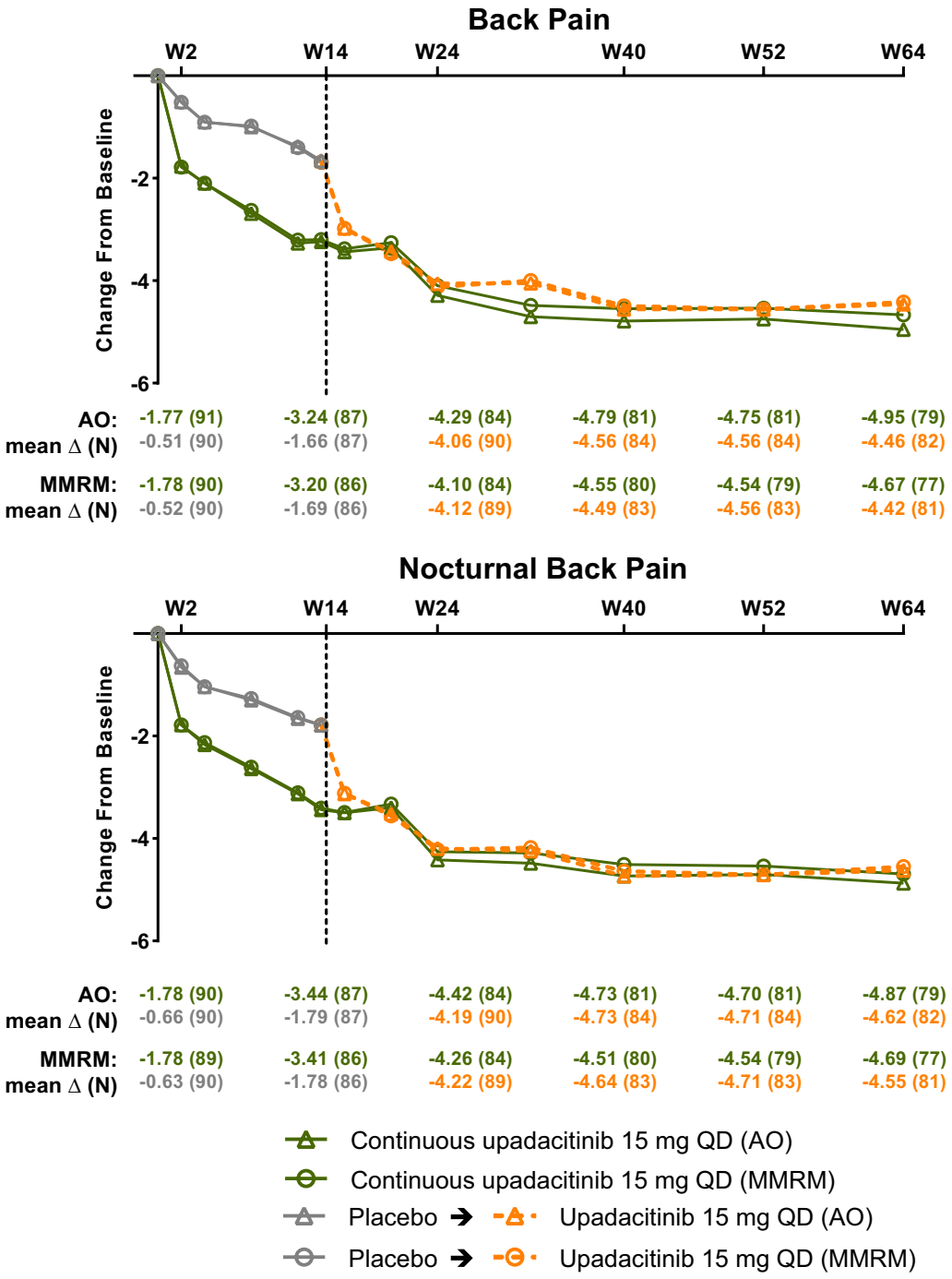


**Figure 5.** Change from baseline (Δ) in back pain and nocturnal back pain over time. All patients randomized to receive placebo received open-label upadacitinib beginning at week 14. Evaluation of back pain was based on the question, "What is the amount of back pain that you experienced at any time during the last week?" and evaluation of nocturnal back pain was based on the question, "What is the amount of back pain at night that you experienced during the last week?" Both were scored on a numerical rating scale of 0–10. AO = as-observed; MMRM = mixed-effects model repeated measures; QD = once daily.

severity, and none led to study drug discontinuation. One patient experienced a grade 3 (≥5 times the upper limit of normal) increase in ALT and 1 patient in AST; no grade 3 or 4 decreases in hemoglobin level or lymphocyte count were observed (Supplementary Table 7, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract).

Five patients experienced grade 3 creatine phosphokinase elevation, and 2 experienced grade 4 elevation; all occurred in young male AS patients, and none led to study drug discontinuation or met the toxicity criteria threshold (Supplementary Table 7). Among these 7 patients, creatine phosphokinase elevations occurred at various time points in relation to the initiation of

**Table 1.** Treatment-emergent adverse events (AEs) in the all-upadacitinib population*

| | |
|---|---|
| Any AE | 618 (260.1) |
| Serious AE† | 14 (5.9) |
| AE leading to discontinuation† | 15 (6.3) |
| Infection | 205 (86.3) |
| Serious infection | 0 (0) |
| Opportunistic infection‡ | 2 (0.8) |
| Herpes zoster§ | 5 (2.1) |
| Active tuberculosis | 0 (0) |
| Creatine phosphokinase elevation¶ | 28 (11.8) |
| Hepatic disorder# | 24 (10.1) |
| Neutropenia** | 7 (2.9) |
| Anemia** | 3 (1.3) |
| Lymphopenia** | 2 (0.8) |
| Renal dysfunction | 0 (0) |
| Gastrointestinal perforation | 0 (0) |
| Malignancy†† | 1 (0.4) |
| Adjudicated MACE | 0 (0) |
| Adjudicated VTE | 0 (0) |
| Uveitis‡‡ | 13 (5.5) |
| Inflammatory bowel disease | 0 (0) |
| Death | 0 (0) |

* Values are the number of events (number of events per 100 patient-years) in all patients receiving upadacitinib 15 mg once daily (n = 182; total of 237.6 patient-years). MACE = major adverse cardiovascular event; VTE = venous thromboembolic event.
† See Supplementary Table 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract, for more details.
‡ Two nonserious events of esophageal candidiasis occurred in the same 60-year-old patient with a history of gastroesophageal reflux disease. Each event was moderate in severity and assessed by the investigator as having a reasonable possibility of being related to study drug. The study drug was temporarily interrupted for each event but was restarted.
§ Five events in 4 patients; all were nonserious and limited to 1 dermatome.
¶ All events were nonserious, and none led to study drug discontinuation. The majority were asymptomatic and based on creatine phosphokinase increases of <4 times the upper limit of normal.
# The majority were based on asymptomatic alanine aminotransferase/aspartate aminotransferase elevations. All were nonserious, and none led to study drug discontinuation.
** All events were nonserious, and none led to study drug discontinuation.
†† Squamous cell carcinoma of the tongue (stage IVa tumor) in a 61-year-old male former smoker (~1 pack per day for 40 years). There was no reasonable possibility the event was related to the study drug, per the investigator.
‡‡ Includes 13 events in 8 patients. All were nonserious and assessed as having no reasonable possibility to be related to the study drug. The majority of events occurred in HLA–B27–positive ankylosing spondylitis patients with a history of uveitis, were mild or moderate in severity, transient, and resolved with local treatment (glucocorticoid eye-drop). One patient discontinued the study. See Supplementary Table 6, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract, for more details.

upadacitinib therapy. Elevations were transient in 5 patients and normalized over time, including the 2 grade 4 increases (Supplementary Figure 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract). Mean creatine phosphokinase values showed an increase from baseline over time, but no major differences in mean hemoglobin level, lymphocyte count, or neutrophil count were observed compared with baseline (Supplementary Figure 9, *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41911/abstract).

## DISCUSSION

SELECT-AXIS 1, the first study to report 1-year data on a JAK inhibitor in AS, showed that upadacitinib 15 mg once daily therapy led to sustained and consistent efficacy over 1 year in both NRI and as-observed analyses in patients with active AS who had an inadequate response to NSAIDs. Improvements were seen in disease activity measures (ASDAS, BASDAI, ASAS, and their components), pain (back pain, nocturnal back pain, and peripheral pain), physical function (BASFI), inflammation (hsCRP), quality of life (ASQoL and the ASAS health index), and other aspects of disease (BASMI and MASES) with continuous upadacitinib therapy. In patients who switched from placebo to upadacitinib at week 14, a similar speed of onset and magnitude of efficacy response was observed through 1 year compared with those who received continuous upadacitinib.

The primary goal of therapy in AS is to maximize a patient's quality of life through control of the signs and symptoms of disease and preservation of physical function and social participation (4), and the SELECT-AXIS 1 study showed wide-ranging benefits of upadacitinib treatment for treating the signs and symptoms of AS. Of note, 39–46% of patients receiving upadacitinib had achieved ASAS showing partial remission or ASDAS ID at the end of 1 year, and >81% reached ASAS40 or ASDAS LDA. Sustained efficacy in AS has also been described for biologic DMARDs, such as TNF or IL-17 inhibitors, and although no head-to-head trials are available, overall, the efficacy of upadacitinib appears to be consistent with that described for TNF and IL-17 inhibitor therapy in AS (28–31). The dropout/retention rate in SELECT-AXIS 1 was also consistent with that for other approved biologic DMARDs (28–30).

Upadacitinib was well tolerated over 237.6 patient-years of exposure, with no new or unexpected safety findings compared with data from the upadacitinib clinical development programs in RA and PsA (32–34). No serious infections, active tuberculosis, venous thromboembolic events, gastrointestinal perforation, major adverse cardiovascular events, renal dysfunction, or deaths were reported. Rates of herpes zoster, opportunistic infections, and malignancy were low and consistent with what has been reported previously in AS patients (35–37). Nonserious and generally asymptomatic events of creatine phosphokinase elevation were observed. Creatine phosphokinase elevations have been observed with JAK inhibitors (9,10,38) and also have been described more frequently with TNF inhibitors in patients with AS than in patients with RA (39,40).

Only limited information is available on the impact of upadacitinib on uveitis and IBD. In this study, no patient developed new-onset uveitis, and events were observed only in patients with a history of uveitis. The rate of uveitis was 5.5 events per 100 patient-years. In addition, no new onset or exacerbation of IBD was observed. Only 4 patients at baseline had a history of IBD in

this study. Whether upadacitinib treatment has an advantage over IL-17 inhibitors, which are not recommended for patients with concomitant active IBD (4), needs further investigation.

Limitations of this study include the open-label nature of period 2, the lack of an active comparator to contextualize efficacy and safety data, and that only 1 dose of upadacitinib was studied. Of note, head-to-head studies in RA and PsA help to put upadacitinib data into context (33,41,42), and upadacitinib exposure–response analyses of the SELECT-AXIS study and of the phase II and III upadacitinib RA studies suggested that upadacitinib pharmacokinetics were similar in patients with AS and patients with RA, and predicted that the 15-mg dose would maximize efficacy in patients with AS (43,44). The upadacitinib 15-mg once daily dose appears to show an optimal benefit–risk profile in RA and PsA (including in PsA patients with axial symptoms) (33,34,42,45,46). In addition, SELECT-AXIS 1 only included a biologic DMARD-naive population and further evaluation on the effect of upadacitinib in biologic DMARD inadequate responders (as examined in the ongoing SELECT-AXIS 2 study) is needed (47). The strengths of SELECT-AXIS 1 include that it was a well-controlled trial that showed consistent maintenance of response without new safety findings compared with the RA and PsA programs.

In summary, upadacitinib 15 mg once daily showed sustained and consistent efficacy over 1 year in patients with active AS. Patients who switched from placebo to upadacitinib at week 14 showed a similar efficacy response compared with those who received continuous upadacitinib. Safety results were comparable with previous upadacitinib studies. Overall, oral upadacitinib therapy over 1 year was efficacious and well tolerated, suggesting it may help address an unmet need for patients with AS who have active disease and an inadequate response to NSAIDs. The long-term efficacy and safety of upadacitinib, including long-term imaging, will be assessed over 2 years in the SELECT-AXIS 1 extension.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Deodhar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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