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

Peter Nash, Pascal Richette, Laure Gossec, Antonio Marchesoni, Christopher Ritchlin, Koji Kato, Erin L Mcdearmon-Blondell, Elizabeth Lesser, Reva Mccaskill, Dai Feng, et al.

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

Peter Nash[1], Pascal Richette[2,3], Laure Gossec[4,5], Antonio Marchesoni[6], Christopher Ritchlin[7], Koji Kato[8], Erin L. McDearmon-Blondell[8], Elizabeth Lesser[8], Reva McCaskill[8], Dai Feng[8], Jaclyn K. Anderson[8] and Eric M. Ruderman[9]

[1]School of Medicine, Griffith University, Brisbane, Queensland, Australia, [2]Lariboisière hospital, AP-HP, Paris University, Rheumatology department, Paris, France, [3]Bioscar Inserm U1132 and Université de Paris, Hôpital Lariboisière, F-75010, Paris, France, [4]Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France, [5]Pitié-Salpêtrière hospital, AP-HP. Sorbonne Université, Rheumatology Department, Paris, France, [6]Humanitas San Pio X, Milan, Italy, [7]Allergy, Immunology and Rheumatology Division, Center for Musculoskeletal Medicine, University of Rochester Medical Center, Rochester, NY, USA, [8]AbbVie Inc, North Chicago, IL, USA, [9]Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Corresponding author: Peter Nash

Postal address: School of Medicine, Griffith University, Gold Coast Campus, Brisbane, Queensland QLD 4222, Australia.

Email: drpnash@tpg.com.au;

ORCiD ID: 0000-0002-2571-788X

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 ≥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

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

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

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

Efficacy outcomes

The proportion of patients achieving efficacy outcomes (Table 2) and the corresponding placebo-subtracted treatment effects (Fig. 1) were consistent between upadacitinib as monotherapy, upadacitinib in combination with MTX, and upadacitinib in combination with any nbDMARD, with associated 95% CI overlapping between the subgroups for each dose (Fig. 1). In addition, comparable treatment effects were mostly observed between the upadacitinib 15 mg and 30 mg doses (Table 2 and Fig. 1).

Placebo-subtracted treatment effects (95% CI) for achievement of ACR20 response at week 12 were 33.7% (24.4–43.1) and 34.0% (27.9–40.1) with upadacitinib 15 mg QD monotherapy and combination therapy, respectively, and 45.7% (36.9–54.5) and 39.6% (33.7–45.5) with upadacitinib 30 mg QD monotherapy and combination therapy, respectively (Fig. 1). Placebo-subtracted treatment effects (95% CI) for achievement of MDA at week 24 were 24.9% (18.1–31.6) and 23.1% (17.8–28.4) with upadacitinib 15 mg QD monotherapy and combination therapy, respectively, and 35.0% (27.8–42.1) and 28.9% (23.5–34.2) with upadacitinib 30 mg QD monotherapy and combination therapy, respectively. Upadacitinib also demonstrated consistency in placebo-subtracted treatment effects between the monotherapy and combination therapy groups for achievement of ACR50 and ACR70 responses at Week 12 and resolution of dactylitis and enthesitis at Week 24 (Fig. 1). For the skin endpoint PASI75 response at Week 16, upadacitinib 15 mg demonstrated consistent placebo-subtracted treatment effects between monotherapy and combination therapy with overlapping CI, while upadacitinib 30 mg showed numerically greater placebo-subtracted values in monotherapy *vs* combination therapy (Fig. 1). Other skin endpoints such as achievement of PASI 90/100 and sIGA 0/1 with at least a 2-point improvement at Week 16 demonstrated consistent placebo-subtracted treatment effects with overlapping CI between monotherapy and combination therapy for both doses (Fig. 1). Change from baseline in pain and HAQ-DI at week 12 in the monotherapy and combination therapy groups also showed comparable results (Fig. 1 and Table 2). ACR20/50/70 responses at week 24 (Supplementary Table S2, available at *Rheumatology* online) were consistent with results at week 12.

Study-specific results for the SELECT-PsA 1 (nbDMARD-IR) and SELECT-PsA 2 (biologic DMARD-IR) studies reflect those of the integrated analysis, with generally comparable proportions of

patients in the monotherapy and combination therapy subgroups of each study achieving ACR20/50/70 responses, MDA, and sIGA 0/1 and at least a 2-point improvement across all treatment subgroups (Supplementary Table S3, available at *Rheumatology* online).

Safety outcomes

Generally, the frequency of AEs and serious AEs was comparable with upadacitinib 15 mg and 30 mg when administered as monotherapy and in combination with MTX alone or any nbDMARD through week 24 (Table 3). The frequency of discontinuation of study drug, patients lost to follow-up, and discontinuation due to lack of efficacy in patients receiving upadacitinib 15 mg were higher in the monotherapy groups compared with the combination therapy groups (Table 4). The higher frequency of discontinuation of study drug was attributed to a relatively smaller sample size in the monotherapy subgroup, and the occurrence of three cases of malignancy other than non-melanoma skin cancer with UPA 15 mg monotherapy (compared with zero cases in the UPA 15 mg combination therapy group) for which discontinuation was required per the protocol.

The frequency of serious infections and herpes zoster was similar for placebo and upadacitinib 15 mg QD as monotherapy or combination therapy but higher in the upadacitinib 30 mg QD monotherapy and combination therapy subgroups (Table 3). All herpes zoster events were mild or moderate in severity except for one severe, non-serious event involving two dermatomes in a patient receiving upadacitinib 30 mg QD with MTX. There were no major adverse cardiovascular events or venous thromboembolic events reported with upadacitinib monotherapy. One non-fatal myocardial infarction was reported in a patient receiving upadacitinib 15 mg QD with MTX, one pulmonary embolism was reported in a patient receiving upadacitinib 15 mg QD with sulfasalazine, and one pulmonary embolism was reported in a patient receiving upadacitinib 30 mg QD with MTX. In addition, one deep vein thrombosis was reported in a patient receiving placebo in the monotherapy group, and one non-fatal myocardial infarction was reported in a patient receiving placebo in combination with MTX.

AEs of hepatic disorder (which were mostly non-serious transaminase elevation) and creatine phosphokinase (CPK) elevation were more common in the combination therapy groups *vs* the monotherapy groups, and more common with upadacitinib 30 mg *vs* upadacitinib 15 mg (Table 3). AEs of anaemia, neutropenia, and lymphopenia were generally consistent across the monotherapy and combination therapy groups (Table 3). Grade 3 or 4 changes in laboratory values were infrequent (Table 5).

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

therapy groups. Hepatic disorders were more frequent with upadacitinib as combination therapy compared with upadacitinib as monotherapy, which is not surprising given the well-known effects of nbDMARDs such as MTX on liver function [20, 21]. CPK elevation also appeared to be higher in the combination therapy *vs* monotherapy groups, particularly in patients receiving upadacitinib 30 mg. However, Grade 3 or 4 changes in transaminases, CPK, and other laboratory parameters were infrequent. Given that the efficacy of upadacitinib monotherapy appeared to be comparable to that of upadacitinib combination therapy, a reduction in the risk of mild laboratory abnormalities could be a benefit of treatment with upadacitinib monotherapy, while also reducing the burden of medication use.

There appeared to be a higher rate of placebo response in the combination therapy groups compared with the monotherapy group. This may reflect the fact that the combination therapy groups had a higher proportion of patients from SELECT-PsA 1, which demonstrated higher placebo responses compared with SELECT-PsA 2 (Supplementary Table S3). In addition, patients in SELECT-PsA 1 and 2 were permitted to receive up to two concomitant nbDMARDs, which may have further increased the placebo response. The relatively high placebo response in SELECT-PsA 1 may be due to the fact that patients in this trial were less treatment refractory than those in SELECT-PsA 2 (nbDMARD-IR versus bDMARD-IR) [11, 12]. However, the placebo response in SELECT-PsA 1 was generally comparable to similar studies of JAK inhibitors in patients with PsA, such as the OPAL Broaden study of tofacitinib [22].

A primary strength of the current analysis is that it is based on a pooled analysis of data from two large, phase 3 clinical trials. Although the comparison of upadacitinib as monotherapy *vs* combination therapy was not a primary objective of the studies, this analysis was planned prior to trial conduct and patients were stratified by current use of ≥1 nbDMARD at randomization. One limitation of the study is that the majority of patients taking a concomitant nbDMARD were receiving MTX, and thus it was not possible to individually assess upadacitinib in combination with other nbDMARDs such as sulfasalazine or leflunomide. In addition, although it was permitted, relatively few patients were receiving upadacitinib in combination with two nbDMARDs, and so the safety and efficacy of this treatment regimen could not be assessed. It should also be noted that all patients who were taking a nbDMARD at study entry met inclusion criteria related to active disease. Thus, these data permit assessment of the safety and efficacy of treatment with upadacitinib added to stable background therapy and are not able to inform the benefit or risk of starting both drugs simultaneously, or adding a nbDMARD to existing upadacitinib therapy. Finally, this analysis focused on 24-week data; long-term efficacy and safety for upadacitinib monotherapy and combination

therapy, including any long-term benefits (such as exploring late stage drug survival with or without combination therapy), will be assessed in the ongoing SELECT-PsA 1 and SELECT-PsA 2 studies.

In conclusion, the results of this analysis show that the efficacy and safety of upadacitinib was generally consistent when administered as monotherapy or in combination with nbDMARDs. This supports the use of upadacitinib with or without nbDMARDs in PsA and suggests that upadacitinib monotherapy may be a useful treatment option in patients with contraindications to MTX or those who are unable to tolerate higher doses.

Acknowledgements

Medical writing support was provided by John Ewbank, PhD, of 2 the Nth (Cheshire, UK) and was funded by AbbVie.

Funding:

This work was supported by AbbVie, who participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.

Disclosures statement:

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

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

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

A.M.: has received speaking fees and/or honoraria from AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, and UCB; and consulting fees from AbbVie.

C.R.: has received consulting fees from AbbVie, Amgen, BMS, Janssen, and Novartis; consulting and being an independent contractor for Amgen; and consulting for and receiving research support from UCB.

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

E.M.R.: has received consulting fees from AbbVie, Amgen, BMS, Gilead, Janssen, Eli Lilly, Novartis, and Pfizer.

Data availability statement:

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis datasets), as well as other information (e.g. protocols and clinical study reports), provided 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 https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

References

1 Coates LC, Gossec L, Ramiro S, et al. New GRAPPA and EULAR recommendations for the management of psoriatic arthritis. Rheumatology (Oxford) 2017;56(8):1251-3.

2 Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79(6):700-12.

3 Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Care Res (Hoboken) 2019;71(1):2-29.

4 Combe B, Behrens F, McHugh N, et al. Comparison of Etanercept Monotherapy and Combination Therapy with Methotrexate in Psoriatic Arthritis: Results from 2 Clinical Trials. J Rheumatol 2016;43(6):1063-7.

5 Ianculescu I, Weisman MH. The role of methotrexate in psoriatic arthritis: what is the evidence? Clin Exp Rheumatol 2015;33(5 Suppl 93):S94-7.

6 Mease PJ, Collier DH, Saunders KC, Li G, Kremer JM, Greenberg JD. Comparative effectiveness of biologic monotherapy versus combination therapy for patients with psoriatic arthritis: results from the Corrona registry. RMD Open 2015;1(1):e000181.

7 Mease PJ, Gladman DD, Collier DH, et al. Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial. Arthritis Rheumatol 2019;71(7):1112-24.

8 Singh JA, Saag KG, Bridges SL, Jr., et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2016;68(1):1-26.

9 Ye W, Coates LC. Should Methotrexate Have Any Place in the Treatment of Psoriatic Arthritis? Rheum Dis Clin North Am 2019;45(3):325-39.

10 Parmentier JM, Voss J, Graff C, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). BMC Rheumatol 2018;2:23.

11 McInnes IB, Anderson JK, Magrey M, et al. Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis. N Engl J Med 2021;384:1227-39.

12 Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis 2020;80:312-20.

13 Mease PJ, Woolley JM, Bitman B, Wang BC, Globe DR, Singh A. Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction. J Rheumatol 2011;38(11):2461-5.

14 Combe B, Tsai TF, Huffstutter JE, et al. Ixekizumab, with or without concomitant methotrexate, improves signs and symptoms of PsA: week 52 results from Spirit-P1 and Spirit-P2 studies. Arthritis Res Ther 2021;23(1):41.

15 Xie Y, Liu Y, Liu Y. Are biologics combined with methotrexate better than biologics monotherapy in psoriasis and psoriatic arthritis: A meta-analysis of randomized controlled trials. Dermatol Ther 2021;34(3):e14926.

16 Nash P, Mease P, Fleischaker B, Wu J, Coates LC, Behrens F. Tofacitinib as monotherapy following methotrexate withdrawal in patients with psoriatic arthritis previously treated with open-label tofacitinib plus methotrexate: a randomised, placebo-controlled substudy of OPAL Balance. Lancet Rheumatology 2021;3:E28-E39.

17 Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54(1):26-37.

18 Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363(9410):675-81.

19 Friedman B, Cronstein B. Methotrexate mechanism in treatment of rheumatoid arthritis. Joint Bone Spine 2019;86(3):301-7.

20 Conway R, Carey JJ. Risk of liver disease in methotrexate treated patients. World J Hepatol 2017;9(26):1092-100.

21 Visser K, van der Heijde DM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature. Clin Exp Rheumatol 2009;27(6):1017-25.

22 Mease P, Hall S, FitzGerald O, et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. N Engl J Med 2017;377(16):1537-50.

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, *n* (%)	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, *n* (%)	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), *n* (%)	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), *n* (%)	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, *n* (%)	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, *n* (%)									
≤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

[a]Values 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, *n/N* (%)	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, *n/N* (%)	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, *n/N* (%)	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, *n/N* (%)[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, *n/N* (%)[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, *n/N* (%)	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, *n/N* (%)[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, *n/N* (%)[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 (2.8)	15/106 (14.2)	39/108 (36.1)	16/194 (8.2)	57/193 (29.5)	61/187 (32.6)	20/233 (8.6)	69/238 (29.0)	74/233 (31.8)
MDA at week 24, *n/N* (%)	5/188 (2.7)	52/189 (27.5)	74/197 (37.6)	43/342 (12.6)	122/353 (34.6)	139/341 (40.8)	53/447 (11.9)	158/451 (35.0)	181/444 (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)

[a]For patients with baseline LEI >0. [b]For patients with baseline LDI >0. [c]For 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, *n* (%)	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
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 (*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)
Discontinuation prior to week 24, *n* (%)	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, *n* (%)	Monotherapy			Combination therapy with MTX			Combination therapy with any nbDMARD (including MTX)		
	PBO (*n* = 183)	UPA 15 mg QD (*n* = 187)	UPA 30 mg QD (*n* = 195)	PBO (*n* = 339)	UPA 15 mg QD (*n* = 350)	UPA 30 mg QD (*n* = 340)	PBO (*n* = 444)	UPA 15 mg QD (*n* = 448)	UPA 30 mg QD (*n* = 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)

Haemoglobin (g/L)									
Grade 3 (<80)	0	0	1 (0.5)	0	0	2 (0.6)	0	0	2 (0.5)
Lymphocytes (10^9/L)									
Grade 3 (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)
Grade 4 (<0.2)	0	0	0	0	0	0	0	0	0
Neutrophils (10^9/L)									
Grade 3 (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)
Grade 4 (<0.5)	0	0	0	0	0	0	0	0	0
Platelets (10^9/L)									
Grade 3 (25–<50)	0[b]	0	0[b]	0[b]	0	1 (0.3)	0[b]	0	1 (0.2)
Grade 4 (<25)	0[b]	0	0[b]	0[b]	0	0	0[b]	0	0
Leucocytes (10^9/L)									
Grade 3 (1.0–<2.0)	1 (0.5)	0	1 (0.5)	0	0	1 (0.3)	0	0	1 (0.2)
Grade 4 (<1.0)	0	0	0	0	0	0	0	0	0

[a]Abnormalities may reflect single, unconfirmed abnormalities. [b]Data 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

[a]For patients with baseline LEI >0. [b]For patients with baseline LDI >0. [c]For 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; 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.

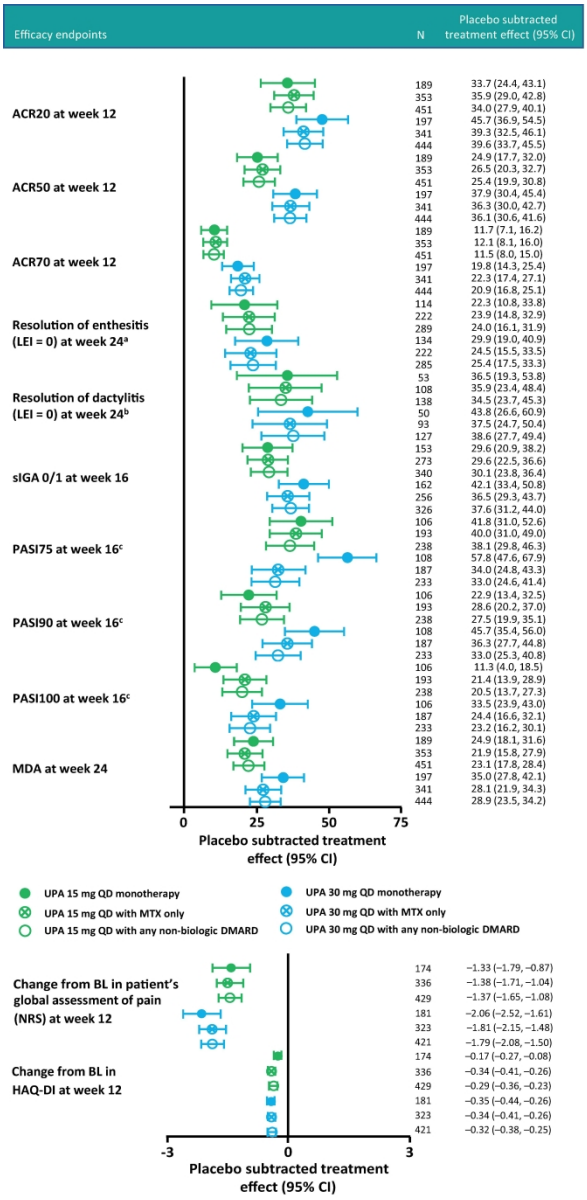

FIG. 1 Integrated efficacy analysis of placebo-subtracted treatment effects

133x274mm (600 x 600 DPI)