Disease Control with Upadacitinib in Patients with Psoriatic Arthritis: A Post Hoc Analysis of the Randomized, Placebo-Controlled SELECT-PsA 1 and 2 Phase 3 Trials

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BRIEF REPORT

Disease Control with Upadacitinib in Patients with Psoriatic Arthritis: A Post Hoc Analysis of the Randomized, Placebo-Controlled SELECT-PsA 1 and 2 Phase 3 Trials

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ABSTRACT

Introduction: Low disease activity (LDA)/remission is the target of treatment in patients with psoriatic arthritis (PsA). We assessed the proportions of patients with PsA receiving upadacitinib who achieved LDA/remission over 1 year.

Methods: This was a post hoc analysis of the double-blind, placebo-controlled SELECT-PsA 1 (also adalimumab-controlled) and SELECT-PsA 2 trials. Treatment targets assessed included LDA/remission defined by Disease Activity in Psoriatic Arthritis ($\leq 14/\leq 4$) and Psoriatic Arthritis Disease Activity Scores ($\leq 3.2/\leq 1.9$), as well as minimal disease activity (MDA)/very low disease activity (VLDA) states (5/7 and 7/7 components, respectively, of MDA criteria). Targets were assessed at 24 and 56 weeks. For binary outcomes, non-responder imputation was used for missing data. Data from patients

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receiving upadacitinib 30 mg was not included in the analysis.
Results: Overall, 1386 patients were analyzed. Disease control (i.e., LDA/MDA) was achieved at 24 weeks in upadacitinib 15 mg-treated patients across both studies: LDA/MDA was achieved by 25–48% of patients receiving upadacitinib 15 mg versus 2–16% of patients receiving placebo, and remission/VLDA rates were 7–14% with upadacitinib 15 mg versus 0–4% with placebo. The proportions of patients achieving treatment targets were numerically similar to upadacitinib 15 mg and adalimumab. All responses were sustained at 56 weeks.
Conclusions: Remission and LDA are feasible targets with upadacitinib treatment in patients with PsA.
Trial Registration: ClinicalTrial.gov identifiers NCT03104400 (SELECT-PsA 1) and NCT03104374 (SELECT-PsA 2).

PLAIN LANGUAGE SUMMARY

Psoriatic arthritis is a disease that causes inflammation of the skin and joints. Doctors measure how bad a patient's disease is by measuring signs and symptoms of the disease, and using these to make a "score." The aim of treatment is to reduce the score to low levels (known as "low disease activity") or very low levels ("remission"). This study looked at results from two clinical trials that compared upadacitinib, a medicine used to treat psoriatic arthritis, with no medicine (placebo) to see how many patients had low disease activity or were in remission after 1 year of treatment. The results showed that more patients who were taking upadacitinib had low disease activity or were in remission after the first 6 months of treatment compared with those who took placebo. This difference between upadacitinib and placebo could still be seen after 1 year of treatment. These results show that treatment with upadacitinib is effective enough for some patients with psoriatic arthritis to achieve low disease activity or remission and to stay at this level, even after more than 1 year of treatment.

Keywords: Upadacitinib; JAK inhibitor; Psoriatic arthritis; SELECT-PsA 1; SELECT-PsA 2

Key Summary Points

Why carry out this study?

Treatment guidelines for psoriatic arthritis (PsA) recommend aiming for remission or low disease activity (LDA), which can be assessed using validated measures such as Disease Activity in Psoriatic Arthritis and Psoriatic Arthritis Disease Activity Score LDA/remission or the states of minimal/very low disease activity (MDA/VLDA).

The aim of this analysis was to evaluate the proportions of patients who achieved the states of LDA/remission and MDA/VLDA while receiving upadacitinib up to week 56 using data from the SELECT-PsA 1 and SELECT-PsA 2 studies.

What was learned from the study?

In the SELECT-PsA 1 and 2 randomized, controlled trials, more patients receiving upadacitinib 15 mg compared with placebo achieved LDA and remission, regardless of the target used to assess disease control. Responses with upadacitinib were similar to those seen with adalimumab.

With upadacitinib treatment, disease control is feasible in patients with PsA, with sustained results for 56 weeks.

INTRODUCTION

Psoriatic arthritis (PsA) is a systemic inflammatory musculoskeletal disease that exists on a

spectrum of disease with psoriasis [1–3]. Patients with PsA can be impacted by disease activity across multiple domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, skin and nail involvement, inflammatory bowel disease, and uveitis, as well as a variety of cardiovascular, psychological, and metabolic comorbidities [2, 3]. Current treatment guidelines recommend a treat-to-target approach aiming for remission (REM) or alternatively for low disease activity (LDA) [1, 3]; however, assessment of PsA disease activity is challenging due to its variable clinical manifestations and differences in rates of favorable outcomes depending on scoring methods used [1]. The key methods to assess REM and LDA in PsA include Disease Activity in Psoriatic Arthritis (DAPSA) LDA/REM, Psoriatic Arthritis Disease Activity Score (PASDAS) LDA/REM, and minimal/very low disease activity (MDA/VLDA) [4].

Upadacitinib is an oral, reversible Janus kinase (JAK) inhibitor with selectivity for JAK1 over JAK2, JAK3, and tyrosine kinase 2. As of 2021, upadacitinib has received regulatory approval for the treatment of PsA by the European Medicines Agency and the Pharmaceuticals and Medical Devices Agency, along with other regulatory agencies. Upadacitinib (15 mg or 30 mg administered once daily [QD]) is being investigated for the treatment of patients with PsA and an inadequate response or intolerance to non-biologic and biologic disease-modifying antirheumatic drugs (nb/bDMARDs) in the phase 3 SELECT-PsA 1 and SELECT-PsA 2 studies, respectively. In both of these studies, upadacitinib was effective in improving the signs and symptoms of PsA, with responses maintained over 56 weeks of treatment [5–8]. In SELECT-PsA 1, upadacitinib 15 mg and 30 mg achieved non-inferiority versus adalimumab for American College of Rheumatology 20% response criteria at week 12 [5]. Here, we report the proportions of patients who achieved the states of LDA/REM and MDA/VLDA while receiving upadacitinib up to week 56 using data from the SELECT-PsA 1 and SELECT-PsA 2 studies [5–8].

METHODS

Trial Design

This was a post hoc analysis of 24-week and 56-week disease activity data from the SELECT-PsA 1 (NCT03104400) and SELECT-PsA 2 (NCT03104374) randomized, controlled, phase 3 trials. The designs of the trials have been previously described in detail [5, 7]. In brief, both were multicenter, double-blind, placebo- (and active- [adalimumab] in the case of SELECT-PsA 1) controlled trials of an initial 24-week duration, followed by an additional 32 weeks of blinded treatment (weeks 24–56), and subsequent long-term extension [5–8].

Patients with prior inadequate response or intolerance to ≥ 1 nbDMARD (nbDMARD-IR; SELECT-PsA 1) or ≥ 1 bDMARD (bDMARD-IR; SELECT-PsA 2) were randomized to receive oral upadacitinib 15 mg QD, upadacitinib 30 mg QD, or placebo switched (1:1) to either upadacitinib 15 mg or 30 mg QD at week 24 (both studies), or subcutaneous adalimumab 40 mg every other week (SELECT-PsA 1 only) [5, 7]. From week 16, all patients who qualified for rescue therapy (i.e., did not achieve ≥ 20% improvement in tender joint count in 68 joints [TJC68] and swollen joint count in 66 joints [SJC66] compared with baseline at weeks 12 and 16) were permitted to have background medication(s) initiated or adjusted. From week 36, patients who had not achieved ≥ 20% improvement in TJC68 and SJC66 compared with baseline at two consecutive visits discontinued study drug and were considered non-responders.

Patients

Patients were aged ≥ 18 years with a diagnosis of active PsA, fulfilled the classification criteria for PsA [9], had historic or current plaque psoriasis, and had SJC ≥ 3 of 66 and TJC ≥ 3 of 68 at baseline [5, 7].

Ethics Declaration

Both trials were conducted according to the International Conference on Harmonization guidelines and the principles of the Declaration of Helsinki of 1964 and its later amendments. All patients provided written informed consent. The trial protocols were approved by the relevant independent ethics committees and institutional review boards of all participating institutions (previously published) and were sponsored by AbbVie, which provided upadacitinib, adalimumab, and placebo. All authors have provided their approval for this version to be published.

Assessments

Outcome measures included the proportions of patients achieving LDA and REM (assessed according to the following scores: DAPSA ≤ 14 / ≤ 4, respectively, and PASDAS ≤ 3.2 / ≤ 1.9, respectively), as well as MDA and VLDA. DAPSA score is a composite score based on the sum of five variables: SJC66, TJC68, Patient's Assessment of Pain (0–10 numeric rating scale [NRS]), Patient's Global Assessment of Disease Activity (PtGA; 0–10 NRS), and high-sensitivity C-reactive protein (hsCRP) test [10]. PASDAS is a composite disease activity measure, which was calculated using the following formula: $0.18 \sqrt{}$(Physician's Global Assessment) + $0.159 \sqrt{}$(PtGA) − $0.253 \sqrt{}$(short form 36-physical component summary) + $0.101 \ln(\text{SJC66} + 1) + 0.048 \ln(\text{TJC68} + 1) + 0.23 \ln(\text{Leeds Enthesitis Index [LEI]} + 1) + 0.37 \ln(\text{tender dactylitis count} + 1) + 0.102 \ln(\text{hsCRP} + 1) + 2 \times 1.5$ [1, 11]. MDA and VLDA were determined based on patients meeting five and seven components, respectively, out of the following seven components: TJC68 ≤ 1; SJC66 ≤ 1; Psoriasis Area Severity Index (PASI) ≤ 1 or body surface area-psoriasis (BSA-Ps) $\leq 3\%$; Patient's Assessment of Pain ≤ 1.5 (0–10 NRS); PtGA ≤ 2 (0–10 NRS); Health Assessment Questionnaire-Disability Index (HAQ-DI) score ≤ 0.5; and tender entheseal points (LEI) ≤ 1 [10].

Statistical Analyses

Analyses were performed on all randomized patients who had received ≥ 1 dose of trial drug, excluding patients in the upadacitinib 30 mg group. For binary outcomes, non-responder imputation (NRI) was used for handling missing data, where patients with missing data at the specified week or those who prematurely discontinued the trial drug were considered as non-responders. For MDA and VLDA, the NRI with additional rescue handling was used, where those who were rescued at week 16 were considered non-responders. For the primary outcome analysis, pairwise comparisons between upadacitinib doses and placebo or adalimumab were conducted using the Cochran–Mantel–Haenszel test adjusting for main stratification factors. The proportion of patients achieving MDA at week 24 with upadacitinib versus placebo was adjusted for multiplicity control.

RESULTS

Patients

A total of 1069 patients from SELECT-PsA 1 and 317 patients from SELECT-PsA 2 were included in the analysis. Patient demographics and clinical characteristics have been published previously [5, 7] and were largely similar across the treatment groups in the two studies (Supplementary Table 1, Supplementary Material).

Efficacy

At week 24, achievement of DAPSA LDA ranged from 4–16% in placebo-treated patients and 35–48% in patients receiving upadacitinib 15 mg, while achievement of PASDAS LDA ranged from 2–16% and 33–46%, respectively (Fig. 1A, B; Supplementary Fig. 1A, B). Achievement of DAPSA REM at week 24 ranged from 0–3% with placebo and 7–11% with upadacitinib 15 mg, and achievement of PASDAS REM ranged from 1–3% and 10–14%, respectively (Fig. 1C, D; Supplementary Fig. 1C, D). A

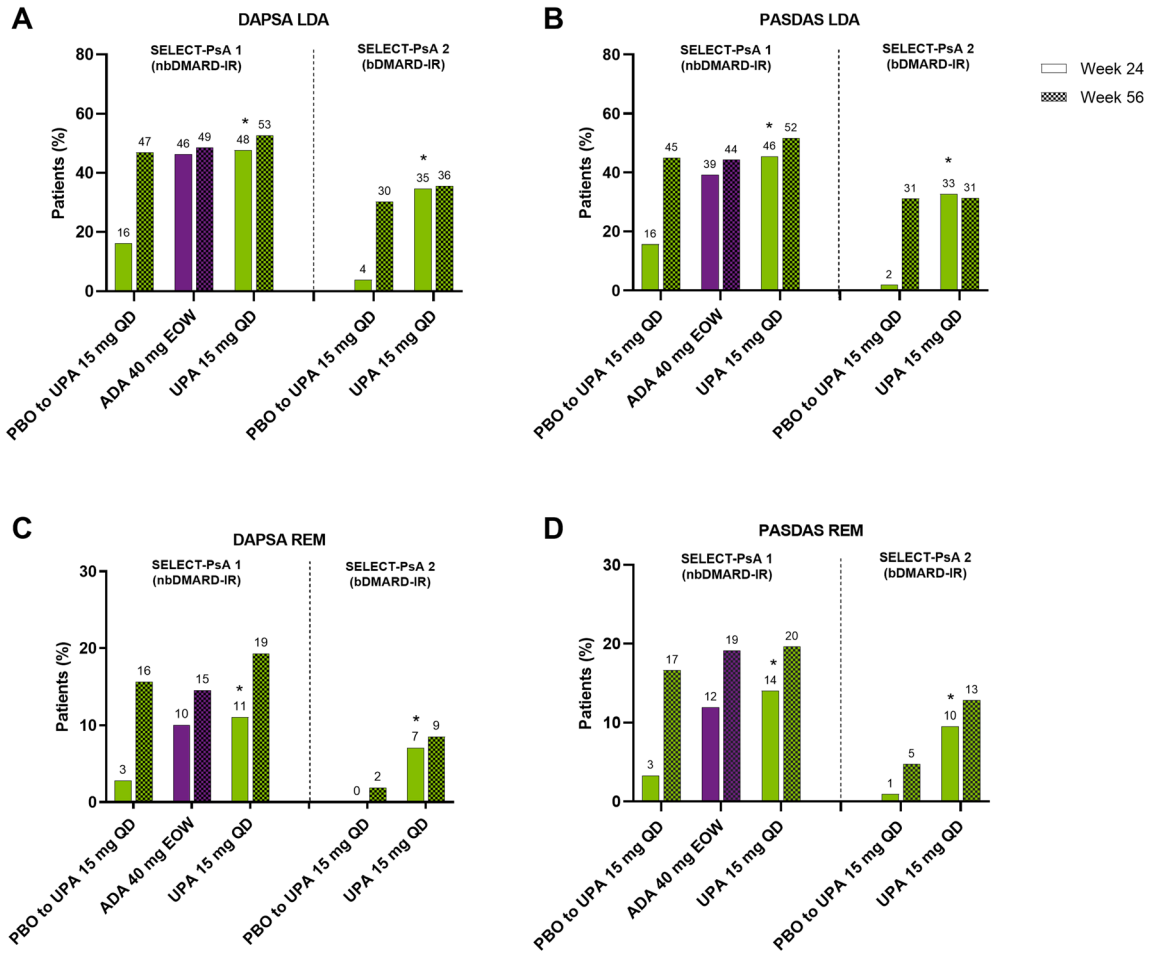

Fig. 1 Proportion of patients achieving DAPSA LDA (**A**), PASDAS LDA (**B**), DAPSA REM (**C**), and PASDAS REM (**D**) at weeks 24 and 56 (NRI). *Nominal $p < 0.05$ versus PBO. *ADA* adalimumab, *bDMARD* biologic disease-modifying antirheumatic drug, *DAPSA* Disease Activity in Psoriatic Arthritis, *EOW* every other week, *IR* inadequate response, *LDA* low disease activity, *nbDMARD* non-biologic disease-modifying antirheumatic drug, *NRI* non-responder imputation, *PASDAS* Psoriatic Arthritis Disease Activity Score, *PBO* placebo, *QD* once daily, *REM* remission, *UPA* upadacitinib. At week 24, all patients who had originally been randomized to PBO were switched to UPA 15 mg QD regardless of response

significantly higher proportion of patients achieved DAPSA/PASDAS LDA or REM at week 24 in the upadacitinib 15 mg compared with the placebo group (nominal $p < 0.05$). The percentage of patients achieving DAPSA/PASDAS LDA and REM broadly increased between week 24 and week 56. LDA or REM rates at week 56 were generally similar in patients who were originally randomized to upadacitinib 15 mg compared with those who switched from placebo to upadacitinib 15 mg at week 24. DAPSA/PASDAS LDA and REM rates were numerically greater in nbDMARD-IR patients receiving upadacitinib than in bDMARD-IR patients receiving upadacitinib.

Significantly greater proportions of patients achieved MDA (Fig. 2A) and VLDA (Fig. 2B) at week 24 with upadacitinib 15 mg versus placebo ($p < 0.05$). MDA and VLDA rates in the group originally randomized to upadacitinib 15 mg were maintained or increased at week 56. Among patients originally randomized to placebo, the proportions of patients who achieved MDA and VLDA increased after switching to upadacitinib 15 mg at week 24.

Among patients who achieved MDA with upadacitinib 15 mg or adalimumab at week 24, the proportion of patients achieving TJC68 ≤ 1 and Patient's Assessment of Pain ≤ 1.5 tended to be lower than that for other MDA components (Fig. 3). The achievement of individual MDA components was broadly similar regardless of whether patients achieved MDA with upadacitinib 15 mg or adalimumab. Conversely, around half of the patients who did not achieve MDA by week 24 still achieved meaningful improvement in skin and enthesitis with upadacitinib 15 mg or adalimumab treatment. Similar trends were observed at week 56 (Fig. 4).

DISCUSSION

This post hoc analysis of data from the SELECT-PsA 1 and SELECT-PsA 2 randomized, controlled trials showed that upadacitinib 15 mg treatment led to desirable states of REM or LDA, which were sustained through 56 weeks.

Guidelines recommend aiming for REM or LDA in PsA [1, 3]. Achieving MDA leads to significantly greater and sustained improvement in quality of life (QoL) [12]. However, REM in PsA is difficult to define, but should be seen as an abrogation of inflammation [3]. Consequently, a range of measures have been used in PsA trials to determine LDA or REM [4, 10]. While DAPSA measures showed higher sensitivity to identify patient-perceived LDA/REM than VLDA/MDA, VLDA/MDA cut-offs were more rigorous and accounted for extra-articular symptoms of PsA such as psoriasis [4, 10, 13]. Patients who achieved MDA or VLDA were also more likely to experience a reduction in radiographic progression, and a positive impact on health-related QoL and work productivity [14]. On the other hand, MDA and PASDAS have been shown to be well correlated between instruments and are highly sensitive and specific for assessing disease activity [4, 10].

Despite the differences between LDA/REM measures in PsA, the results from our analysis suggested that similar proportions of upadacitinib-treated patients achieved LDA/REM at weeks 24 and 56 across the outcome measures assessed. While upadacitinib treatment was associated with greater LDA/REM rates than placebo in both nbDMARD-IR patients and bDMARD-IR patients, the treatment effect of upadacitinib was greater in nbDMARD-IR patients than bDMARD-IR patients, as expected. Regardless of outcome measures, LDA/

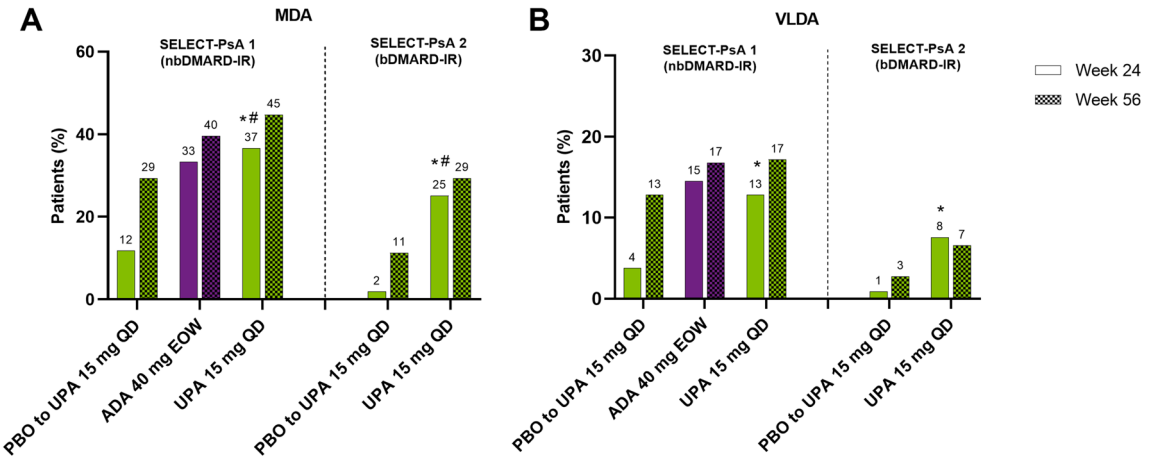

Fig. 2 Proportion of patients achieving MDA (**A**) and VLDA (**B**) at weeks 24 and 56 (NRI). *Nominal $p < 0.05$ versus PBO. #Statistically significant in the multiplicity-controlled analysis. *ADA* adalimumab, *bDMARD* biologic disease-modifying antirheumatic drug, *EOW* every other week, *IR* inadequate response, *MDA* minimal disease activity, *nbDMARD* non-biologic disease-modifying antirheumatic drug, *NRI* non-responder imputation, *PBO* placebo, *QD* once daily, *UPA* upadacitinib, *VLDA* very low disease activity. At week 24, all patients who had originally been randomized to PBO were switched to UPA 15 mg QD regardless of response

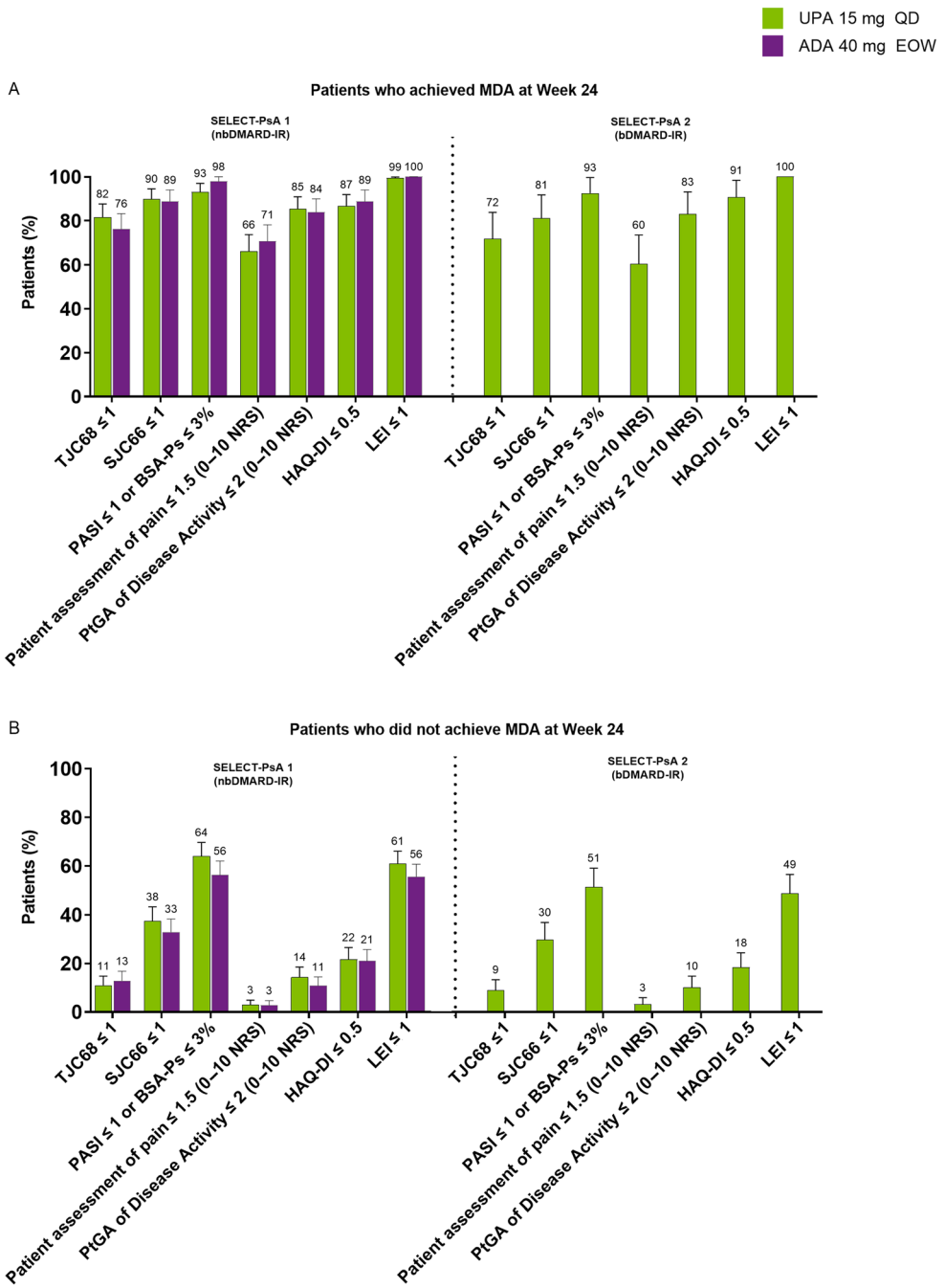

Fig. 3 Proportion of patients achieving MDA components among upadacitinib- or adalimumab-treated patients who achieved MDA (**A**) and did not achieve MDA (**B**) at week 24 (NRI). *ADA* adalimumab, *bDMARD* biologic disease-modifying antirheumatic drug, *BSA-Ps* body surface area-psoriasis, *EOW* every other week, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *IR* inadequate response, *LEI* Leeds Enthesitis Index, *MDA* minimal disease activity, *nbDMARD* non-biologic disease-modifying antirheumatic drug, *NRI* non-responder imputation, *NRS* numeric rating scale, *PASI* Psoriasis Area Severity Index, *PtGA* Patient's Global Assessment of Disease Activity, *QD* once daily, *SJC66* swollen joint count in 66 joints, *TJC68* tender joint count in 68 joints, *UPA* upadacitinib

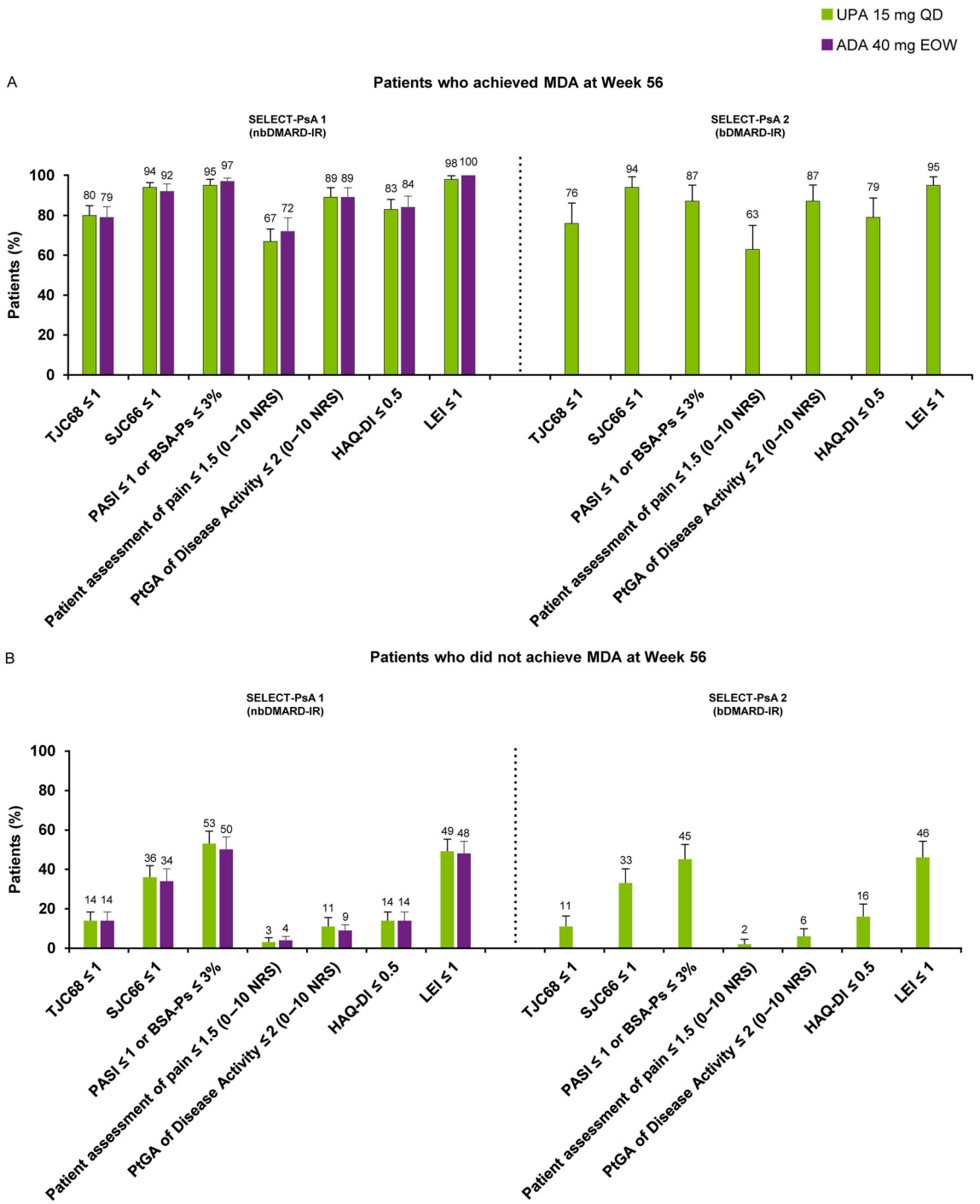

Fig. 4 Proportion of patients achieving MDA components among upadacitinib- or adalimumab-treated patients who achieved MDA (**A**) and did not achieve MDA (**B**) at week 56 (NRI). *ADA* adalimumab, *bDMARD* biologic disease-modifying antirheumatic drug, *BSA-Ps* body surface area-psoriasis, *EOW* every other week, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *IR* inadequate response, *LEI* Leeds Enthesitis Index, *MDA* minimal disease activity, *nbDMARD* non-biologic disease-modifying antirheumatic drug, *NRI* non-responder imputation, *NRS* numeric rating scale, *PASI* Psoriasis Area Severity Index, *PtGA* Patient's Global Assessment of Disease Activity, *QD* once daily, *SJC66* swollen joint count in 66 joints, *TJC68* tender joint count in 68 joints, *UPA* upadacitinib

REM rates were generally similar between patients receiving upadacitinib 15 mg and adalimumab.

Patients who achieved MDA with upadacitinib or adalimumab demonstrated similar clinically important improvements across individual MDA/VLDA components, including improvements in skin symptoms, enthesitis, and physical function. This provides further evidence of disease control with upadacitinib. However, very few patients who achieved MDA experienced clinically important improvement in pain and TJC68 when compared with other MDA/VLDA components. This may be due to the relatively stringent threshold for pain used in the MDA criteria ($\leq$ 1.5 on a 0–1 NRS), and the high number of tender joints present at baseline in both the SELECT-PSA 1 and 2 trials.

The limitations of this study include the post hoc nature of the analysis, with data at week 24 and week 56 not powered to detect differences between upadacitinib and adalimumab. However, these data are taken from two rigorous randomized, controlled trials with a reasonably large patient population, and using the conservative approach of NRI might mitigate any bias favoring the active treatment.

CONCLUSIONS

These data show that a greater proportion of patients with PsA treated with upadacitinib 15 mg frequently achieve disease control, measured by LDA or REM, compared with placebo over 56 weeks. Further studies are needed to confirm the link between disease control and long-term QoL for patients.

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Declarations

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Authorship All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions Dr. Mease was involved in study conception and design, data collection, analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript. Dr. Kavanaugh was involved in study conception and design, data collection, analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript. Dr. Gladman was involved in study conception and design, data collection, analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript. Prof. FitzGerald was involved in study conception and design, data collection, analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript. Dr. Soriano was involved in study conception and design, data collection, analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript. Prof. Nash was involved in study conception and design, data collection, analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript. Dr. Feng was involved in study conception and design, data analysis and interpretation, statistical analysis, drafting the article, and revising it for critically important

intellectual content, and approving the final version of the manuscript. Dr. Lertratanakul was involved in study conception and design, data analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript. Dr. Douglas was involved in study conception and design, data analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript. Dr. Lippe was involved in study conception and design, data analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript. Prof. Gossec was involved in study conception and design, data collection, analysis and interpretation, drafting the article, and revising it for critically important intellectual content, and approving the final version of the manuscript.

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Compliance with Ethics Guidelines Both trials were conducted according to the International Conference on Harmonization guidelines and the principles of the Declaration of Helsinki of 1964 and its later amendments. All patients provided written informed consent. The trial protocols were approved by the relevant independent ethics committees and institutional review boards of all participating institutions (previously published) and were sponsored by AbbVie, which provided upadacitinib, adalimumab, and placebo. All authors have provided their approval for this version to be published.

Data Availability AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols and clinical study reports), 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 and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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