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► **To cite this version:**

Peter Nash, Pascal Richette, Laure Gossec, Antonio Marchesoni, Christopher Ritchlin, et al.. Upadacitinib as monotherapy and in combination with non-biologic disease-modifying antirheumatic drugs for psoriatic arthritis. *Rheumatology*, In press, 10.1093/rheumatology/keab905 . hal-03468516

HAL Id: hal-03468516

<https://hal.sorbonne-universite.fr/hal-03468516v1>

Submitted on 7 Dec 2021

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Upadacitinib as monotherapy and in combination with non-biologic disease-modifying antirheumatic drugs for psoriatic arthritis

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ABSTRACT

Objective. To assess the efficacy and safety of upadacitinib, an oral Janus kinase inhibitor, as monotherapy or in combination with non-biologic DMARDs (nbDMARDs) in patients with PsA.

Methods. Pooled data were analysed from patients with prior inadequate response or intolerance to ≥ 1 nbDMARD (SELECT-PsA 1) or ≥ 1 biologic DMARD (SELECT-PsA 2) who received placebo, upadacitinib 15 mg once daily (QD), or upadacitinib 30 mg QD as monotherapy or in combination with ≤ 2 nbDMARDs for 24 weeks. Efficacy outcomes included achievement of American College of Rheumatology responses, Psoriasis Area and Severity Index responses, and minimal disease activity, and change from baseline and clinically meaningful improvement in Health Assessment Questionnaire-Disability Index. Adverse events (AEs) were summarized.

Results. 1916 patients were included; 574 (30%) received monotherapy and 1342 (70%) received combination therapy. Placebo-subtracted treatment effects (95% CI) for ACR20 at week 12 were 33.7% (24.4–43.1) and 34.0% (27.9–40.1) for upadacitinib 15 mg QD monotherapy and combination therapy, respectively, and 45.7% (36.9–54.5) and 39.6% (33.7–45.5) for upadacitinib 30 mg QD monotherapy and combination therapy, respectively. Treatment effects for other outcomes were consistent between monotherapy and combination therapy. AE frequency was generally similar for upadacitinib monotherapy and combination therapy, although hepatic disorders and creatine phosphokinase elevation were more common with combination therapy vs monotherapy.

Conclusion. The efficacy and safety of upadacitinib were generally consistent when administered as monotherapy or in combination with nbDMARDs through 24 weeks, supporting the use of upadacitinib with or without nbDMARDs in PsA.

Trial registration: ClinicalTrials.gov, <https://clinicaltrials.gov>, SELECT-PsA 1 (NCT03104400); SELECT-PsA 2 (NCT03104374)

Key words: psoriatic arthritis, Janus kinase inhibitor, monotherapy, upadacitinib

Rheumatology key messages

- Upadacitinib showed comparable efficacy as monotherapy and in combination with non-biologic DMARDs in PsA.
- The safety profile of upadacitinib was generally similar with monotherapy and combination therapy.
- Hepatic disorder events and creatine phosphokinase elevation were less common with monotherapy vs combination therapy.

Introduction

Research advances have translated into diverse treatment options for PsA including conventional synthetic DMARDs (csDMARDs), biologic DMARDs, and targeted synthetic DMARDs, with the potential to achieve low disease activity across various clinical domains [1-3]. However, questions remain regarding optimal treatment algorithms and treatment pattern, and one key question for clinicians is whether comedication with csDMARDs is useful for patients with PsA [1-3].

The efficacy of csDMARDs such as methotrexate (MTX) as concomitant therapy in PsA is not established, and several studies have demonstrated that MTX provides little additional benefit when combined with biologics or targeted synthetic DMARDs [4-7]. For example, an analysis of two etanercept clinical trials found that etanercept was equally effective with or without MTX in patients with PsA [4]. Treatment guidelines for PsA differ on whether csDMARDs should be used as concomitant therapy; the European League Against Rheumatism guidelines [2] recommend combining biologics with csDMARDs (while acknowledging there is little evidence to support this) whereas the American College of Rheumatology guidelines [8] favour biologic monotherapy. In addition to a lack of clarity regarding the efficacy of combination therapy, many patients have contraindications to MTX or are unable to tolerate higher doses [5, 9]. Agents with novel mechanisms of action that are effective as monotherapy would therefore be a useful treatment option for PsA.

Upadacitinib is an oral Janus kinase (JAK) inhibitor designed to selectively target JAK1 over the other JAK family enzymes: JAK2, JAK3, or tyrosine kinase 2 [10]. Upadacitinib has been assessed for the treatment of PsA in two global phase 3 trials, SELECT-PsA 1 and SELECT-PsA 2 [11, 12]. In both of these trials, upadacitinib 15 mg and 30 mg once daily (QD) were significantly more effective than placebo in improving key clinical manifestations of PsA.

Here we report data from a pooled subgroup analysis of the two SELECT-PsA studies assessing efficacy and safety outcomes in patients who were treated with upadacitinib as monotherapy or in combination with non-biologic DMARDs (nbDMARDs).

Methods

Patients

In SELECT-PsA 1 (NCT03104400) [11] and SELECT-PsA 2 (NCT03104374) [12], patients with active PsA (≥ 3 swollen and ≥ 3 tender joints) and active or historical psoriasis were blindly randomized to upadacitinib 15 mg QD, upadacitinib 30 mg QD, placebo, or adalimumab 40 mg every other week (SELECT-PsA 1 only) for 24 weeks. Patients in SELECT-PsA 1 had prior inadequate response (IR) or intolerance to ≥ 1 nbDMARD [11] and patients in SELECT-PsA 2 had prior IR or intolerance to ≥ 1 biologic DMARD [12]. Starting from week 16, patients who did not achieve $\geq 20\%$ improvement in tender and swollen joint counts compared with baseline at both week 12 and week 16 were offered rescue therapy, which allowed patients to add or modify existing nbDMARDs, NSAIDs, acetaminophen, low potency opioid medications, or corticosteroids in accordance to protocol.

The two trials were conducted according to the International Conference on Harmonization Guidelines, the Declaration of Helsinki, and applicable local country regulations. All study-related documents were approved by independent ethics committees and institutional review boards of the participating centres (Supplementary Table S1, available at *Rheumatology* online). All patients provided written informed consent.

Comedications of interest

Patients were classed as receiving monotherapy if they received upadacitinib alone, or combination therapy if they received background treatment with 1 or 2 nbDMARDs (MTX [≤ 25 mg/week], sulfasalazine [≤ 3000 mg/day], leflunomide [≤ 20 mg/day], apremilast [≤ 60 mg/day], hydroxychloroquine [≤ 400 mg/day], and less commonly bucillamine [≤ 300 mg/day] and iguratimod [≤ 50 mg/day]). Concomitant use of biologic DMARDs was not permitted.

Outcomes

Efficacy endpoints included the proportion of patients achieving American College of Rheumatology (ACR) 20/50/70 responses at weeks 12 and 24, Static Investigator Global Assessment of Psoriasis of 0 or 1 (sIGA 0/1) and at least a 2-point improvement from baseline at week 16, Psoriasis Area Severity Index (PASI) 75/90/100 responses at week 16, resolution of enthesitis at week 24, resolution of dactylitis at week 24, minimal disease activity (MDA) at week 24, and clinically meaningful improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI) (improvement of ≥ 0.35 vs baseline [13]) at week 12. Changes from baseline in pain and HAQ-DI at week 12 were also

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3 assessed. Safety outcomes were summarized by the frequency of adverse events (AEs) and
4 laboratory abnormalities over 24 weeks.
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Statistical analysis

All patients who had received at least one dose of study drug were pooled and included in the efficacy analyses. Patients receiving adalimumab in SELECT-PsA 1 were excluded from this analysis. The clinical trials were designed *a priori* for this analysis and patients were stratified by current use of ≥ 1 nbDMARD at randomization.

Demographic and clinical characteristics are presented using descriptive statistics. For binary efficacy endpoints, frequencies and percentages are reported, with non-responder imputation used for missing data; point estimates and 95% confidence intervals (CI) for placebo-subtracted differences were calculated based on Cochran–Mantel–Haenszel analysis adjusting for study. For continuous endpoints, within group least squares (LS) means (95% CI) and between group LS means (95% CI) are presented and were calculated based on the mixed-effects model repeated measures analysis with unstructured variance–covariance matrix. The model included treatment, visit, treatment-by-visit interaction, and study as fixed factors, and the continuous fixed covariate of baseline measurement. Safety data in patients who received at least one dose of study drug are presented descriptively. Laboratory abnormalities were graded according to the Common Toxicity Criteria developed by the National Cancer Institute (Version 4.03).

Results

Patients

In total, 1916 patients were included in the analysis, of whom 574 (30.0%) received upadacitinib monotherapy (SELECT-PsA 1 $n = 229$ [39.9%]; SELECT-PsA 2 $n = 345$ [60.1%]) and 1342 (70.0%) received upadacitinib in combination with any nbDMARD (SELECT-PsA 1 $n = 1046$ [77.9%]; SELECT-PsA 2 $n = 296$ [22.1%]). Of the 1342 patients receiving combination therapy with any nbDMARD (including MTX), a subset of 1036 (77.2%) patients received upadacitinib with MTX alone; this subgroup was analysed separately.

Baseline demographic and disease characteristics were generally balanced across the treatment arms and between patients receiving monotherapy and combination therapy, either with MTX only or with any nbDMARD (Table 1). Across all the groups, slightly more than half of patients were female and mean age was approximately 51–52 years. Mean duration since PsA diagnosis was longer in the monotherapy group compared with the combination therapy groups. Mean PASI score in patients with body surface area $>3\%$ at baseline ranged from 10.2 to 12.7 in the monotherapy

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3 subgroup and 8.8 to 11.5 in the combination therapy subgroups. At baseline, around one-quarter of
4 patients had dactylitis and over half of patients had enthesitis.
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8 Efficacy outcomes 9

10 The proportion of patients achieving efficacy outcomes (Table 2) and the corresponding placebo-
11 subtracted treatment effects (Fig. 1) were consistent between upadacitinib as monotherapy,
12 upadacitinib in combination with MTX, and upadacitinib in combination with any nbDMARD, with
13 associated 95% CI overlapping between the subgroups for each dose (Fig. 1). In addition, comparable
14 treatment effects were mostly observed between the upadacitinib 15 mg and 30 mg doses (Table 2
15 and Fig. 1).
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22 Placebo-subtracted treatment effects (95% CI) for achievement of ACR20 response at week 12
23 were 33.7% (24.4–43.1) and 34.0% (27.9–40.1) with upadacitinib 15 mg QD monotherapy and
24 combination therapy, respectively, and 45.7% (36.9–54.5) and 39.6% (33.7–45.5) with upadacitinib
25 30 mg QD monotherapy and combination therapy, respectively (Fig. 1). Placebo-subtracted
26 treatment effects (95% CI) for achievement of MDA at week 24 were 24.9% (18.1–31.6) and 23.1%
27 (17.8–28.4) with upadacitinib 15 mg QD monotherapy and combination therapy, respectively, and
28 35.0% (27.8–42.1) and 28.9% (23.5–34.2) with upadacitinib 30 mg QD monotherapy and
29 combination therapy, respectively. Upadacitinib also demonstrated consistency in placebo-
30 subtracted treatment effects between the monotherapy and combination therapy groups for
31 achievement of ACR50 and ACR70 responses at Week 12 and resolution of dactylitis and enthesitis
32 at Week 24 (Fig. 1). For the skin endpoint PASI75 response at Week 16, upadacitinib 15 mg
33 demonstrated consistent placebo-subtracted treatment effects between monotherapy and
34 combination therapy with overlapping CI, while upadacitinib 30 mg showed numerically greater
35 placebo-subtracted values in monotherapy vs combination therapy (Fig. 1). Other skin endpoints
36 such as achievement of PASI 90/100 and sIGA 0/1 with at least a 2-point improvement at Week 16
37 demonstrated consistent placebo-subtracted treatment effects with overlapping CI between
38 monotherapy and combination therapy for both doses (Fig. 1). Change from baseline in pain and
39 HAQ-DI at week 12 in the monotherapy and combination therapy groups also showed comparable
40 results (Fig. 1 and Table 2). ACR20/50/70 responses at week 24 (Supplementary Table S2, available
41 at *Rheumatology* online) were consistent with results at week 12.
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57 Study-specific results for the SELECT-PsA 1 (nbDMARD-IR) and SELECT-PsA 2 (biologic DMARD-
58 IR) studies reflect those of the integrated analysis, with generally comparable proportions of
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3 patients in the monotherapy and combination therapy subgroups of each study achieving
4 ACR20/50/70 responses, MDA, and sIGA 0/1 and at least a 2-point improvement across all treatment
5 subgroups (Supplementary Table S3, available at *Rheumatology* online).
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8 9 10 Safety outcomes

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12 Generally, the frequency of AEs and serious AEs was comparable with upadacitinib 15 mg and 30 mg
13 when administered as monotherapy and in combination with MTX alone or any nbDMARD through
14 week 24 (Table 3). The frequency of discontinuation of study drug, patients lost to follow-up, and
15 discontinuation due to lack of efficacy in patients receiving upadacitinib 15 mg were higher in the
16 monotherapy groups compared with the combination therapy groups (Table 4). The higher
17 frequency of discontinuation of study drug was attributed to a relatively smaller sample size in the
18 monotherapy subgroup, and the occurrence of three cases of malignancy other than non-melanoma
19 skin cancer with UPA 15 mg monotherapy (compared with zero cases in the UPA 15 mg combination
20 therapy group) for which discontinuation was required per the protocol.
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29 The frequency of serious infections and herpes zoster was similar for placebo and upadacitinib
30 15 mg QD as monotherapy or combination therapy but higher in the upadacitinib 30 mg QD
31 monotherapy and combination therapy subgroups (Table 3). All herpes zoster events were mild or
32 moderate in severity except for one severe, non-serious event involving two dermatomes in a
33 patient receiving upadacitinib 30 mg QD with MTX. There were no major adverse cardiovascular
34 events or venous thromboembolic events reported with upadacitinib monotherapy. One non-fatal
35 myocardial infarction was reported in a patient receiving upadacitinib 15 mg QD with MTX, one
36 pulmonary embolism was reported in a patient receiving upadacitinib 15 mg QD with sulfasalazine,
37 and one pulmonary embolism was reported in a patient receiving upadacitinib 30 mg QD with MTX.
38 In addition, one deep vein thrombosis was reported in a patient receiving placebo in the
39 monotherapy group, and one non-fatal myocardial infarction was reported in a patient receiving
40 placebo in combination with MTX.
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50 AEs of hepatic disorder (which were mostly non-serious transaminase elevation) and creatine
51 phosphokinase (CPK) elevation were more common in the combination therapy groups vs the
52 monotherapy groups, and more common with upadacitinib 30 mg vs upadacitinib 15 mg (Table 3).
53 AEs of anaemia, neutropenia, and lymphopenia were generally consistent across the monotherapy
54 and combination therapy groups (Table 3). Grade 3 or 4 changes in laboratory values were
55 infrequent (Table 5).
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Discussion

In this analysis, upadacitinib used as a monotherapy or in combination with nbDMARDs (including both MTX alone or any nbDMARD) was similarly well tolerated and effective in treating the major clinical manifestations of PsA including musculoskeletal symptoms (peripheral arthritis, enthesitis, and dactylitis), psoriasis, physical function, and pain.

The finding that upadacitinib combination therapy in PsA does not provide significant improvements in efficacy over monotherapy is consistent with observations investigating the efficacy of other PsA therapies used in combination with MTX or other nbDMARDs. A propensity score-matched analysis of a large registry of patients with PsA ($n = 497$) treated either with a combination of a tumour necrosis factor inhibitor (TNFi) and a nbDMARD or TNFi monotherapy demonstrated no difference between groups in time to remission defined as achieving 28-joint Disease Activity Score using C-reactive protein <2.6 (DAS28[CRP]) [6]. Similarly, a pooled analysis of two 24-week, placebo-controlled trials of subcutaneous etanercept (25 mg twice weekly or 50 mg once weekly) with ($n = 322$) or without MTX ($n = 152$) in patients with PsA showed a similar proportion of patients across the two groups achieving ACR20 [4]. Furthermore, in the Study of Etanercept and MTX in Subjects with Psoriatic Arthritis (SEAM-PsA) trial, both etanercept monotherapy and MTX combination therapy showed greater efficacy than MTX monotherapy in patients with PsA, according to ACR20 and MDA response rates and extent of radiographic progression at follow-up [7]. Similarly, a post hoc analysis of 455 patients in the SPIRIT-P1 and SPIRIT-P2 trials found that treatment with once-monthly or once-fortnightly ixekizumab improved the signs and symptoms of PsA either alone or in combination with MTX [14]. More recently, a meta-analysis of randomized controlled trials found that addition of MTX to biologics led to no clinical improvements vs biologic monotherapy in patients with PsA [15]. Within the same drug class, a study of tofacitinib found that withdrawal of MTX in patients receiving stable combination therapy did not result in clinically meaningful changes in disease activity or safety [16]. Interestingly, these data contrast with observations in RA, where combining biologic DMARDs with MTX results in increased efficacy [17, 18]. This is thought to be due to the reduction of anti-drug antibodies by MTX, resulting in increased drug survival [19]. However, this effect is not relevant to upadacitinib since it does not induce immunogenicity in patients.

The data from our analysis also suggest that upadacitinib was well tolerated when used as a monotherapy and when administered in combination either with MTX alone or any nbDMARD, with the majority of AEs seen at comparable frequencies across the monotherapy and combination

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3 therapy groups. Hepatic disorders were more frequent with upadacitinib as combination therapy
4 compared with upadacitinib as monotherapy, which is not surprising given the well-known effects of
5 nbDMARDs such as MTX on liver function [20, 21]. CPK elevation also appeared to be higher in the
6 combination therapy vs monotherapy groups, particularly in patients receiving upadacitinib 30 mg.
7 However, Grade 3 or 4 changes in transaminases, CPK, and other laboratory parameters were
8 infrequent. Given that the efficacy of upadacitinib monotherapy appeared to be comparable to that
9 of upadacitinib combination therapy, a reduction in the risk of mild laboratory abnormalities could
10 be a benefit of treatment with upadacitinib monotherapy, while also reducing the burden of
11 medication use.
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20 There appeared to be a higher rate of placebo response in the combination therapy groups
21 compared with the monotherapy group. This may reflect the fact that the combination therapy
22 groups had a higher proportion of patients from SELECT-PsA 1, which demonstrated higher placebo
23 responses compared with SELECT-PsA 2 (Supplementary Table S3). In addition, patients in SELECT-
24 PsA 1 and 2 were permitted to receive up to two concomitant nbDMARDs, which may have further
25 increased the placebo response. The relatively high placebo response in SELECT-PsA 1 may be due to
26 the fact that patients in this trial were less treatment refractory than those in SELECT-PsA 2
27 (nbDMARD-IR versus bDMARD-IR) [11, 12]. However, the placebo response in SELECT-PsA 1 was
28 generally comparable to similar studies of JAK inhibitors in patients with PsA, such as the OPAL
29 Broaden study of tofacitinib [22].
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38 A primary strength of the current analysis is that it is based on a pooled analysis of data from
39 two large, phase 3 clinical trials. Although the comparison of upadacitinib as monotherapy vs
40 combination therapy was not a primary objective of the studies, this analysis was planned prior to
41 trial conduct and patients were stratified by current use of ≥ 1 nbDMARD at randomization. One
42 limitation of the study is that the majority of patients taking a concomitant nbDMARD were
43 receiving MTX, and thus it was not possible to individually assess upadacitinib in combination with
44 other nbDMARDs such as sulfasalazine or leflunomide. In addition, although it was permitted,
45 relatively few patients were receiving upadacitinib in combination with two nbDMARDs, and so the
46 safety and efficacy of this treatment regimen could not be assessed. It should also be noted that all
47 patients who were taking a nbDMARD at study entry met inclusion criteria related to active disease.
48 Thus, these data permit assessment of the safety and efficacy of treatment with upadacitinib added
49 to stable background therapy and are not able to inform the benefit or risk of starting both drugs
50 simultaneously, or adding a nbDMARD to existing upadacitinib therapy. Finally, this analysis focused
51 on 24-week data; long-term efficacy and safety for upadacitinib monotherapy and combination
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3 therapy, including any long-term benefits (such as exploring late stage drug survival with or without
4 combination therapy), will be assessed in the ongoing SELECT-PsA 1 and SELECT-PsA 2 studies.
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8 In conclusion, the results of this analysis show that the efficacy and safety of upadacitinib was
9 generally consistent when administered as monotherapy or in combination with nbDMARDs. This
10 supports the use of upadacitinib with or without nbDMARDs in PsA and suggests that upadacitinib
11 monotherapy may be a useful treatment option in patients with contraindications to MTX or those
12 who are unable to tolerate higher doses.
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18 **Acknowledgements**

19
20
21 Medical writing support was provided by John Ewbank, PhD, of 2 the Nth (Cheshire, UK) and was
22 funded by AbbVie.
23
24

25 *Funding:*

26
27
28 This work was supported by AbbVie, who participated in the study design, research, analysis, data
29 collection, interpretation of data, reviewing, and approval of the publication. All authors had access
30 to relevant data and participated in the drafting, review, and approval of this publication. No
31 honoraria or payments were made for authorship.
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36 *Disclosures statement:*

37
38 P.N.: has received funding for clinical trials, research grants, and honoraria for lectures and advice
39 from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, Roche, Sanofi-Aventis, and
40 UCB.
41
42

43
44 P.R.: has received honoraria from AbbVie, Amgen, Biogen, BMS, Celgene, Eli Lilly, Janssen, Novartis,
45 Pfizer, Roche, Sanofi-Aventis, and UCB.
46
47

48 L.G.: has received research grants from Amgen, Galapagos, Eli Lilly, Pfizer, Sandoz, and Sanofi; and
49 consulting fees from AbbVie, Amgen, BMS, Biogen, Celgene, Galapagos, Gilead, Janssen, Eli Lilly,
50 Novartis, Pfizer, Samsung Bioepis, Sanofi-Aventis, and UCB.
51
52

53 A.M.: has received speaking fees and/or honoraria from AbbVie, Eli Lilly, Janssen, Novartis, Pfizer,
54 and UCB; and consulting fees from AbbVie.
55
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3 C.R.: has received consulting fees from AbbVie, Amgen, BMS, Janssen, and Novartis; consulting and
4 being an independent contractor for Amgen; and consulting for and receiving research support from
5 UCB.
6
7

8 K.K., E.L.M-B., E.L., R.M., D.F., J.K.A.: are AbbVie employees and may own stock or options.
9

10
11 E.M.R.: has received consulting fees from AbbVie, Amgen, BMS, Gilead, Janssen, Eli Lilly, Novartis,
12 and Pfizer.
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15 *Data availability statement:*

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17 AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This
18 includes access to anonymized, individual, and trial-level data (analysis datasets), as well as other
19 information (e.g. protocols and clinical study reports), provided the trials are not part of an ongoing
20 or planned regulatory submission. This includes requests for clinical trial data for unlicensed
21 products and indications. These clinical trial data can be requested by any qualified researchers who
22 engage in rigorous, independent scientific research, and will be provided following review and
23 approval of a research proposal and statistical analysis plan, and execution of a Data Sharing
24 Agreement.
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28 Data requests can be submitted at any time and the data will be accessible for 12 months, with
29 possible extensions considered. For more information on the process, or to submit a request, visit
30 [https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-](https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html)
31 [sharing/data-and-information-sharing-with-qualified-researchers.html](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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Tables and figures

TABLE 1 Baseline demographics and disease characteristics

Parameter ^a	Monotherapy			Combination therapy with MTX			Combination therapy with any nbDMARD (including MTX)		
	PBO N = 188	UPA 15 mg QD N = 189	UPA 30 mg QD N = 197	PBO N = 342	UPA 15 mg QD N = 353	UPA 30 mg QD N = 341	PBO N = 447	UPA 15 mg QD N = 451	UPA 30 mg QD N = 444
Female, <i>n</i> (%)	102 (54.3)	105 (55.6)	101 (51.3)	173 (50.6)	195 (55.2)	190 (55.7)	229 (51.2)	246 (54.5)	250 (56.3)
Age (years)	52.8 ± 11.5	52.2 ± 12.8	50.7 ± 11.5	51.2 ± 12.3	51.4 ± 12.0	51.3 ± 12.6	51.1 ± 12.3	52.0 ± 11.9	51.1 ± 12.7
BMI ≥25 kg/m ² , <i>n</i> (%)	145 (77.1)	152 (80.4)	160 (81.2)	274 (80.1)	279 (79.0)	267 (78.3)	356 (79.6)	361 (80.0)	338 (76.1)
Duration since PsA diagnosis (years)	9.0 ± 9.5	8.6 ± 8.4	8.4 ± 8.7	7.2 ± 8.3	6.5 ± 7.3	6.8 ± 6.9	7.3 ± 8.1	6.8 ± 7.6	6.6 ± 6.8
PASI (for baseline BSA ≥3%)	12.7 ± 12.1	11.8 ± 10.8	10.2 ± 10.4	11.5 ± 11.5	9.5 ± 9.5	8.8 ± 8.2	10.8 ± 11.0	9.1 ± 9.0	8.8 ± 8.1
Presence of dactylitis (LDI >0), <i>n</i> (%)	54 (28.7)	53 (28.0)	50 (25.4)	95 (27.8)	108 (30.6)	93 (27.3)	136 (30.4)	138 (30.6)	127 (28.6)
Presence of enthesitis (LEI >0), <i>n</i> (%)	118 (62.8)	114 (60.3)	134 (68.0)	202 (59.1)	222 (62.9)	222 (65.1)	267 (59.7)	289 (64.1)	285 (64.2)
TJC68	22.7 ± 16.8	23.4 ± 17.0	22.8 ± 15.2	21.5 ± 15.5	21.0 ± 14.7	20.5 ± 13.9	21.4 ± 15.2	21.2 ± 15.2	20.3 ± 14.0
SJC66	10.5 ± 7.2	11.7 ± 9.1	11.7 ± 9.0	12.1 ± 9.1	11.5 ± 9.0	11.4 ± 8.0	11.7 ± 8.9	11.4 ± 8.9	11.3 ± 7.6
Corticosteroid use at BL, <i>n</i> (%)	18.9 (9.6)	27 (14.3)	12 (6.1)	59 (17.3)	52 (14.7)	54 (15.8)	76 (17.0)	68 (15.1)	72 (16.2)
MTX dose at BL, <i>n</i> (%)									
≤15 mg	–	–	–	209 (61.1)	227 (64.3)	201 (58.9)	224 (50.1)	239 (53.0)	221 (49.8)
>15 mg	–	–	–	131 (38.3)	124 (35.1)	139 (40.8)	149 (33.3)	138 (30.6)	151 (34.0)
Patient's assessment of pain	6.5 ± 2.0	6.4 ± 2.1	6.1 ± 2.1	6.2 ± 2.2	6.2 ± 2.1	6.1 ± 2.1	6.2 ± 2.2	6.2 ± 2.1	6.0 ± 2.1
HAQ-DI	1.1 ± 0.7	1.1 ± 0.6	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.6	1.1 ± 0.6	1.2 ± 0.7	1.1 ± 0.6	1.1 ± 0.6

^aValues are mean ± s.d. unless otherwise indicated. Non-biologic DMARDs permitted: methotrexate, sulfasalazine, leflunomide, apremilast, hydroxychlorine, bucillamine, and iguratimod. BL: baseline; BMI: body mass index; BSA: body surface area; HAQ-DI: Health Assessment Questionnaire-Disability Index; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MTX: methotrexate; nbDMARD: non-biologic DMARD; PASI: Psoriasis Area Severity Index; PBO: placebo; QD: once daily; s.d.: standard deviation; SJC66: Swollen Joint Count in 66 joints; TJC68: Tender Joint Count in 68 joints; UPA: upadacitinib.

TABLE 2 Summary of efficacy by UPA as monotherapy or combination therapy

Parameter	Monotherapy			Combination therapy with MTX			Combination therapy with any nbDMARD (including MTX)		
	PBO	UPA 15 mg QD	UPA 30 mg QD	PBO	UPA 15 mg QD	UPA 30 mg QD	PBO	UPA 15 mg QD	UPA 30 mg QD
ACR20 at week 12, <i>n/N</i> (%)	47/188 (25.0)	111/189 (58.7)	139/197 (70.6)	120/342 (35.1)	251/353 (71.1)	254/341 (74.5)	157/447 (35.1)	312/451 (69.2)	332/444 (74.8)
ACR50 at week 12, <i>n/N</i> (%)	9/188 (4.8)	56/189 (29.6)	84/197 (42.6)	44/342 (12.9)	139/353 (39.4)	168/341 (49.3)	57/447 (12.8)	172/451 (38.1)	217/444 (48.9)
ACR70 at week 12, <i>n/N</i> (%)	0	22/189 (11.6)	39/197 (19.8)	8/342 (2.3)	51/353 (14.4)	84/341 (24.6)	11/447 (2.5)	63/451 (14.0)	104/444 (23.4)
Resolution of enthesitis (LEI = 0) at week 24, <i>n/N</i> (%) ^a	23/118 (19.5)	48/114 (42.1)	66/134 (49.3)	61/202 (30.2)	121/222 (54.5)	122/222 (55.0)	77/267 (28.8)	154/289 (53.3)	156/285 (54.7)
Resolution of dactylitis (LDI = 0) at week 24, <i>n/N</i> (%) ^b	12/54 (22.2)	31/53 (58.5)	33/50 (66.0)	40/95 (42.1)	85/108 (78.7)	75/93 (80.6)	56/136 (41.2)	105/138 (76.1)	102/127 (80.3)
sIGA 0/1 and ≥2 point improvement from BL at week 16, <i>n/N</i> (%)	11/150 (7.3)	56/153 (36.6)	80/162 (49.4)	32/264 (12.1)	114/273 (41.8)	125/256 (48.8)	38/326 (11.7)	142/340 (41.8)	161/326 (49.4)
PASI75 at week 16, <i>n/N</i> (%) ^c	9/109 (8.3)	53/106 (50.0)	71/108 (65.7)	46/194 (23.7)	123/193 (63.7)	108/187 (57.8)	57/233 (24.5)	149/238 (62.6)	134/233 (57.5)
PASI90 at week 16, <i>n/N</i> (%) ^c	6/109 (5.5)	30/106 (28.3)	55/108 (50.9)	25/194 (12.9)	80/193 (41.5)	92/187 (49.2)	31/233 (13.3)	97/238 (40.8)	108/233 (46.4)

PASI100 at week 16, n/N (%) ^c	3/109	15/106	39/108	16/194	57/193	61/187	20/233	69/238	74/233
	(2.8)	(14.2)	(36.1)	(8.2)	(29.5)	(32.6)	(8.6)	(29.0)	(31.8)
MDA at week 24, n/N (%)	5/188	52/189	74/197	43/342	122/353	139/341	53/447	158/451	181/444
	(2.7)	(27.5)	(37.6)	(12.6)	(34.6)	(40.8)	(11.9)	(35.0)	(40.8)
Change from BL in pain at week 12, Δ (95% CI)	-0.63 (-0.96, - 0.30)	-1.96 (-2.28, - 1.64)	-2.69 (-3.01, - 2.38)	-0.91 (-1.16, - 0.67)	-2.29 (-2.53, - 2.05)	-2.73 (-2.97, - 2.48)	-0.84 (-1.05, - 0.63)	-2.21 (-2.42, - 2.00)	-2.63 (-2.85, - 2.42)
Change from BL in HAQ-DI at week 12, Δ (95% CI)	-0.14 (-0.21, - 0.07)	-0.31 (-0.38, - 0.25)	-0.49 (-0.55, - 0.43)	-0.10 (-0.15, - 0.04)	-0.43 (-0.49, - 0.38)	-0.43 (-0.49, - 0.38)	-0.11 (-0.16, - 0.06)	-0.40 (-0.45, - 0.36)	-0.43 (-0.48, - 0.38)

^aFor patients with baseline LEI >0. ^bFor patients with baseline LDI >0. ^cFor patients with ≥3% body surface area psoriasis at baseline. ACR20/50/70: 20%/50%/70% improvement in American College of Rheumatology response criteria; BL: baseline; CI: confidence interval; HAQ-DI: Health Assessment Questionnaire-Disability Index; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; MTX: methotrexate; nbDMARD: non-biologic DMARD; PASI75/90/100: 75%/90%/100% improvement in Psoriasis Area Severity Index; PBO: placebo; QD: once daily; sIGA 0/1: Static Investigator Global Assessment of Psoriasis of 0 or 1; UPA: upadacitinib.

TABLE 3 Summary of AEs by UPA as monotherapy or combination therapy

Parameter, <i>n</i> (%)	Monotherapy			Combination therapy with MTX			Combination therapy with any nbDMARD (including MTX)		
	PBO <i>N</i> = 188	UPA 15 mg QD <i>N</i> = 189	UPA 30 mg QD <i>N</i> = 197	PBO <i>N</i> = 342	UPA 15 mg QD <i>N</i> = 353	UPA 30 mg QD <i>N</i> = 341	PBO <i>N</i> = 447	UPA 15 mg QD <i>N</i> = 451	UPA 30 mg QD <i>N</i> = 444
Any AE	127 (67.6)	124 (65.6)	145 (73.6)	191 (55.8)	225 (63.7)	248 (72.7)	264 (59.1)	298 (66.1)	331 (74.5)
Serious AE	8 (4.3)	9 (4.8)	9 (4.6)	8 (2.3)	14 (4.0)	32 (9.4)	9 (2.0)	17 (3.8)	35 (7.9)
AE leading to D/C of study drug	13 (6.9)	14 (7.4)	14 (7.1)	6 (1.8)	10 (2.8)	25 (7.3)	11 (2.5)	14 (3.1)	27 (6.1)
Deaths	1 (0.5)	0	0	1 (0.3)	0	0	1 (0.2)	0	0
Infection	65 (34.6)	67 (35.4)	88 (44.7)	97 (28.4)	129 (36.5)	155 (45.5)	148 (33.1)	173 (38.4)	203 (45.7)
Serious infection	2 (1.1)	1 (0.5)	2 (1.0)	2 (0.6)	3 (0.8)	13 (3.8)	3 (0.7)	5 (1.1)	15 (3.4)
Opportunistic infection excluding tuberculosis and herpes zoster	0	0	2 (1.0)	0	1 (0.3)	2 (0.6)	0	1 (0.2)	2 (0.5)
Herpes zoster	2 (1.1)	2 (1.1)	6 (3.0)	2 (0.6)	4 (1.1)	6 (1.8)	3 (0.7)	5 (1.1)	7 (1.6)
Active tuberculosis	0	0	0	0	0	0	0	0	0
Malignancy other than NMSC	0	3 (1.6)	1 (0.5)	0	0	2 (0.6)	0	0	2 (0.5)
NMSC	0	0	0	1 (0.3)	0	2 (0.6)	1 (0.2)	1 (0.2)	3 (0.7)
GI perforation (adjudicated)	0	0	0	0	0	0	0	0	0
MACE (adjudicated)	0	0	0	1 (0.3)	1 (0.3)	0	1 (0.2)	1 (0.2)	0
VTE (adjudicated)	1 (0.5)	0	0	0	0	1 (0.3)	0	1 (0.2)	1 (0.2)
Hepatic disorder	5 (2.7)	8 (4.2)	14 (7.1)	12 (3.5)	28 (7.9)	45 (13.2)	14 (3.1)	35 (7.8)	56 (12.6)
Anaemia	3 (1.6)	1 (0.5)	11 (5.6)	3 (0.9)	5 (1.4)	12 (3.5)	3 (0.7)	6 (1.3)	23 (5.2)

Neutropenia	1 (0.5)	2 (1.1)	6 (3.0)	0	4 (1.1)	12 (3.5)	1 (0.2)	4 (0.9)	21 (4.7)
Lymphopenia	0	2 (1.1)	2 (1.0)	4 (1.2)	4 (1.1)	12 (3.5)	5 (1.1)	6 (1.3)	15 (3.4)
CPK elevation	3 (1.6)	10 (5.3)	11 (5.6)	5 (1.5)	21 (5.9)	34 (10.0)	7 (1.6)	32 (7.1)	42 (9.5)

AE: adverse event; CPK: creatine phosphokinase; D/C: discontinuation; GI: gastrointestinal; MACE: major adverse cardiovascular events; MTX: methotrexate; nbDMARD: non-biologic DMARD; NMSC: non-melanoma skin cancer; PBO: placebo; QD: once daily; UPA: upadacitinib; VTE: venous thromboembolism.

TABLE 4 Reasons for discontinuation through week 24 by monotherapy or combination therapy

Parameter	Monotherapy			Combination therapy with MTX			Combination therapy with any nbDMARD (including MTX)		
	PBO (<i>n</i> = 188)	UPA 15 mg QD (<i>n</i> = 189)	UPA 30 mg QD (<i>n</i> = 197)	PBO (<i>n</i> = 342)	UPA 15 mg QD (<i>n</i> = 353)	UPA 30 mg QD (<i>n</i> = 341)	PBO (<i>n</i> = 447)	UPA 15 mg QD (<i>n</i> = 451)	UPA 30 mg QD (<i>n</i> = 444)
Discontinuation prior to week 24, <i>n</i> (%)	42 (22.3)	26 (13.8)	23 (11.7)	33 (9.6)	23 (6.5)	32 (9.4)	45 (10.1)	30 (6.7)	40 (9.0)
Adverse event	13 (6.9)	14 (7.4)	12 (6.1)	6 (1.8)	9 (2.5)	22 (6.5)	11 (2.5)	13 (2.9)	24 (5.4)
Withdrawal by patient	11 (5.9)	1 (0.5)	8 (4.1)	17 (5.0)	8 (2.3)	6 (1.8)	22 (4.9)	9 (2.0)	9 (2.0)
Lost to follow-up	5 (2.7)	6 (3.2)	1 (0.5)	4 (1.2)	4 (1.1)	1 (0.3)	4 (0.9)	4 (0.9)	2 (0.5)
Lack of efficacy	20 (10.6)	5 (2.6)	1 (0.5)	6 (1.8)	1 (0.3)	1 (0.3)	8 (1.8)	1 (0.2)	2 (0.5)
Other	2 (1.1)	2 (1.1)	3 (1.5)	2 (0.6)	4 (1.1)	3 (0.9)	4 (0.9)	6 (1.3)	4 (0.9)

Patient who discontinued study drug are counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations. MTX: methotrexate; nbDMARD: non-biologic DMARD; PBO: placebo; QD: once daily; UPA: upadacitinib.

TABLE 5 Percentage of patients with Grade 3 or Grade 4 laboratory abnormalities^a

Parameter, <i>n</i> (%)	Monotherapy			Combination therapy with MTX			Combination therapy with any nbDMARD (including MTX)		
	PBO (<i>n</i> = 183)	UPA 15 mg QD (<i>n</i> = 187)	UPA 30 mg QD (<i>n</i> = 195)	PBO (<i>n</i> = 339)	UPA 15 mg QD (<i>n</i> = 350)	UPA 30 mg QD (<i>n</i> = 340)	PBO (<i>n</i> = 444)	UPA 15 mg QD (<i>n</i> = 448)	UPA 30 mg QD (<i>n</i> = 443)
Alanine aminotransferase (U/L)									
Grade 3 (>5.0–20.0 ×ULN)	2 (1.1)	1 (0.5)	3 (1.5)	3 (0.9) ^b	4 (1.1)	3 (0.9)	6 (1.4) ^b	5 (1.1)	3 (0.7)
Grade 4 (>20.0 ×ULN)	0	0	0	0 ^b	0	0	0 ^b	0	0
Aspartate aminotransferase (U/L)									
Grade 3 (>5.0–20.0 ×ULN)	0	1 (0.5)	0 ^b	2 (0.6) ^b	1 (0.3)	2 (0.6)	3 (0.7) ^b	1 (0.2)	3 (0.7)
Grade 4 (>20.0 ×ULN)	0	0	0 ^b	0 ^b	0	1 (0.3)	0 ^b	0	1 (0.2)
Creatine kinase (U/L)									
Grade 3 (>5.0–10.0 ×ULN)	1 (0.5)	2 (1.1)	5 (2.6)	1 (0.3)	5 (1.4)	6 (1.8)	3 (0.7)	5 (1.1)	7 (1.6)
Grade 4 (>10.0 ×ULN)	1 (0.5)	0	0	2 (0.6)	2 (0.6)	3 (0.9)	2 (0.5)	2 (0.4)	4 (0.9)

1										
2										
3	Haemoglobin (g/L)									
4										
5	Grade 3 (<80)	0	0	1 (0.5)	0	0	2 (0.6)	0	0	2 (0.5)
6	Lymphocytes (10 ⁹ /L)									
7										
8	Grade 3									
9	(0.2–<0.5)	0	1 (0.5)	2 (1.0)	1 (0.3)	3 (0.9)	9 (2.6)	1 (0.2)	4 (0.9)	9 (2.0)
10										
11	Grade 4 (<0.2)	0	0	0	0	0	0	0	0	0
12	Neutrophils (10 ⁹ /L)									
13										
14	Grade 3									
15	(0.5–<1.0)	1 (0.5)	2 (1.1)	5 (2.6)	1 (0.3)	1 (0.3)	4 (1.2)	1 (0.2)	2 (0.4)	5 (1.1)
16										
17	Grade 4 (<0.5)	0	0	0	0	0	0	0	0	0
18	Platelets (10 ⁹ /L)									
19										
20	Grade 3									
21	(25–<50)	0 ^b	0	0 ^b	0 ^b	0	1 (0.3)	0 ^b	0	1 (0.2)
22										
23	Grade 4 (<25)	0 ^b	0	0 ^b	0 ^b	0	0	0 ^b	0	0
24	Leucocytes (10 ⁹ /L)									
25										
26	Grade 3									
27	(1.0–<2.0)	1 (0.5)	0	1 (0.5)	0	0	1 (0.3)	0	0	1 (0.2)
28										
29	Grade 4 (<1.0)	0	0	0	0	0	0	0	0	0
30										
31										
32										
33										

^aAbnormalities may reflect single, unconfirmed abnormalities. ^bData missing for $n = 1$ patient. BMI: body mass index; MTX: methotrexate; nbDMARD: non-biologic DMARD; PBO: placebo; QD: once daily; ULN: upper limit of normal; UPA: upadacitinib.

Figure legends

FIG. 1 Integrated efficacy analysis of placebo-subtracted treatment effects

^aFor patients with baseline LEI >0. ^bFor patients with baseline LDI >0. ^cFor patients with $\geq 3\%$ body surface area psoriasis at baseline.

ACR20/50/70: 20%/50%/70% improvement in American College of Rheumatology response criteria;

BL: baseline; CI: confidence interval; HAQ-DI: Health Assessment Questionnaire-Disability Index; LDI:

Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; MTX:

methotrexate; NRS: numeric rating scale; PASI75/90/100: 75%/90%/100% improvement in Psoriasis

Area Severity Index; QD: once daily; sIGA 0/1: Static Investigator Global Assessment of Psoriasis of 0 or 1 and at least a 2 point improvement from baseline; UPA: upadacitinib.

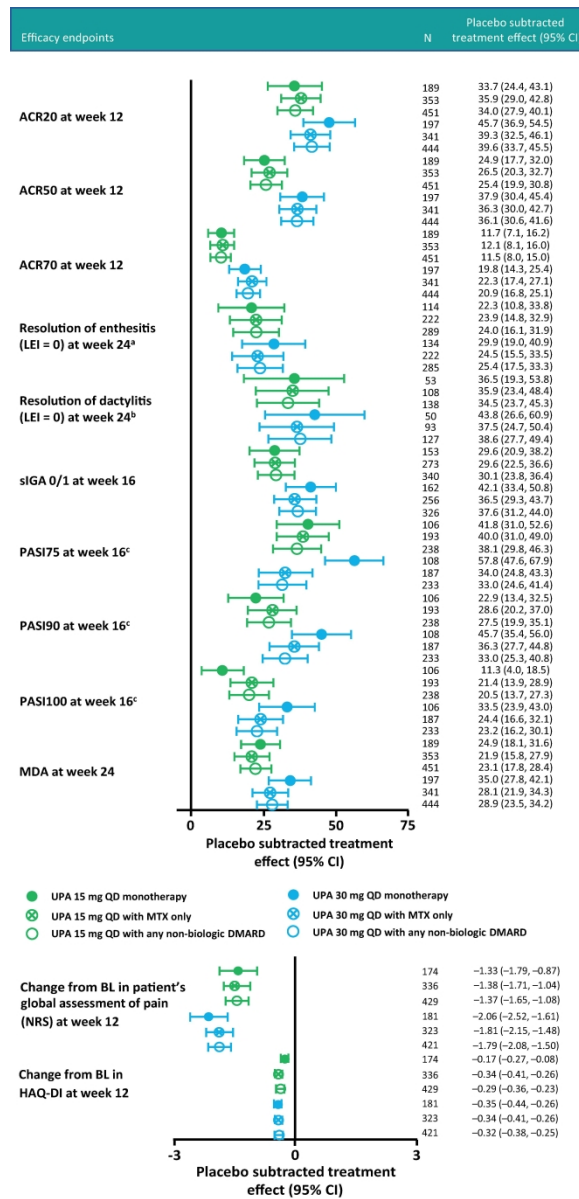


FIG. 1 Integrated efficacy analysis of placebo-subtracted treatment effects

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