



BRIEF REPORT

Efficacy and Safety of Upadacitinib in Patients with Psoriatic Arthritis: 2-Year Results from the Phase 3 SELECT-PsA 1 Study

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ABSTRACT

Introduction: Efficacy and safety of the Janus kinase (JAK) inhibitor upadacitinib (UPA) was evaluated in patients with psoriatic arthritis (PsA) through week 104 of the ongoing long-term extension of the phase 3 trial SELECT-PsA 1.

Methods: Exploratory analyses of all primary and secondary endpoints (non-responder imputation and as observed for binary endpoints; mixed-effect model repeated measures

and as observed for continuous endpoints), and summary of treatment-emergent adverse events, in patients receiving UPA 15 mg (UPA15) or 30 mg (UPA30) once daily, or adalimumab 40 mg (ADA) every other week, through week 104 are reported.

Results: Of 1704 patients, 25.4% discontinued the study drug by week 104. Proportions of patients achieving $\geq 20\%/50\%/70\%$ improvement in American College of Rheumatology criteria (ACR20/50/70), $\geq 75\%/90\%/100\%$ improvement in Psoriasis Area and Severity Index (PASI75/90/100), or minimal disease activity (MDA) were maintained through week 104; greater responses by nominal *P* value were

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observed with UPA15 and UPA30 versus ADA for ACR20/50/70 and MDA. Mean change from baseline in modified total Sharp/van der Heijde Score (mTSS) was similar across groups and to week 56 results. The safety profile of UPA was generally comparable to ADA and not altered from week 56 data. Rates of serious infection, herpes zoster, anemia, neutropenia, lymphopenia, and elevated creatine phosphokinase remained numerically higher with UPA15 and/or UPA30 versus ADA. Rates of malignancies excluding non-melanoma skin cancer (NMSC), major adverse cardiovascular events, and venous thromboembolism were similar across groups; rates of NMSC were higher with UPA versus ADA. Two deaths were reported with UPA15, one with UPA30, and one with ADA.

Conclusions: In PsA patients, efficacy responses were similar or greater with UPA15 or UPA30 versus ADA through week 104, and inhibition of radiographic progression was maintained. No new safety risks were identified with exposure to UPA through 2 years (week 104).

Clinical Trial Registration: ClinicalTrials.gov, NCT03104400.

Keywords: 2-year; Adalimumab; Janus kinase (JAK) inhibitor; Non-biologic disease-modifying anti-rheumatic drug (non-bDMARD); Psoriatic arthritis (PsA); Safety; SELECT-PsA 1; Upadacitinib

Key Summary Points

Why carry out this study?

In the phase 3 SELECT-PsA 1 study, patients with active psoriatic arthritis (PsA) and an inadequate response or intolerance to ≥ 1 non-biologic disease-modifying anti-rheumatic drug (non-bDMARD) showed improvement in the signs and symptoms of PsA with upadacitinib 15 mg or upadacitinib 30 mg, an oral Janus kinase (JAK) inhibitor.

The objective of this analysis was to evaluate the efficacy and safety of upadacitinib versus adalimumab through week 104 from the ongoing long-term extension of SELECT-PsA 1.

What was learned from the study?

Efficacy responses, including those related to peripheral arthritis, skin outcomes, enthesitis/dactylitis, and patient-reported pain and physical function, were similar or greater with upadacitinib 15 mg or upadacitinib 30 mg versus adalimumab through week 104 using non-responder imputation (NRI) and as observed (AO) for binary endpoints, or mixed-effect model repeated measures (MMRM) and AO for continuous endpoints, with nominal *P* values, and inhibition of radiographic progression was maintained during this time frame.

Similar efficacy, including improvements in peripheral arthritis as measured by greater proportions of patients achieving $\geq 20\%/50\%/70\%$ improvement in the American College of Rheumatology criteria (ACR20/50/70) and the proportions of patients who achieved tender (TJC68) or swollen (SJC66) joint counts equal to 0, were observed with upadacitinib 15 mg and upadacitinib 30 mg.

No new safety risks were identified with exposure to upadacitinib through 2 years (week 104).

INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous, chronic, inflammatory, musculoskeletal disease, which is characterized by peripheral arthritis, enthesitis, dactylitis, axial disease, and skin changes, with symptoms occurring individually or in combination [1–3]. Effective therapies aim to maximize health-related quality of life through control of symptoms and signs, prevention of structural damage, and optimization of functional status [2, 3]. Despite recent therapeutic advances, 30–40% of PsA patients fail to achieve an adequate response [4]. Better understanding of the impacts of available therapies can help guide treatment decisions to improve patient outcomes.

In the randomized, double-blind, phase 3 SELECT-PsA 1 study, patients with active PsA and an inadequate response or intolerance to ≥ 1 non-biologic disease-modifying anti-rheumatic drug (non-bDMARD) showed improvement in the signs and symptoms of PsA with once-daily upadacitinib 15 mg or 30 mg, an oral Janus kinase (JAK) inhibitor, through week 56 [5, 6]. To better understand the impacts of upadacitinib in patients with PsA, our objective was to evaluate the efficacy and safety of upadacitinib (15 mg and 30 mg) versus adalimumab through week 104 from the ongoing long-term extension of SELECT-PsA 1.

METHODS

Full methodological details for SELECT-PsA 1 (NCT03104400), including study dates and size, inclusion/exclusion criteria, randomization and blinding, and details about the endpoints assessed, have been published previously [5, 6] and are provided in brief below. The study protocol was amended for patients treated with upadacitinib 30 mg once daily to be switched to the commercial marketed dose of upadacitinib 15 mg once daily. Timing of the switch will vary per patient and study site, with the earliest switch occurring at the week 104 visit.

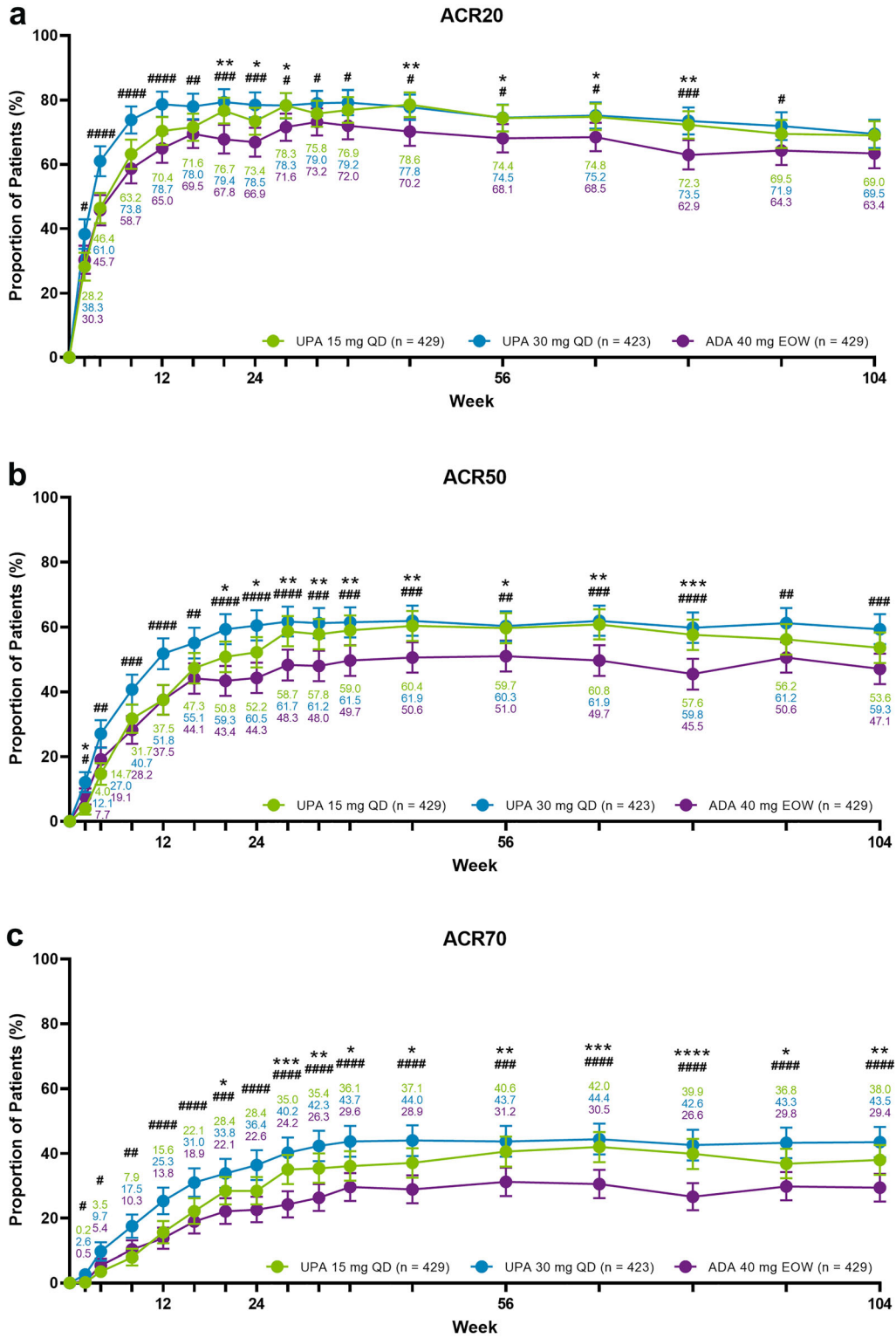
Patients and Study Design

Adults (≥ 18 years of age) with a clinical diagnosis of active PsA, who also fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR) [7], and had an inadequate response or intolerance to ≥ 1 non-bDMARD were eligible for inclusion in the SELECT-PsA 1 study. Patients were randomized to receive blinded once-daily oral upadacitinib 15 mg or 30 mg, placebo, or every other week subcutaneous adalimumab 40 mg for the first 24 weeks. At week 24, patients assigned to placebo at baseline were switched to blinded upadacitinib 15 mg or 30 mg, and those randomized to active therapy remained on the same treatment and dose. Blinding was maintained until all patients reached the week 56 visit. Stable treatment with nonsteroidal anti-inflammatory drugs, corticosteroids, and ≤ 2 non-bDMARDs was allowed. Starting at week 16, patients who did not achieve $\geq 20\%$ improvement in tender and swollen joint counts compared with baseline would be qualified for rescue therapy, where they were permitted to initiate or change background medication(s). The open-label long-term extension of SELECT-PsA 1 is currently ongoing and is planned for up to 5 years.

SELECT-PsA 1 was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations governing clinical trial conduct, and the Declaration of Helsinki 1964 and its later amendments. As per Good Clinical Practice (GCP), the study protocols were approved by an independent ethics committee (IEC)/institutional review board (IRB) at each site (Supplementary Table 1). All patients provided written informed consent.

Outcomes

Efficacy endpoints were assessed through week 104 for this analysis. The proportions of patients achieving $\geq 20\%/50\%/70\%$ improvement in the American College of Rheumatology (ACR) criteria (ACR20/50/70), tender joint count 68 (TJC68) or swollen joint count 66



◀**Fig. 1** ACR20, ACR50, and ACR70 through week 104 (NRI). Proportions of patients achieving ACR20 (a), ACR50 (b), or ACR70 (c). Data were analyzed using Cochran–Mantel–Haenszel tests with NRI and are shown as response rates with 95% CIs. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ upadacitinib 15 mg versus adalimumab; # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$, #### $P < 0.0001$ upadacitinib 30 mg versus adalimumab; nominal P values are shown and were not multiplicity controlled. ACR20/50/70 $\geq 20\%/50\%/70\%$ improvement in American College of Rheumatology response criteria, ADA adalimumab, CI confidence interval, EOW every other week, NRI non-responder imputation, QD once daily, UPA upadacitinib

(SJC66) equal to 0 (in patients with TJC68 or SJC66 > 0 at baseline, respectively), $\geq 75\%/90\%/100\%$ improvement in the Psoriasis Area and Severity Index (PASI75/90/100) in patients with psoriasis affecting $\geq 3\%$ of body surface area at baseline (with higher scores indicating more severe disease), resolution of enthesitis [defined as Leeds Enthesitis Index (LEI) = 0 for patients with LEI > 0 at baseline] or dactylitis [Leeds Dactylitis Index (LDI) = 0 for patients with LDI > 0 at baseline], no radiographic progression [defined as change from baseline in the

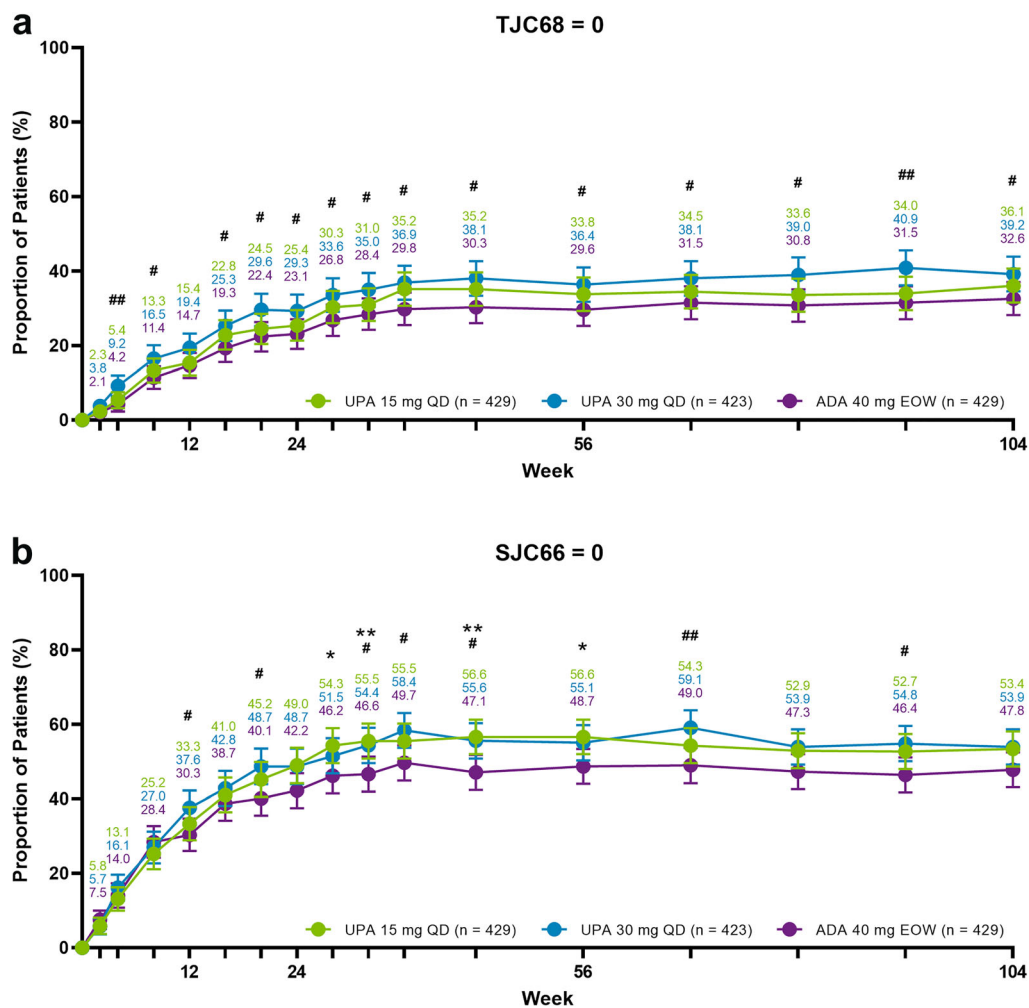
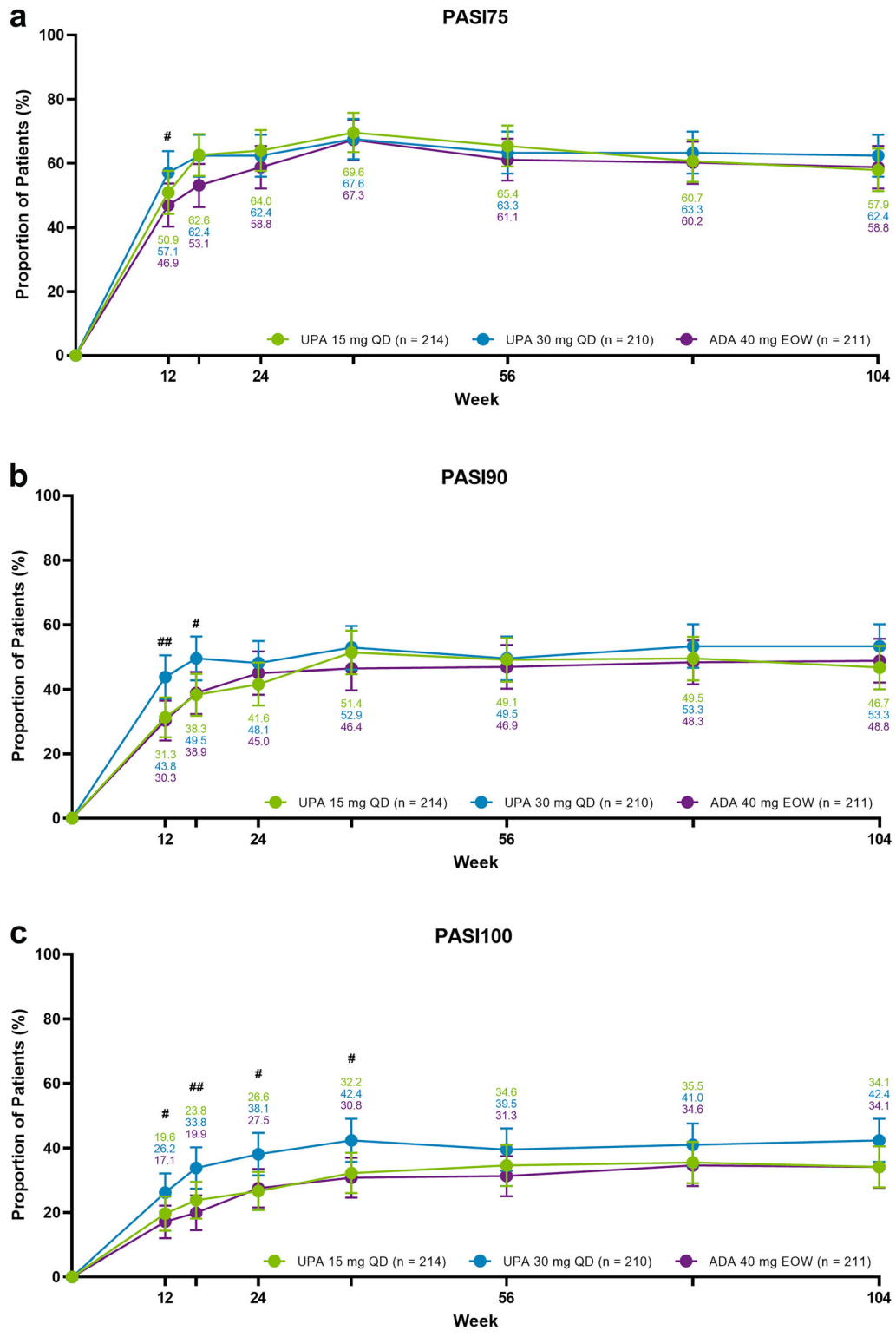


Fig. 2 TJC68 = 0 and SJC66 = 0 through week 104 (NRI). Proportions of patients achieving a TJC68 score of 0 (a) or SJC66 score of 0 (b) in patients with TJC68 > 0 or SJC66 > 0 at baseline, respectively. Data were analyzed using Cochran–Mantel–Haenszel tests with NRI and are shown as response rates with 95% CIs. * $P < 0.05$, ** $P < 0.01$

upadacitinib 15 mg versus adalimumab; # $P < 0.05$, ## $P < 0.01$ upadacitinib 30 mg versus adalimumab; nominal P values are shown and were not multiplicity controlled. ADA adalimumab, CI confidence interval, EOW every other week, NRI non-responder imputation, QD once daily, SJC66 swollen joint count 66, TJC68 tender joint count 68, UPA upadacitinib



◀ **Fig. 3** PASI75, PASI90, and PASI100 through week 104 (NRI). Proportions of patients achieving PASI75 (a), PASI90 (b), or PASI100 (c) in patients with psoriasis affecting $\geq 3\%$ of body surface area at baseline. Data were analyzed using Cochran–Mantel–Haenszel tests with NRI and are shown as response rates with 95% CIs. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ upadacitinib 30 mg versus adalimumab; nominal P values are shown and were not multiplicity controlled. *ADA* adalimumab, *CI* confidence interval, *EOW* every other week, *NRI* non-responder imputation, *PASI75/PASI90/PASI100* $\geq 75\%/90\%/100\%$ improvement in Psoriasis Area Severity Index, *QD* once daily, *UPA* upadacitinib

modified total Sharp/van der Heijde Score (mTSS) ≤ 0 or ≤ 0.5], minimal disease activity (MDA) (determined by fulfilling five of the seven MDA criteria) [8], and $\geq 50\%$ improvement from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50) were assessed.

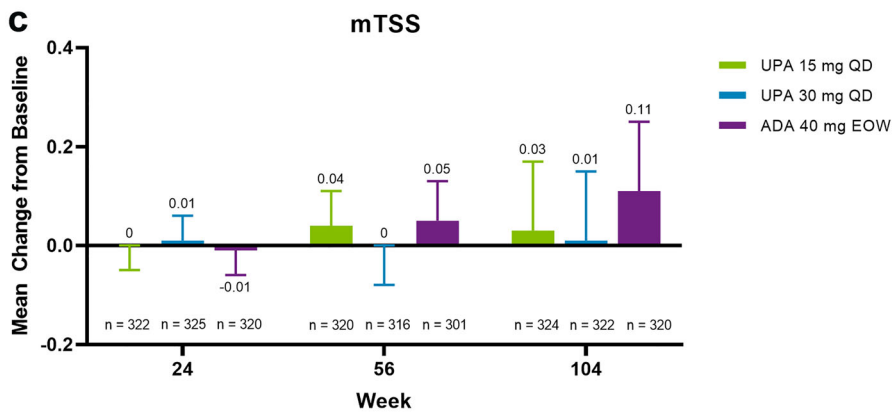
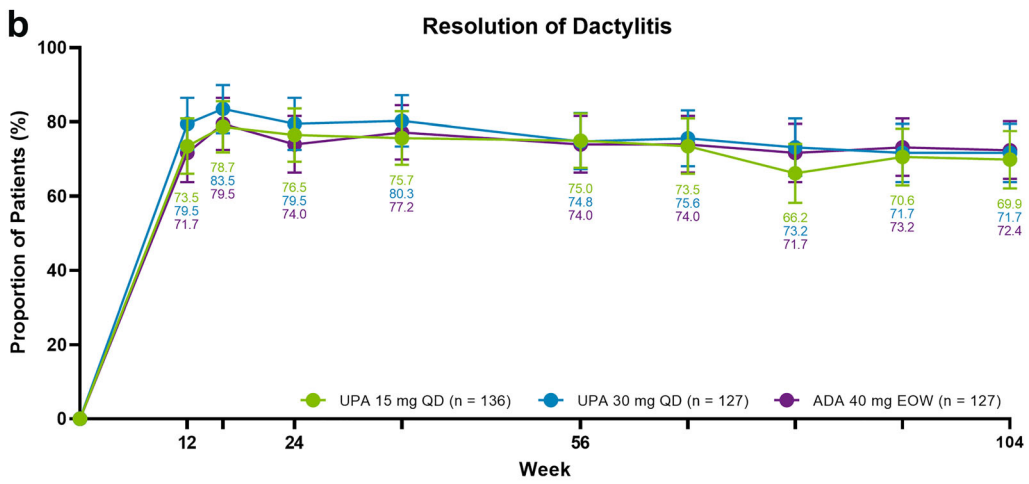
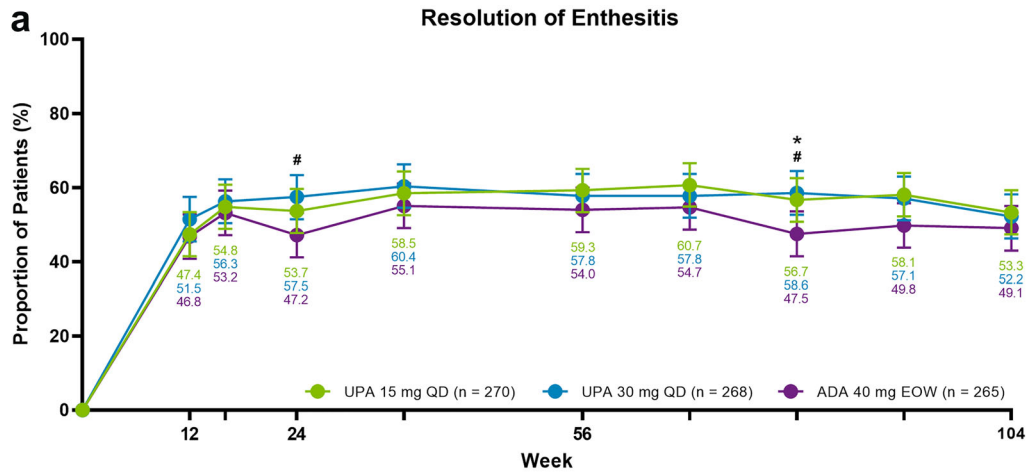
In addition, mean change from baseline in the mTSS, patient's assessment of pain [numeric rating scale (NRS), range 0–10, with higher scores indicating greater pain], Health Assessment Questionnaire-Disability Index (HAQ-DI) score (range 0–3, with higher scores indicating greater disability), Ankylosing Spondylitis Disease Activity Score (ASDAS), and BASDAI were also assessed. Measurements related to axial disease (ASDAS, BASDAI, and BASDAI50) were assessed in the subset of patients that were determined by investigator assessment, using the totality of clinical information, to have psoriatic spondylitis at baseline.

For this analysis, safety data were summarized by treatment groups for all patients who received ≥ 1 dose of study drug through week 104. Treatment-emergent adverse events (TEAEs) were coded per the Medical Dictionary for Regulatory Activities (MedDRA; v 22.0) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (v 5.0). Deaths and cardiovascular events were adjudicated by a blinded, independent, external committee using prespecified definitions. Gastrointestinal perforations were adjudicated by a blinded committee of sponsor-employed experts.

Statistical Analysis

For this 2-year (week 104) analysis of SELECT-PsA 1, data are summarized for all randomized patients who received ≥ 1 dose of study drug. Clinical responses at each time point through week 104 were assessed for the continuous upadacitinib (15 mg and 30 mg), adalimumab, and placebo switch groups (i.e., placebo switched to upadacitinib 15 mg or 30 mg at week 24). Efficacy data for patients who switched from upadacitinib 30 mg to upadacitinib 15 mg are included in their originally randomized groups (i.e., placebo to upadacitinib 30 mg or continuous upadacitinib 30 mg). All data were analyzed using SAS version 9.4 (Cary, NC, USA).

Binary efficacy endpoints (proportion of patients achieving ACR20/50/70, TJC68 or SJC66 equal to 0, PASI75/90/100, resolution of enthesitis or dactylitis, no radiographic progression, MDA, and BASDAI50) were analyzed using Cochran–Mantel–Haenszel tests adjusted for the main stratification factor of current DMARD use (yes/no) for the upadacitinib versus adalimumab comparisons. Non-responder imputation (NRI) was used for missing binary data and for patients who discontinued the study drug. Binary efficacy endpoints are summarized as response rates with 95% confidence intervals (CIs). Continuous efficacy endpoints (change from baseline in mTSS, patient's assessment of pain, HAQ-DI, ASDAS, and BASDAI) were analyzed using mixed-effect model repeated measures (MMRM) based on as observed (AO) data. The MMRM analysis included treatment, visit, treatment-by-visit interaction, and current DMARD use (yes/no) as fixed factors, and the corresponding baseline value as a covariate. A patient's discontinuation status was also included in the MMRM model. Missing data were handled by MMRM, assuming missing at random. Continuous efficacy endpoints are summarized as least squares means with 95% CIs. Differences between upadacitinib 15 mg or upadacitinib 30 mg and adalimumab at each time point through week 104 for the continuous treatment groups are based on MMRM models. All associated nominal P values for the upadacitinib versus adalimumab comparisons were not multiplicity controlled. In addition, summary statistics based on AO data are shown



◀**Fig. 4** Resolution of enthesitis (NRI), resolution of dactylitis (NRI), and Modified Total Sharp/van der Heijde Score (MMRM) through week 104. Proportions of patients with resolution of enthesitis (defined as LEI = 0, in patients with baseline LEI > 0) (a), resolution of dactylitis (defined as LDI = 0, in patients with baseline LDI > 0) (b), or mean change from baseline in mTSS (c). Enthesitis and dactylitis data were analyzed using Cochran–Mantel–Haenszel tests with NRI and are shown as response rates with 95% CIs. mTSS data were analyzed using MMRM and are shown as least squares means with 95% CIs. * $P < 0.05$ upadacitinib 15 mg versus adalimumab; # $P < 0.05$ upadacitinib 30 mg versus adalimumab; nominal P values are shown and were not multiplicity controlled. *ADA* adalimumab, *CI* confidence interval, *EOW* every other week, *LDI* Leeds Dactylitis Index, *LEI* Leeds Enthesitis Index, *MMRM* mixed-effect model for repeated measures, *mTSS* modified total Sharp/van der Heijde Score, *NRI* non-responder imputation, *QD* once daily, *UPA* upadacitinib

for both binary (as response rates) and continuous (as means) efficacy endpoints.

Exposure-adjusted event rates [EAERs; events per 100 patient years (E/100 PY)] of TEAEs are summarized (with 95% CIs shown) for patients who received ≥ 1 dose of study drug through week 104. The upadacitinib 15 mg and 30 mg groups include patients who were assigned to placebo at baseline and switched to upadacitinib treatment at week 24. For patients who switched from once-daily upadacitinib 30 mg to upadacitinib 15 mg, adverse events and exposure to upadacitinib 30 mg were censored at the time of dose switch. Subsequent adverse events and exposure starting from the day of first upadacitinib 15 mg dose are summarized as a separate group (i.e., upadacitinib 15 mg switched from upadacitinib 30 mg).

RESULTS

Patient Disposition, Baseline Demographics, and Disease Characteristics

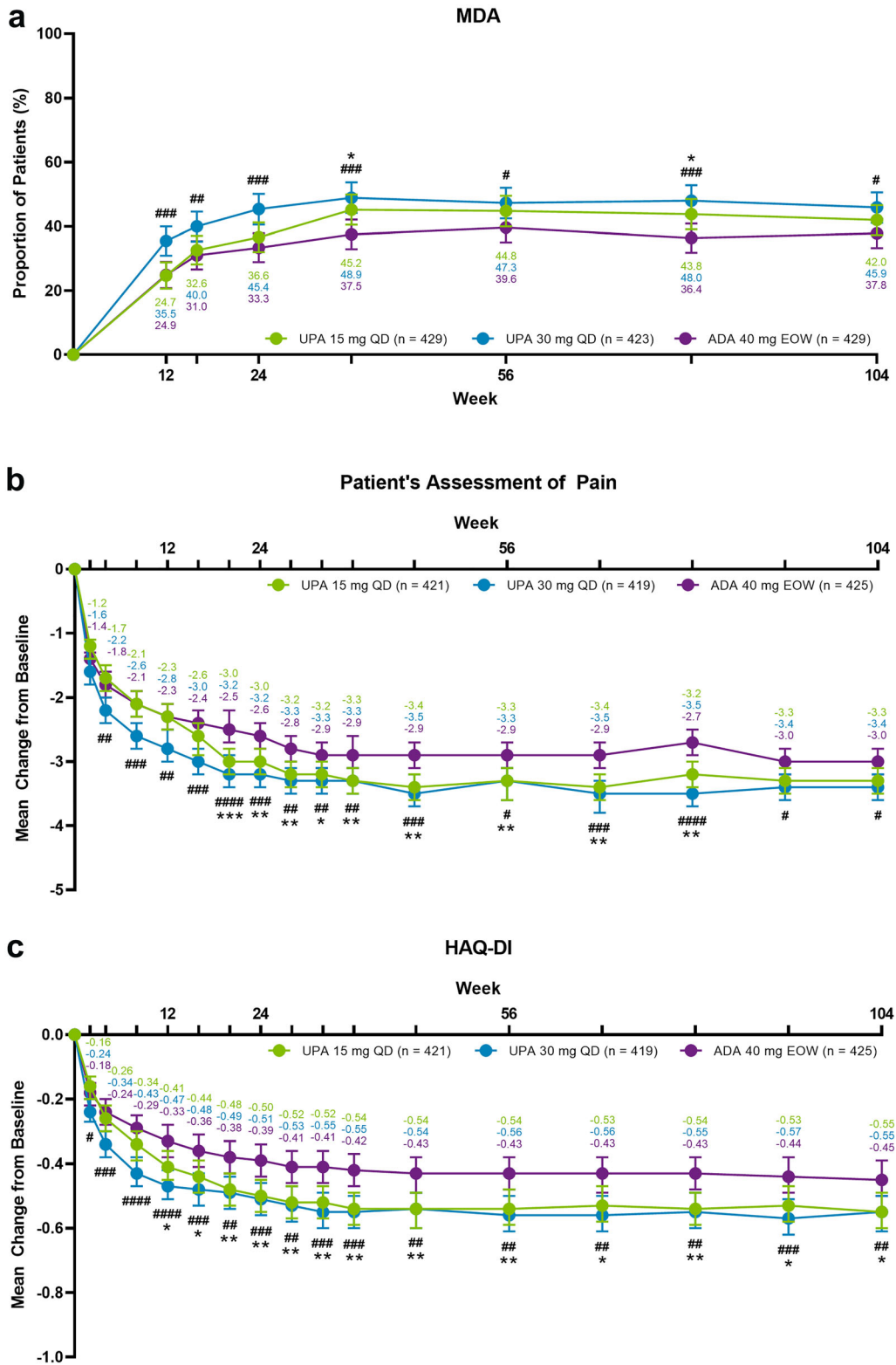
Of 1704 patients that received ≥ 1 dose of study drug in SELECT-PsA 1, 25.4% ($n = 432/1704$)

discontinued study drug by week 104 (Supplementary Table 2). The most common reasons cited for discontinuation were adverse event, lack of efficacy, and withdrawal by patient. Baseline patient demographics, medication use, and disease characteristics have been reported previously and were balanced across treatment groups (summarized in Supplementary Table 3) [5, 6]. A total of 22 patients switched from upadacitinib 30 mg to upadacitinib 15 mg at their week 104 visit, and are reported as a separate group in the safety analysis.

Efficacy

Across the efficacy endpoints assessed, including those measuring peripheral arthritis, skin outcomes, enthesitis, dactylitis, and patient-reported outcomes including pain and physical function, patients treated with upadacitinib 15 mg or 30 mg showed sustained efficacy through week 104, which was consistent with previous findings at week 56 [6]. Over time, clinical responses were similar or greater with upadacitinib 15 mg or 30 mg versus adalimumab through week 104.

Specifically, the proportions of patients achieving ACR20/50/70 responses were maintained through week 104 across all treatment groups. Greater proportions of patients treated with upadacitinib 15 mg or 30 mg achieved ACR20/50/70 responses compared with adalimumab (NRI analysis: Fig. 1a–c; AO analysis: Supplementary Fig. 1a–c). The proportions of patients achieving TJC68 or SJC66 equal to 0 were higher with upadacitinib 15 mg or 30 mg versus adalimumab, which were maintained over time (NRI: Fig. 2a, b; AO: Supplementary Fig. 2a, b). Improvements in skin outcomes as assessed by PASI75/90/100 were consistent across the time points evaluated for all treatment groups (NRI: Fig. 3a–c; AO: Supplementary Fig. 3a–c). The proportions of patients that achieved resolution of enthesitis or dactylitis were comparable across groups and were maintained over time (NRI: Fig. 4a, b; AO: Supplementary Fig. 4a, b). Mean change from baseline in mTSS was minimal, generally similar across treatment groups, and comparable to that



◀**Fig. 5** Minimal disease activity (NRI), patient's assessment of pain (MMRM), and Health Assessment Questionnaire-Disability Index (MMRM) through week 104. Proportion of patients achieving MDA (a), mean change from baseline in patient's assessment of pain (NRS) (b), or mean change from baseline in HAQ-DI (c). MDA data were analyzed using Cochran–Mantel–Haenszel tests with non-responder imputation and are shown as response rates with 95% CIs. Pain and HAQ-DI data were analyzed using a mixed-effect model for repeated measures and are shown as least squares means with 95% CIs. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ upadacitinib 15 mg versus adalimumab; # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$, #### $P < 0.0001$ upadacitinib 30 mg versus adalimumab; nominal P values are shown and were not multiplicity controlled. ADA adalimumab, CI confidence interval, EOW every other week, HAQ-DI Health Assessment Questionnaire-Disability Index, MDA minimal disease activity, NRS numeric rating scale, QD once daily, UPA upadacitinib

observed at week 56 (MMRM analysis: Fig. 4c; AO: Supplementary Fig. 5a) [6]. A high proportion of patients across all treatment groups had no radiographic progression, defined as mean change in mTSS ≤ 0 or ≤ 0.5 , through week 104 (AO: Supplementary Fig. 5b, c). Higher proportions of patients treated with upadacitinib 15 mg or 30 mg achieved MDA versus adalimumab, with clinical responses maintained over time for all treatment groups (NRI: Fig. 5a; AO: Supplementary Fig. 6a). Sustained improvements in the patient's assessment of pain and HAQ-DI were observed with upadacitinib 15 mg or 30 mg versus adalimumab through week 104 (MMRM: Fig. 5b, c; AO: Supplementary Fig. 6b, c). In PsA patients with axial involvement defined by investigator assessment, greater improvements in the ASDAS score were observed with upadacitinib 30 mg versus adalimumab through week 104, and often numerically greater improvements were observed with upadacitinib 15 mg versus adalimumab (MMRM: Fig. 6a; AO: Supplementary Fig. 7a). Similar to ASDAS, patients treated with upadacitinib 15 mg or 30 mg showed greater improvements in the overall BASDAI score versus adalimumab, with clinical responses maintained over time (MMRM: Fig. 6b; AO: Supplementary Fig. 7b). A greater proportion of

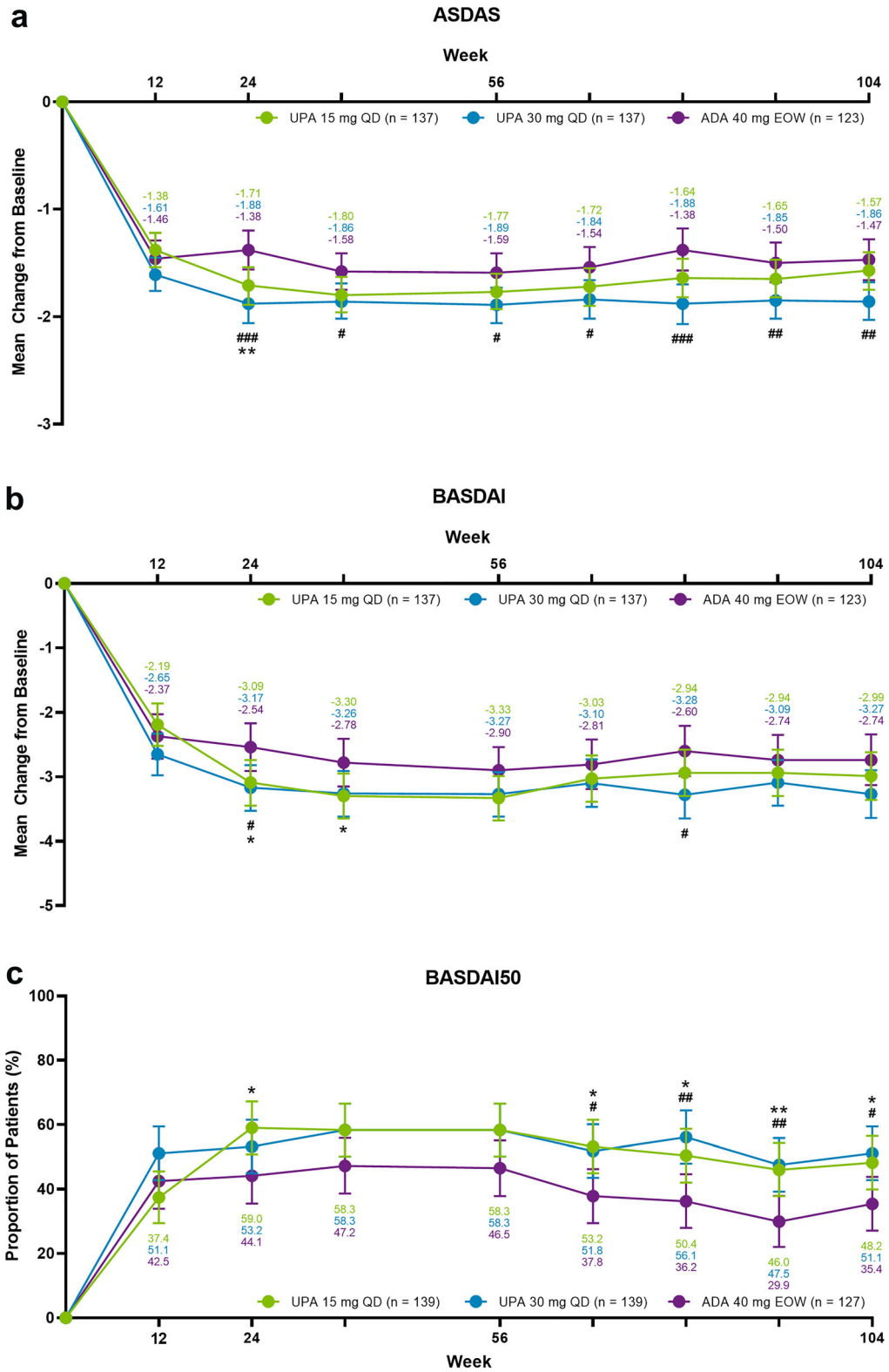
patients achieved a BASDAI50 response with upadacitinib 15 mg or 30 mg compared with adalimumab, with continuous separation observed between the upadacitinib groups and adalimumab between weeks 56 and 104 of the study (NRI: Fig. 6c; AO: Supplementary Fig. 7c).

At week 104, clinical responses across the efficacy endpoints were generally comparable between the placebo switch groups (i.e., placebo switched to upadacitinib 15 mg or 30 mg at week 24) and those originally randomized to upadacitinib at baseline (AO: Supplementary Table 4).

Safety

The safety profile of upadacitinib was generally comparable to adalimumab at week 104 (Fig. 7; Supplementary Table 5) and consistent with that observed at week 56 of the study [6]. Through week 104, the EAER (E/100 PY) for overall TEAEs was 325.5 (95% CI: 314.4, 336.9) with upadacitinib 30 mg, 283.4 (273.1, 294.0) with upadacitinib 15 mg, and 261.4 (249.7, 273.4) with adalimumab. The rate of serious TEAEs was higher with upadacitinib 30 mg [12.0 (9.9, 14.3)] than upadacitinib 15 mg [9.0 (7.2, 11.0)] or adalimumab [8.9 (6.8, 11.3)]. TEAEs leading to discontinuation of study drug were lowest with upadacitinib 15 mg [4.4 (3.2, 5.9)] compared with adalimumab [6.8 (5.0, 9.0)] or upadacitinib 30 mg [7.1 (5.6, 9.0)].

Rates of serious infection (with or without COVID), herpes zoster, anemia, lymphopenia, and elevated creatine phosphokinase (CPK) remained numerically higher with both upadacitinib treatment groups versus adalimumab. Higher rates of serious infection (with or without COVID), herpes zoster, anemia, neutropenia, and CPK elevations were reported with upadacitinib 30 mg than with upadacitinib 15 mg. Opportunistic infection [excluding tuberculosis (TB) and herpes zoster] was reported infrequently in the upadacitinib groups (≤ 0.8 E/100 PY); no events of opportunistic infection were reported in the adalimumab group. The most common serious infections were COVID-19 pneumonia (seven events) with upadacitinib 15 mg ($n = 617$), pneumonia



◀**Fig. 6** Ankylosing Spondylitis Disease Activity Score (MMRM), Bath Ankylosing Spondylitis Disease Activity Index (MMRM), and BASDAI50 (NRI) through week 104. Mean change from baseline in ASDAS (a), mean change from baseline in BASDAI (b), or proportion of patients achieving BASDAI50 (c) in patients with investigator-identified psoriatic spondylitis at baseline. ASDAS and BASDAI data were analyzed using a mixed-effect model for repeated measures and are shown as least squares means with 95% CIs. BASDAI50 data were analyzed using Cochran–Mantel–Haenszel tests with non-responder imputation and are shown as response rates with 95% CIs. * $P < 0.05$, ** $P < 0.01$ upadacitinib 15 mg versus adalimumab; # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$ upadacitinib 30 mg versus adalimumab; nominal P -values are shown and were not multiplicity controlled. *ADA* adalimumab, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASDAI50* $\geq 50\%$ improvement from baseline in the Bath Ankylosing Spondylitis Disease Activity Index, *CI* confidence interval, *EOW* every other week, *QD* once daily, *UPA* upadacitinib

(eight events) with upadacitinib 30 mg ($n = 613$), and cellulitis (two events) with adalimumab ($n = 429$). Serious infections without COVID were relatively comparable between upadacitinib 15 mg and adalimumab. Most of the laboratory events, herpes zoster, and opportunistic infections were non-serious, mild-to-moderate in severity, clinically manageable, and did not lead to treatment discontinuation. Non-melanoma skin cancer (NMSC) was reported more frequently in patients receiving upadacitinib than adalimumab. These skin cancers were generally non-serious and treated at outpatient clinics with surgical excision. Reports of malignancies excluding NMSC (0.6–0.7 E/100 PY), major adverse cardiovascular events (MACE) (0.2–0.3 E/100 PY), and venous thromboembolism (VTE) (0.2–0.5 E/100 PY) remained infrequent; the rates of these events were relatively similar across treatment groups and were consistent with week 56 data [6]. No cases of lymphoma were reported. In patients who switched from upadacitinib 30 mg to 15 mg ($n = 22$), one event of lymphopenia was reported at the week 104 visit.

There were two deaths reported in the upadacitinib 15 mg treatment group, one due to metastatic lung cancer and one due to lower respiratory tract infection; one death in the upadacitinib 30 mg group due to interstitial lung disease; and one death in the adalimumab group due to a traffic accident. Other events including active tuberculous (TB), gastrointestinal (GI) perforation, renal dysfunction, inflammatory bowel disease (IBD), and uveitis were infrequently reported (≤ 0.2 E/100 PY) in this study.

DISCUSSION

Here, we present the 2-year (week 104) results from the phase 3 SELECT-PsA 1 study in patients with active PsA and an inadequate response or intolerance to ≥ 1 non-bDMARD. Compared with the active comparator and standard of care, adalimumab, patients treated with upadacitinib 15 mg or 30 mg showed similar or greater clinical responses across efficacy endpoints related to musculoskeletal and skin symptoms, patient-reported pain and physical function, and inhibition of radiographic progression, which were maintained through week 104. Of note, higher proportions of patients treated with upadacitinib 15 mg or 30 mg achieved MDA starting at week 12 compared with those treated with adalimumab, and maintained this response through week 104. Treat-to-target strategies in PsA often aim to optimize treatment until MDA is achieved and maintained, which can lead to reductions in arthritis and psoriasis disease activity, as well as improvements in patient-reported outcomes related to physical function and quality of life [9, 10]. Similar efficacy, including improvements in peripheral arthritis as measured by greater ACR20/50/70 responses and the proportions of patients that achieved TJC68 or SJC66 equal to 0, were observed at week 104 with upadacitinib 15 mg and 30 mg. At week 104, clinical responses in patients who switched from placebo to upadacitinib at week 24 were generally comparable to responses in patients randomized to upadacitinib at baseline, further

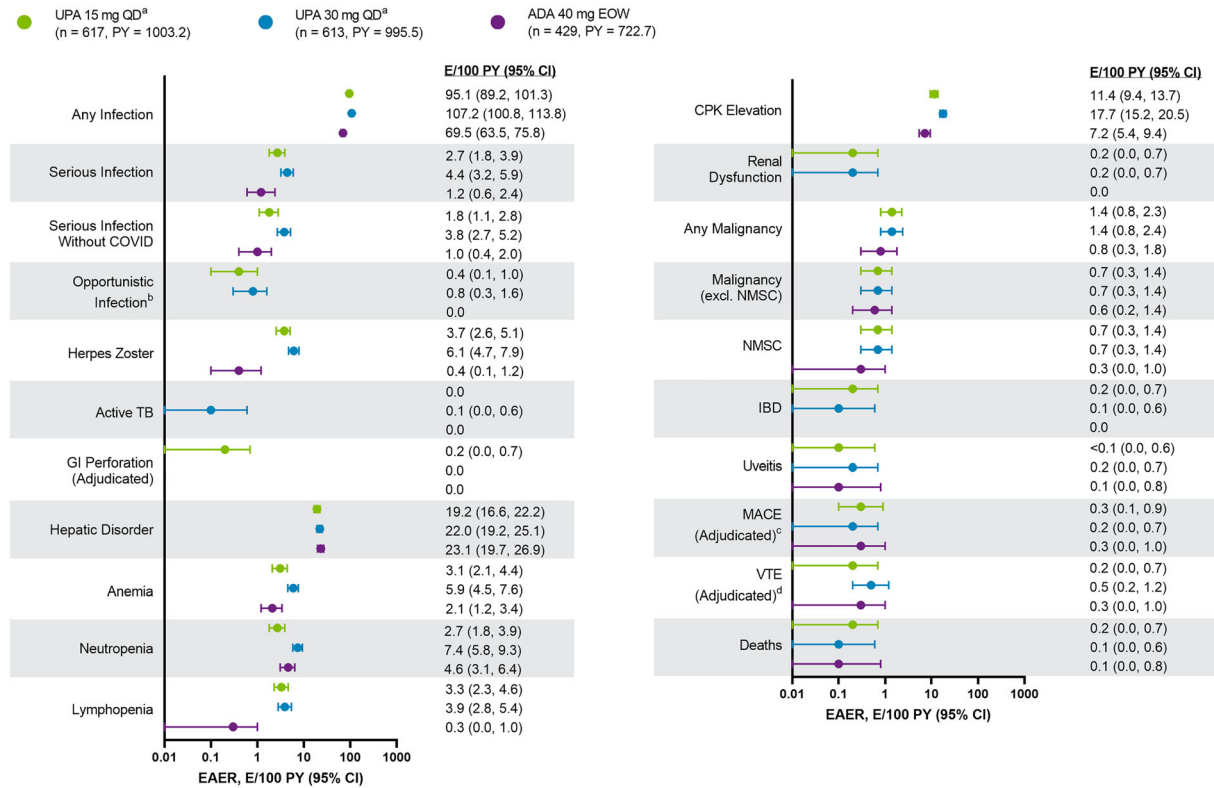


Fig. 7 Exposure-adjusted event rates of treatment-emergent adverse events through week 104. Number of events are provided in Supplementary Table 5. ^aIncludes placebo patients that switched to upadacitinib. ^bOpportunistic infections excluding TB and herpes zoster. ^cMACE defined as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. ^dVTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE) (fatal and

non-fatal). *ADA* adalimumab, *CI* confidence interval, *CPK* creatine phosphokinase, *EAER* exposure-adjusted event rate, *EOW* every other week, *GI* gastrointestinal, *IBD* inflammatory bowel disease, *MACE* major adverse cardiovascular events, *NMSC* non-melanoma skin cancer, *PBO* placebo, *PY* patient years, *QD* once daily, *TB* tuberculosis, *UPA* upadacitinib, *VTE* venous thromboembolism

demonstrating improved efficacy outcomes following upadacitinib treatment.

The safety profile of upadacitinib at week 104 in SELECT-PsA 1 was consistent with that observed at week 56 [6], and its known safety profile from the rheumatoid arthritis [11–17] and ankylosing spondylitis [18] clinical programs. Upadacitinib is known to be associated with an increased risk of serious infection, opportunistic infection, and herpes zoster. Similar findings were noted in this study, with numerically higher rates of these events, as well as serious infection without COVID, observed with upadacitinib 15 mg and/or upadacitinib 30 mg compared with adalimumab. Rates of malignancies excluding NMSC, MACE, and VTE

were low and similar across all treatment groups, consistent with previous findings at week 56 [6]. NMSC was reported with higher rates in the upadacitinib groups compared with adalimumab. Based on the overall evaluation of upadacitinib data available, the events of NMSC have been assessed to have a possible causal relationship with upadacitinib [19].

A limitation of this 2-year (week 104) study is that the analyses were not powered for pre-specified statistical comparisons of upadacitinib versus adalimumab; therefore, nominal *P* values are shown and were not multiplicity controlled. Another limitation is the lack of imaging confirmation for the diagnosis of psoriatic spondylitis in this study. Axial involvement was

determined by the investigator based on the totality of available clinical information and was not confirmed by imaging in all patients. This limitation should be considered when interpreting efficacy endpoints related to axial disease (i.e., ASDAS and BASDAI). However, in a post-hoc analysis of SELECT-PsA 1 and SELECT-PsA 2, irrespective of the predefined assessment for axial involvement applied [i.e., investigator judgement alone or both investigator judgement and PRO-based criteria (BASDAI \geq 4 and BASDAI Q2 \geq 4)], patients with active PsA and axial involvement demonstrated improvements in their axial symptoms with upadacitinib 15 mg, often with greater numerical responses versus adalimumab, which were maintained over follow-up to 56 weeks [20, 21].

CONCLUSION

In summary, efficacy responses in patients with active PsA for endpoints related to peripheral arthritis, skin outcomes, enthesitis, dactylitis, pain, and physical function were similar or greater with upadacitinib 15 mg or 30 mg versus adalimumab through week 104 in SELECT-PsA 1. Inhibition of radiographic progression was maintained at week 104 and was comparable to that observed previously at week 56. Similar efficacy, including improvements in peripheral arthritis, was observed with upadacitinib 15 mg and 30 mg. Furthermore, no new safety risks were identified with exposure to upadacitinib through 2 years (week 104). These data further support the safety and efficacy of upadacitinib for the treatment of patients with PsA.

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Compliance with Ethics Guidelines. SELECT-PsA 1 was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

guidelines, applicable regulations governing clinical trial conduct, and the Declaration of Helsinki 1964 and its later amendments. As per Good Clinical Practice (GCP), the trial protocols were approved by an independent ethics committee (IEC)/institutional review board (IRB) at each site (Supplementary Table 1). All patients provided written informed consent.

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 (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 US 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://www.abbvieclinicaltrials.com/hcp/data-sharing/html>.

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