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ORIGINAL ARTICLE

Effect of tofacitinib on patient-reported outcomes in patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors in the phase III, randomised controlled trial: OPAL Beyond

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ABSTRACT

Objectives Tofacitinib is an oral Janus kinase inhibitor for treatment of psoriatic arthritis (PsA). Patient-reported outcomes (PROs) were evaluated in patients with PsA with inadequate responses to tumour necrosis factor inhibitors (TNFi-IR) in a 6-month, phase III randomised controlled trial (OPAL Beyond [NCT01882439]).

Methods Patients (N=394) received tofacitinib 5 or 10 mg twice daily or placebo (advancing to tofacitinib 5 or 10 mg twice daily at month 3). Least squares mean changes from baseline and percentages of patients reporting improvements ≥minimum clinically important differences and scores ≥normative values were determined in Patient Global Assessment of disease activity (PtGA), Pain, Patient Global Joint and Skin Assessment (PGJS), Short Form-36 Health Survey version 2 (SF-36v2), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), EuroQol 5-Dimensions-3-level (EQ-5D-3L), EQ-VAS and Ankylosing Spondylitis Quality of Life (ASQoL). Nominal p values are without multiple comparison adjustments.

Results At month 3, PtGA, Pain, PGJS, SF-36v2 Physical Component Summary (PCS), physical functioning (PF), bodily pain (BP), vitality and social functioning (SF) domains, FACIT-Fatigue Total score, EQ-5D-3L pain/discomfort, EQ-VAS and ASQoL scores exceeded placebo with both tofacitinib doses (role physical [RP] with 10 mg twice daily only; p≤0.05). Patients reporting improvements ≥MCID (%) in PtGA, PGJS, Pain, ASQoL and SF-36v2 PCS, PF, RP, BP, SF (both tofacitinib doses) exceeded placebo (p≤0.05).

Conclusion TNFi-IR patients with PsA receiving tofacitinib reported statistically and clinically meaningful improvements in PROs versus placebo over 3 months, which were maintained to month 6. Despite lower baseline scores, these improvements were similar to the csDMARD-IR TNFi-naive OPAL Broaden trial.

Key messages

What is already known about this subject?
► The efficacy and safety of tofacitinib 5 and 10 mg twice daily in patients with psoriatic arthritis (PsA) have been demonstrated in two phase III randomised controlled trials (RCTs).
► Patient-reported outcomes (PROs), measuring PsA-specific skin and joint disease activity, are included in the domains to be assessed in PsA RCTs recommended by Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and Outcome Measures in Rheumatology and complement physician assessments and laboratory measures of disease activity.

What does this study add?
► This post-hoc analysis of patients with PsA and an inadequate response to tumour necrosis factor inhibitors (TNFi-IR) reported significant improvements, exceeding placebo, across a range of PROs, demonstrating that tofacitinib not only treats the signs and symptoms of PsA, but can also improve patient function and quality of life.
► These improvements were reported for both tofacitinib doses within 2–4 weeks and were maintained to month 6.

How might this impact on clinical practice?
► Tofacitinib may be used to improve PROs in TNFi-IR patients with PsA.

INTRODUCTION

Psoriatic arthritis (PsA), a chronic inflammatory disease, causes pain and swelling in the joints,[1] and is associated with considerable impairment in physical function and health-related quality of life (HRQoL).[2–4]

PsA-specific measures such as skin and joint disease activity, and pain, can be assessed using a number of patient-reported outcomes (PROs): Patient Global Assessment of disease activity (PtGA) and/or Patient Global Joint and Skin Assessment (PGJS),[5] Health Assessment Questionnaire Disability Index (HAQ-DI),[6] Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), the generic Short Form-36 Health Survey version 2 (SF-36v2),[7] EuroQol 5-Dimensions-3-level (EQ-5D-3L),[8] disease-specific Ankylosing Spondylitis Quality of Life (ASQoL)[9] and Dermatology Life Quality Index (DLQI).[10] Several of these instruments assess the core set of domains, outlined by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-Outcome Measures in Rheumatology (OMERACT) PsA working group recommendations, which are to be assessed in all PsA randomised controlled trials (RCTs) and longitudinal observational studies.[11] The development of these recommendations also included patient focus groups, reflecting the importance of PROs to both clinician and patients. Another GRAPPA-OMERACT initiative has found that several of the above instruments (eg, HAQ-DI) demonstrate evidence of reliability and validity in the measurement of PROs in PsA.[12]

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of PsA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily have been demonstrated in two phase III RCTs of 6 to 12 months' duration in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARD-IR) or tumour necrosis factor inhibitors (TNFi-IR) with active PsA (OPAL Beyond: NCT01882439; OPAL Broaden: NCT01877668),[13 14] and in an ongoing long-term extension study (OPAL Balance: NCT01976364).

Minimum clinically important differences (MCIDs) are key concepts in determining if changes due to treatment are not only significant, but also clinically meaningful to patients, based on improvements reported in patients' global assessment of disease activity.[15] While various other methods have also been developed to assess clinically important differences,[16–18] in this trial we evaluated the percentage of patients reporting previously defined improvements ≥MCID at month 3 in each treatment group. This is in line with previously reported phase III RCTs in patients with PsA.[19] We also compared the percentages of patients with scores ≥normative values, at month 3 in each treatment group.

The objective of these analyses was to evaluate the effect of tofacitinib treatment on PROs in patients with PsA who were TNFi-IR from the OPAL Beyond RCT.

METHODS
Study design
OPAL Beyond was a phase III RCT conducted in 98 centres worldwide, between June 2013 and April 2016. Eligible patients were ≥18 years old (≥20 years in Taiwan); TNFi-IR; with a diagnosis of PsA for ≥6 months; fulfilled the ClASsification criteria for Psoriatic ARthritis (CASPAR),[20] with active plaque psoriasis at screening and active arthritis (≥3 swollen and ≥3 tender joints) at screening and baseline. Exclusion criteria were as previously reported.

Eligible patients were randomised 2:2:1:1 to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo advanced to tofacitinib 5 mg twice daily or placebo advanced to tofacitinib 10 mg twice daily. Placebo groups advanced in a blinded manner to tofacitinib at month 3. All patients continued treatment with a stable dose of a single csDMARD, the most frequent being methotrexate.

Assessment of PROs
PROs were assessed up to month 6. MCIDs values were defined as mean improvements from baseline to month 3 in a treatment group, based on previously published data.[7 21]

PtGA by visual analogue scale (VAS, mm), Pain-VAS and HAQ-DI[13] were evaluated at baseline, week 2 and months 1, 2, 3, 4 and 6.[5 22]

Additionally, the following were evaluated at baseline, months 1, 3 and 6 and the percentages of patients reporting improvements ≥MCID analysed[7 19 21 23–26]: PGJS as a combined global score, and separate joint and skin scores, due to the potential divergence in the self-assessment of joint and skin disease activities[5]; SF-36v2 Physical Component Summary (PCS) and Mental Component Summary (MCS) and eight (norm-based) domain scores (physical functioning [PF], role physical [RP], bodily pain [BP], general health [GH], vitality [VT], social functioning [SF], role emotional [RE], mental health [MH])[7]; FACIT-Fatigue Total score[27]; EQ-5D-3L dimension scores; overall health state (evaluated using EuroQol Health State-VAS [EQ-VAS])[8] and ASQoL.[9] The ranges and cut-offs for these values are detailed in the online supplementary material 1.

PtGA, Pain, SF-36v2, EQ-5D-3L, FACIT-Fatigue and ASQoL were secondary outcome measures and SF-36v2 PF domain and FACIT-Fatigue were predefined secondary efficacy endpoints at Month 3. HAQ-DI responses have been reported previously.[13]

Statistical analysis
For continuous endpoints, least squares mean changes from baseline were compared between tofacitinib (5 and 10 mg twice daily) versus placebo for time points up to month 3 using a repeated-measures model with the fixed effects of treatment, visit, treatment-by-visit interaction, geographic location and baseline values, without imputation for missing values. The two placebo sequences were combined into a single placebo group as the placebo-controlled period ended at month 3. Results after month 3 were generated using a second repeated-measures model with two placebo sequences modelled separately.

For binary endpoints, p values were calculated for comparing percentages between treatment groups, based on the normal approximation for the difference

in binomial percentages. The same method was used to analyse the percentages of patients reporting normative values (defined in the online supplementary material 1). Missing values were not imputed, except for HAQ-DI response based on MCID, where non-responder imputation was prespecified for this efficacy measure. Nominal p values for the difference between tofacitinib (5 and 10 mg twice daily) versus placebo were reported without adjustment for multiplicity. For all endpoints, significance level was set at p≤0.05 throughout.

For each outcome and treatment comparison, the standardised response mean (SRM) was calculated as the ratio of the difference in mean changes from baseline between treatment groups to the pooled SD of change scores (across all three groups).[28][29] These standardised treatment differences are represented in SD units with <0.20 taken as 'trivial', 0.20 'small', 0.50 'medium' and 0.80 'large' treatment effects.[30]

For illustrative purposes and to facilitate viewing improvements in HRQoL simultaneously across eight domains,[31] spydergrams were generated using SF-36v2 domain raw scores (range: 0–100; age-gender norms matched to study population).

Based on responses ≥MCID, numbers needed to treat (NNT) were calculated, defined as the inverse of the difference between PRO response rates in tofacitinib and placebo groups at month 3. A separate benchmark analysis included the percentages of patients reporting scores ≥normative values, with 'normative' referring to scores in the US general population, without chronic disease.

Pearson correlation coefficients (|r|) were assessed at month 3 with particular interest in HAQ-DI and SF-36v2 PF domain; Pain (VAS) and SF-36v2 BP domain and EQ-5D-3L pain/discomfort dimension; correlations between FACIT-Fatigue Total score and SF-36v2 VT domain are to be published in a future publication. Statistical significance for testing the null hypothesis of Pearson correlations equal to zero was calculated based on Student's t distribution.

RESULTS

Patient demographics and baseline characteristics

Baseline patient demographics, reported previously, were broadly similar across treatment groups.[13]

In total, 131 and 132 patients received tofacitinib 5 and 10 mg twice daily, respectively, and 131 placebo patients advanced to tofacitinib treatment at month 3. The majority of patients were Caucasian (92.1%), female (55.3%), with a mean age of 50.0 (SD 12.0 years) and mean disease duration of 9.1–9.6 years. Baseline disease characteristics were similar across treatment groups, except for mean tender joint count, which was highest in the tofacitinib 10 mg twice daily group. The average number of TNFi previously used was 1.5–1.7 across treatment groups and 11%–14% of patients had previously used biological DMARDs other than TNFi.[13]

PROs

Baseline PRO scores were comparable across treatment groups (table 1). Significant improvements from baseline were reported at month 3 with both doses of tofacitinib compared with placebo in PtGA; Pain; HAQ-DI; PGJS; SF-36v2 PCS and four SF-36v2 domain scores (PF, BP, VT, SF); FACIT-Fatigue; EQ-5D-3L pain/discomfort and health state (EQ-VAS); and ASQoL (all p≤0.05; table 1). Patients receiving tofacitinib 10 mg twice daily reported improvements in SF-36v2 RP domain versus placebo (tofacitinib 10 mg p≤0.05; table 1). Numerically greater improvements were reported in all EQ-5D-3L dimensions compared with placebo, except for usual activities (similar for all groups).

SRMs of the results shown in table 1 (data not shown) suggest that the magnitude of treatment effect falls into four categories: (1) medium effect (SRM ~0.50; PtGA-VAS; Pain-VAS; PGJS-VAS arthritis, psoriasis; SF-36v2 BP), (2) small-to-medium effect (SRM, 0.2–0.5; HAQ-DI; SF-36v2 PCS, PF, RP, SF; FACIT-Fatigue Total score, experience, impact; EQ-5D-3L pain/discomfort; EQ-VAS), (3) small effect (SRM ~0.2; SF-36v2, GH, VT, MH; EQ-5D-3L mobility, self-care, usual activities) and (4) trivial effect (SRM <0.2; SF-36v2 MCS, RE; EQ-5D-3L usual activities, anxiety/depression).

PtGA, Pain and PGJS

Significantly greater improvements from baseline, compared with placebo, were apparent for both tofacitinib doses at the first post-baseline assessment for PtGA and Pain (week 2; all p≤0.05; figure 1A,B), and PGJS (month 1; both doses p<0.001; figure 1C). Improvements from baseline in these endpoints were maintained through month 6. These improvements were reflected in patients advancing from placebo to tofacitinib 5 or 10 mg twice daily, who reported similar improvements after month 3.

The percentages of patients reporting improvements in PtGA, Pain and PGJS ≥MCID were significantly higher in patients receiving tofacitinib 5 or 10 mg twice daily compared with placebo (figure 2). NNT values were generally similar for both tofacitinib doses (figure 2).

SF-36v2 PCS and MCS and domain scores

Patients receiving tofacitinib 5 or 10 mg twice daily reported improved SF-36v2 PCS scores compared with placebo at month 1, maintained to month 3 (all p≤0.01; figure 3A). Patients who advanced from placebo to tofacitinib 5 or 10 mg twice daily reported similar improvements in SF-36v2 after month 3. No improvements in SF-36v2 MCS were reported at month 3 (table 1).

Significant improvements in SF-36v2 domains PF, BP, VT and SF domain scores were reported at month 3 with both doses of tofacitinib (all p≤0.05; table 1). In addition, improvements in RP were reported following tofacitinib 10 mg twice daily at month 3 compared with placebo (p≤0.05; table 1).

Spydergrams of SF-36v2 domains on a 0–100 scale are shown in figure 3B. At month 3, similar improvements

Table 1 Mean baseline values and LSM changes from baseline to month 3 for PROs

|	Baseline, mean (SD)			Month 3 LSM change from baseline (SE)		
	Tofacitinib 5 mg twice daily (N=131)	Tofacitinib 10 mg twice daily (N=132)	Placebo (N=131)	Tofacitinib 5 mg twice daily (N=131)	Tofacitinib 10 mg twice daily (N=132)	Placebo (N=131)
PtGA-VAS (mm)	57.42 (22.89)	58.52 (22.26)	55.76 (23.73)	−21.59 (2.23)***	−19.88 (2.25)***	−7.14 (2.25)
Pain-VAS (mm)	56.35 (24.13)	59.45 (22.30)	54.91 (25.27)	−21.66 (2.16)***	−20.88 (2.19)***	−7.72 (2.18)
HAQ-DI	1.26 (0.69)	1.37 (0.61)	1.25 (0.76)	−0.39 (0.05)***	−0.35 (0.05)***	−0.14 (0.05)
PGJS-VAS (mm)						
Arthritis and psoriasis	65.37 (21.31)	68.16 (21.31)	62.85 (24.38)	−26.35 (2.17)***	−28.22 (2.22)***	−10.56 (2.21)
Arthritis	66.62 (20.61)	67.88 (22.41)	62.65 (24.62)	−25.11 (2.25)***	−26.69 (2.29)***	−11.48 (2.29)
Psoriasis	53.50 (29.54)	58.88 (29.38)	54.63 (28.69)	−22.42 (2.29)***	−27.61 (2.34)***	−7.65 (2.33)
SF-36v2 PCS score	33.57 (8.46)	31.73 (8.93)	34.70 (9.55)	5.18 (0.68)***	5.34 (0.69)***	1.77 (0.69)
SF-36v2 MCS score	39.76 (12.64)	39.84 (12.28)	40.59 (12.66)	4.94 (0.88)	4.28 (0.88)	2.97 (0.88)
SF-36v2 norm-based domain scores						
PF	33.45 (10.43)	32.12 (9.87)	34.03 (10.99)	5.00 (0.72)**	4.08 (0.73)*	1.69 (0.73)
RP	34.63 (10.34)	32.69 (9.25)	35.86 (10.69)	4.99 (0.81)	5.44 (0.81)*	2.85 (0.81)
BP	33.24 (7.88)	32.63 (6.94)	35.42 (8.73)	7.00 (0.79)***	7.59 (0.80)***	2.10 (0.80)
GH	34.71 (8.71)	33.53 (9.29)	35.60 (10.09)	3.67 (0.64)	3.92 (0.65)	2.45 (0.65)
VT	39.70 (10.22)	38.51 (9.02)	40.25 (10.73)	4.95 (0.83)*	4.75 (0.84)*	2.41 (0.84)
SF	36.46 (11.47)	35.26 (11.12)	37.56 (11.81)	6.25 (0.84)**	5.46 (0.86)*	2.89 (0.86)
RE	35.50 (13.95)	35.49 (13.49)	36.03 (14.12)	5.44 (1.00)	4.84 (1.00)	3.85 (1.00)
MH	38.33 (11.84)	38.90 (10.97)	40.19 (12.45)	4.36 (0.85)	4.11 (0.87)	2.11 (0.87)
FACIT-Fatigue						
Total score	26.1 (12.15)	26.1 (10.27)	27.5 (11.58)	7.0 (0.81)***	5.8 (0.82)*	3.0 (0.82)
Experience domain score	8.2 (5.07)	8.1 (4.29)	8.6 (4.80)	3.1 (0.38)**	2.6 (0.39)*	1.5 (0.39)
Impact domain score	17.8 (7.56)	18.0 (6.48)	18.9 (7.36)	3.9 (0.48)***	3.2 (0.49)*	1.6 (0.49)
EQ-5D-3L dimension scores						
Mobility	1.68 (0.47)	1.78 (0.42)	1.71 (0.46)	−0.17 (0.04)*	−0.15 (0.04)	−0.05 (0.04)
Self-care	1.46 (0.50)	1.61 (0.49)	1.50 (0.56)	−0.15 (0.04)	−0.15 (0.04)	−0.04 (0.04)
Usual activities	1.91 (0.46)	1.98 (0.43)	1.92 (0.49)	−0.23 (0.04)	−0.22 (0.04)	−0.15 (0.04)
Pain/discomfort	2.24 (0.46)	2.27 (0.46)	2.21 (0.46)	−0.32 (0.04)**	−0.29 (0.04)**	−0.12 (0.04)
Anxiety/depression	1.69 (0.60)	1.73 (0.57)	1.73 (0.71)	−0.19 (0.04)	−0.20 (0.05)	−0.12 (0.05)
EQ-VAS (mm)	51.98 (22.30)	48.83 (21.49)	53.39 (22.34)	8.62 (1.85)*	12.33 (1.90)***	2.64 (1.90)
ASQoL	11.4 (4.83)	12.2 (4.45)	10.7 (5.20)	−3.8 (0.38)***	−3.5 (0.39)***	−1.5 (0.40)

N is the number of patients per group in the Full Analysis Set; the number of patients evaluable for each baseline characteristic may be fewer than N.

*p≤0.05, **p<0.01, ***p<0.001 compared with placebo; results at month 3 were based on a repeated -measures model including data up to month 3 for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and combined placebo group without imputation for missing values.

ASQoL, Ankylosing Spondylitis Quality of Life; BP, bodily pain; EQ-5D-3L, EuroQol 5-Dimensions-3-level; EQ-VAS, EuroQol Health State visual analogue scale; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; GH, general health; HAQ-DI, Health Assessment Questionnaire Disability Index; LSM, least squares mean; MCS, Mental Component Summary; MH, mental health; PCS, Physical Component Summary; PF, physical functioning; PGJS, Patient Global Joint Skin Assessment; PRO, patient-reported outcome; PtGA, Patient Global Assessment of disease activity; RE, role emotional; RF, role physical; SF, social functioning; SF-36v2, Short Form-36 Health Survey version 2; VAS, visual analogue scale; VT, vitality.

from baseline were reported for GH, RE and MH for all groups, with greater improvements in all other SF-36v2 domains with both tofacitinib doses compared with placebo, except RP, superior to placebo only with tofacitinib 10 mg twice daily.

The percentages of patients reporting improvements ≥MCID at month 3 were significantly higher with both tofacitinib doses compared with placebo in SF-36v2 PCS, and PF, RP, BP and SF (figure 2). The percentages of patients reporting scores ≥normative values were
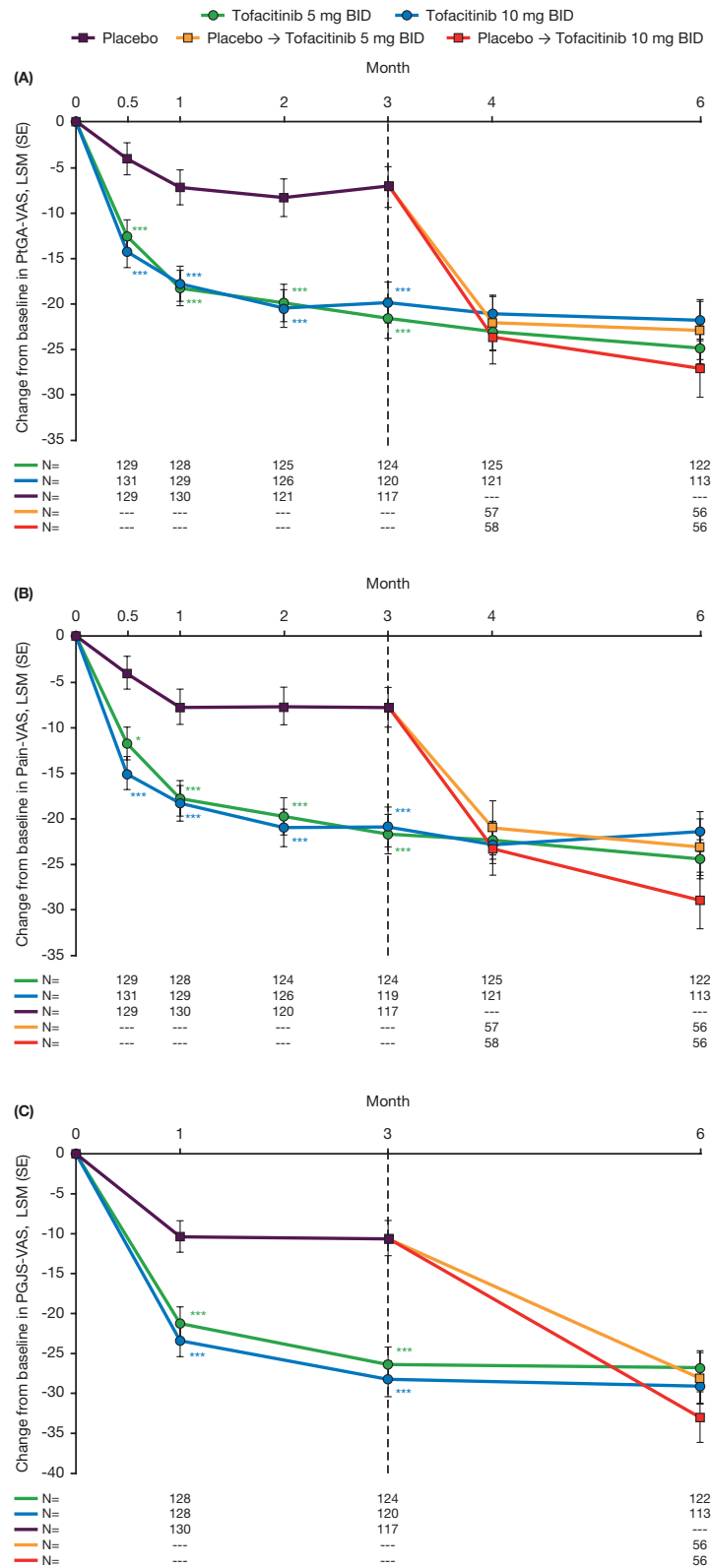
Figure 1 Least squares mean (LSM) changes from baseline: (A) Patient Global Assessment of disease activity visual analogue scale (PtGA-VAS) (mm); (B) Pain-VAS (mm); (C) Patient Global Joint and Skin Assessment (PGJS-VAS) (mm) arthritis and psoriasis. *p≤0.05, **p<0.01, ***p<0.001 compared with placebo; results up to month 3 were based on a repeated-measures model including data up to month 3 for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and combined placebo group. Results after month 3 were based on a second repeated-measures model including data up to end of study for the four treatment sequences (tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo → tofacitinib 5 mg twice daily and placebo → tofacitinib 10 mg twice daily), reporting results after month 3 only. Missing values were not imputed. N is number of patients evaluable at each visit. BID, twice daily.
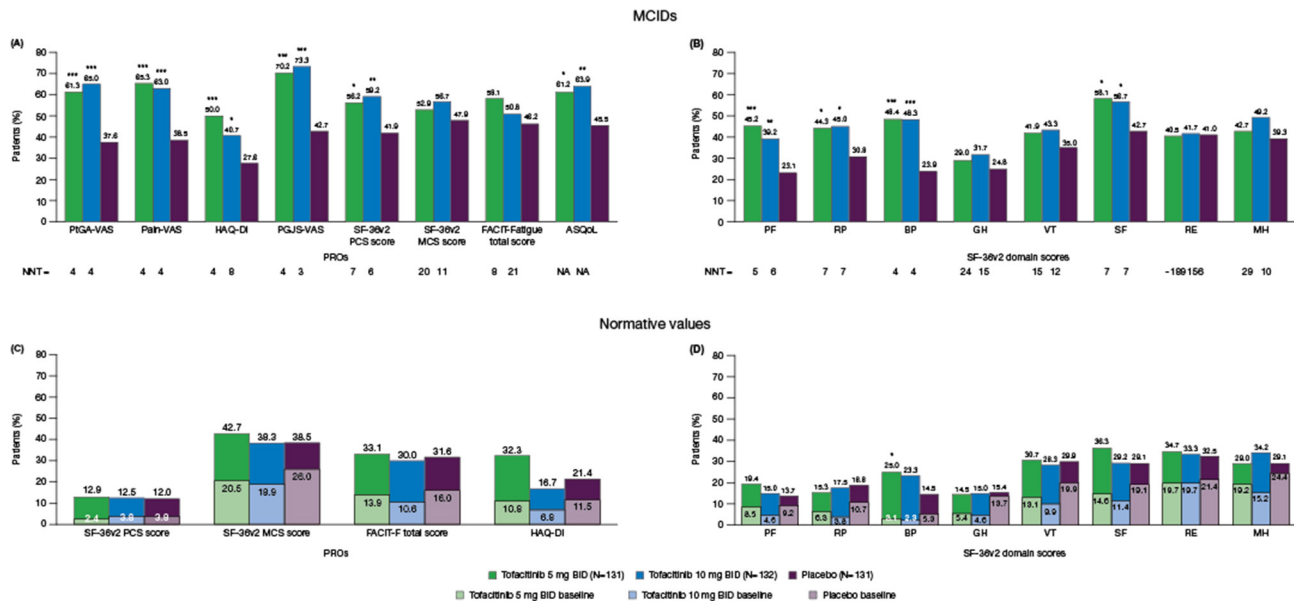
Figure 2 Percentages of patients reporting improvements from baseline ≥minimum clinically important difference (MCID) and numbers needed to treat (NNTs) in (A) patient-reported outcomes (PROs), (B) Short Form-36 Health Survey version 2 (SF-36v2) domain scores; and percentages of patients reporting scores ≥normative values in (C) PROs; (D) SF-36v2 domain scores, at month 3. *$p \leq 0.05$; **$p<0.01$; ***$p<0.001$ compared with placebo; p values were based on the normal approximation for the difference in binomial percentages without imputation for missing values (except Health Assessment Questionnaire Disability Index [HAQ-DI] MCID response, which used non-responder imputation); N is the number of patients per group in the Full Analysis Set; the number of patients evaluable for each PRO endpoint may be fewer than N; MCID cut-offs: Patient Global Assessment of disease activity visual analogue scale (PtGA-VAS) decrease from baseline ≥10 mm; Pain-VAS decrease from baseline ≥10 mm; Patient Global Joint and Skin Assessment (PGJS)-VAS decrease from baseline ≥10 mm; SF-36v2: Physical Component Summary (PCS) and Mental Component Summary (MCS) increase from baseline ≥2.5, SF-36v2 domain scores increase from baseline ≥5.0; Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) increase from baseline ≥4.0; ASQoL decrease from baseline ≥1.8; HAQ-DI decrease from baseline ≥0.35; MCIDs are defined here in terms of mean change from baseline to month 3 in a treatment group; NNT calculated by the inverse of the percentage of patients receiving tofacitinib reporting improvements ≥MCIDs minus the percentage of patients in the placebo group reporting improvements ≥MCIDs; the percentage of patients reporting scores ≥normative values: HAQ-DI <0.25, FACIT-Fatigue ≥40.1, SF-36v2 each of the component summary and domain scores ≥50. ASQoL, Ankylosing Spondylitis Quality of Life; BID, twice daily; BP, bodily pain; GH, general health; MH, mental health; NA, not available; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.

numerically higher with both tofacitinib doses compared with placebo for most domains (figure 2). Significantly more patients receiving tofacitinib 5 mg twice daily reported scores ≥normative values in BP compared with placebo. NNTs were similar for tofacitinib doses and <10 in SF-36v2 PCS, PF, RP, BP and SF (figure 2).

FACIT-Fatigue Total score and ASQoL
Patients reported improved FACIT-Fatigue Total scores compared with placebo in both tofacitinib doses at month 1 (earliest time point), maintained to months 3 (all $p \leq 0.05$; figure 4A) and 6. Patients advancing from placebo to tofacitinib 5 or 10 mg twice daily reported similar improvements after month 3 (figure 4A). While numerically higher compared with placebo, there was no significant difference between the percentages of patients reporting improvements in FACIT-Fatigue Total score ≥MCID in tofacitinib-treated patients (figure 2). Patients reporting scores ≥normative values were similar for tofacitinib and placebo (figure 2). NNT values were lower in patients receiving tofacitinib 5 mg twice daily compared with tofacitinib 10 mg twice daily (figure 2).

Improvements in ASQoL exceeded placebo at month 1 with both doses of tofacitinib and were sustained to month 3 (all $p<0.01$; figure 3B). Patients who advanced from placebo to tofacitinib 5 or 10 mg twice daily at month 3 reported similar improvement after month 3. The percentages of patients reporting improvements in ASQoL ≥MCID were significantly higher for patients receiving tofacitinib 5 or 10 mg twice daily compared with placebo (figure 2).

Correlation analyses
Correlation analyses of preselected PRO endpoints (based on subject matter knowledge and clinical rationale) are shown in table 2. Correlations between HAQ-DI and Pain at month 3 were high. As expected, EQ-5D-3L pain/discomfort and SF-36v2 PF and BP domains were negatively correlated. Pain and SF-36v2 PF and BP domains were moderately (|r|>0.30–≤0.60) or highly (|r|>0.60) negatively correlated with both tofacitinib doses and placebo at month 3.

DISCUSSION
In this study, TNFi-IR patients with active PsA reported improved PROs following treatment with tofacitinib 5
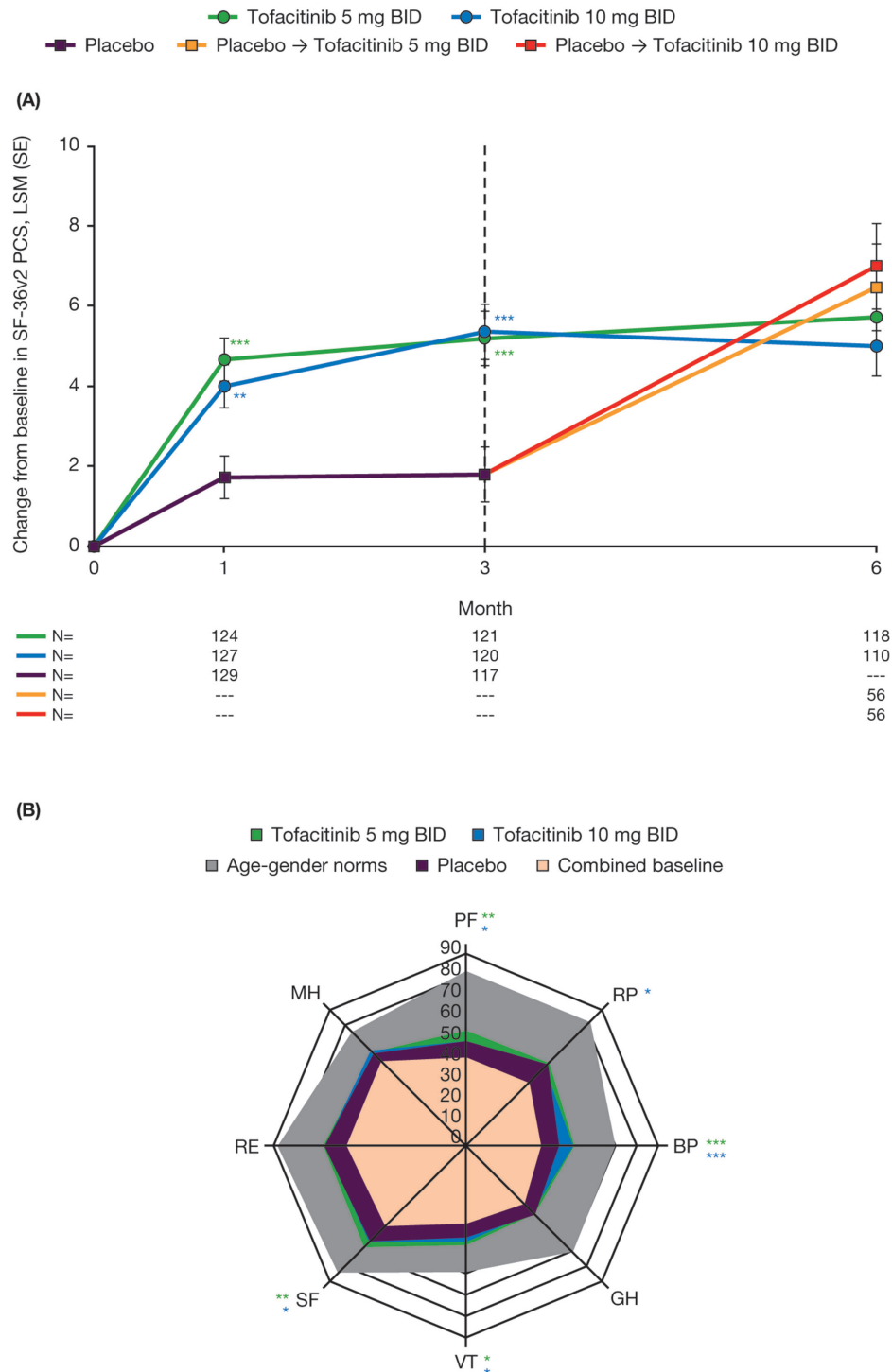
Figure 3 (A) Least squares mean (LSM) changes from baseline in Short Form-36 Health Survey version 2 Physical Component Summary (SF-36v2 PCS) score and (B) spydergram of domain scores from baseline to month 3 versus age-matched and gender-matched norms. (A) *p≤0.05, **p<0.01, compared with placebo; results up to month 3 were based on a repeated measures model including data (norm-based) up to month 3 for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and combined placebo group. Results after month 3 were based on a second repeated-measures model including data up to end of study for the four treatment sequences (tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo → tofacitinib 5 mg twice daily and placebo → tofacitinib 10 mg twice daily), reporting results after month 3 only. Missing values were not imputed. Dashed line indicates end of placebo-controlled period. N represents the number of patients evaluable at each visit. (B) *p≤0.05, **p<0.01, ***p<0.001 compared with placebo; spydergrams generated using domain raw scores (range: 0–100); US age-gender norms were matched to the protocol population; spydergrams are for illustrative purposes only; p values were generated using a repeated-measures model for comparisons with placebo based on LSM changes from baseline in domain norm-based scores at month 3 (table 1). Missing values were not imputed. BID, twice daily; BP, bodily pain; GH, general health; MH, mental health; PF physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.
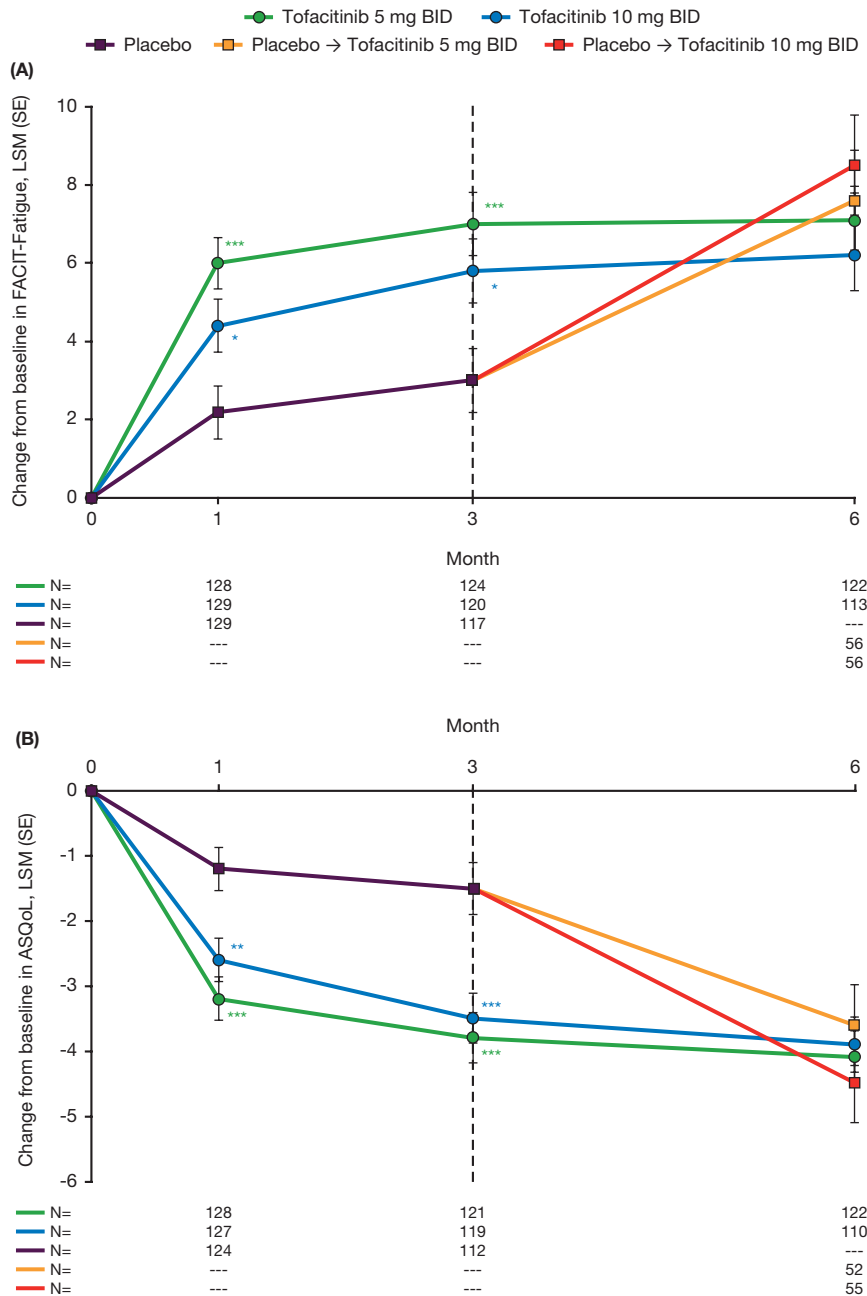
Figure 4 Least squares mean (LSM) change from baseline in (A) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Total score and (B) Ankylosing Spondylitis Quality of Life (ASQoL). *$p \leq 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with placebo; results up to month 3 were based on a repeated-measures model including data up to month 3 for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and combined placebo group. Results after month 3 were based on a second repeated-measures model including data up to end of study for the four treatment sequences (tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo → tofacitinib 5 mg twice daily and placebo → tofacitinib 10 mg twice daily), reporting results after month 3 only. Missing values were not imputed. N is the number of patients evaluable at each visit. BID, twice daily.

and 10 mg twice daily versus placebo at the first time point assessed. Improvements from baseline in these outcomes were maintained or improved to month 6. Percentages of patients reporting scores ≥normative values and NNTs, based on improvements ≥MCID, were generally similar in patients receiving tofacitinib 5 and 10 mg twice daily at month 3. Further, patients who advanced from placebo to tofacitinib 5 or 10 mg twice daily reported improvements

in similar PROs, based on the repeated-measures models, after month 3.

In tandem with this study, a similar analysis was also performed in csDMARD-IR TNFi-naive patients with active PsA enrolled in the OPAL Broaden RCT (results detailed in a separate publication[32]). This parallel study reported clinically meaningful improvements across various PROs compared with placebo at month 3, maintained to month

Table 2 Correlation analyses of PRO endpoints at month 3

	HAQ-DI	SF-36v2† PF	SF-36v2† BP	Pain-VAS	EQ-5D-3L P/D
Tofacitinib 5 mg twice daily (N=124)					
HAQ-DI	1	−0.80	−0.71	0.63	0.55
SF-36v2† PF	–	1	0.70	−0.59	−0.51
SF-36v2† BP	–	–	1	−0.78	−0.62
Pain-VAS	–	–	–	1	0.61
EQ-5D-3L P/D	–	–	–	–	1
Tofacitinib 10 mg twice daily (N=119)					
HAQ-DI	1	−0.79	−0.72	0.66	0.57
SF-36v2† PF	–	1	0.79	−0.70	−0.52
SF-36v2† BP	–	–	1	−0.74	−0.64
Pain-VAS	–	–	–	1	0.61
EQ-5D-3L P/D	–	–	–	–	1
Placebo (N=117)					
HAQ-DI	1	−0.81	−0.70	0.62	0.45
SF-36v2† PF	–	1	0.72	−0.63	−0.48
SF-36v2† BP	–	–	1	−0.78	−0.63
Pain-VAS	–	–	–	1	0.61
EQ-5D-3L P/D	–	–	–	–	1

All correlations were ***p<0.001, based on Student's t distribution (N-2 degree of freedom) to test the null hypothesis of no correlation; the analysis included patients with observations at a visit of interest in Full Analysis Set.

†SF-36v2 scores are norm-based.

BP, bodily pain; EQ-5D-3L, EuroQol 5-Dimensions-3-level; HAQ-DI, Health Assessment Questionnaire Disability Index; N, the number of patients included in calculating the sample correlation; P/D, pain/discomfort; PF, physical functioning; PRO, patient-reported outcome; SF-36v2, Short Form-36 Health Survey version 2; VAS, visual analogue scale.

12, which were similar to those receiving adalimumab. Furthermore, NNTs were low across a range of PROs and as many as 39% of patients receiving tofacitinib reported scores ≥normative values.

Baseline values reported by TNFi-naive patients participating in OPAL Beyond were generally worse than those in patients in OPAL Broaden.[32] Despite these values indicating greater disease activity in patients participating in OPAL Beyond, similar improvements were reported in PROs in the active treatment groups. Specifically, statistically significant responses were generally observed across the same PROs with both tofacitinib doses in both RCTs (PtGA; Pain; PGJS, arthritis and psoriasis, arthritis, psoriasis; SF-36v2 PCS score, and PF and VT domains; FACIT-Fatigue Total score; EQ-5D-3L pain/discomfort dimension; EQ-VAS; ASQoL; HAQ-DI). Consistent with previously published studies, SF-36v2 domains were illustrated by a spydergram to facilitate the assessment of multiple domains simultaneously.[33 34] This demonstrated that the domains were improved compared with baseline, but were lower than age-gender norms matched to the protocol population, with a similar trend observed in OPAL Broaden. Furthermore, improvements were also broadly similar between OPAL Beyond and OPAL Broaden, despite different baseline values.

Some domain scores (SF-36v2 MCS score, and GH, RE and MH domains; EQ-5D-3L self-care, usual activities and anxiety/depression dimensions) were not significantly improved with both tofacitinib doses compared with placebo at month 3, implying that there may be no treatment effect on these domains. However, as these improvements were numerically greater, these measures may not be sufficiently sensitive to detect small improvements as they are generic and not specific to PsA. Additionally, these domains (eg, SF-36v2 MCS score, RE, MH) may have larger variability than other domains and may require larger sample sizes to detect a difference between treatment groups.

OPAL Beyond (and OPAL Broaden) are the first tofacitinib studies to examine changes in PROs based on MCID and normative values in patients with PsA, both of which aid the interpretation of trial data.[35] Assessing improvements ≥MCID and scores ≥normative values offer interpretation of their clinical meaningfulness to patients, clinicians and policymakers.[15 36] Further, NNTs estimate effectiveness by determining how many patients must be treated for one to receive a benefit.[37]

Statistically significant improvements ≥MCID were evident across a range of PROs in this RCT. Generally, these PROs were also significant in the OPAL Broaden study, with the exception of FACIT-Fatigue Total score, which was significant only in OPAL Broaden.[32] SF-36v2 domain score improvements ≥MCIDs were reported for both tofacitinib doses in PF and BP in both studies. However, different

responses were reported in RP, SF and GH domains, where RP and SF were significant, compared with placebo, only in OPAL Beyond and GH was only significant in OPAL Broaden. These changes, across PROs, were also reflected by low NNTs; in the current study, NNTs <10 were reported across both treatment arms in PtGA, Pain, PGJS (arthritis and psoriasis), HAQ-DI, SF-36v2 PCS and four domains (PF, RP, BP, SF). This is in general agreement with NNTs in the OPAL Broaden study (with the exception of SF [both doses] and FACIT-Fatigue Total score [10 mg twice daily]), which also demonstrated comparable values to that of adalimumab. In both studies, these analyses demonstrate the effectiveness of tofacitinib in improving outcomes across a range of PROs.[32]

Establishment of normative values for those without chronic conditions allows for further assessment of therapy efficacy, providing an objective measure of comparability between specific measures in those with and without chronic disease. There was a significant change in BP in tofacitinib 5 mg twice daily at month 3, demonstrating a score comparable to those without arthritis or other chronic conditions. This differs from the findings of OPAL Broaden, where statistically significant improvements were reported in more PROs, specifically: both tofacitinib doses in BP and SF; tofacitinib 5 mg twice daily in MCS score; and tofacitinib 10 mg twice daily in PCS score, PF, GH and MH. This implies that it is possible in some PROs to attain function comparable to that of the non-disease state. Comparison between these two populations may also imply that those who were TNFi-IR are less likely to achieve normative scores indicative of a non-disease state.

The reported correlations are similar to previously reported correlations between PROs in PsA.[38–41] Furthermore, all PROs included in the correlation analysis were at least moderately correlated, implying that these improvements are important and consistent with successful treatment.

Previous phase III RCTs have detailed the effect of specific therapies in patients with PsA.[42 43] However, data are currently limited and the results of this study demonstrate the benefit of tofacitinib treatment in this more treatment-refractory population. Previous studies have shown effect of new therapies on PROs in patients with PsA. This study demonstrates that improvement in PROs can be achieved with tofacitinib, even in patients who had failed to respond to TNFi therapy.

A limitation is that the placebo-controlled period was restricted to 3 months. In addition, this RCT population did not include individuals from all countries and nationalities; hence, further studies with more varied patient populations would be beneficial. Although data are presented to month 6, the ongoing long-term extension study will delineate long-term effect of tofacitinib across these PROs.

In conclusion, TNFi-IR patients with active PsA who received tofacitinib reported clinically meaningful improvements in PROs compared with placebo over 3 months. These improvements were maintained for 6 months in OPAL Beyond and for 12 months in OPAL Broaden.[32] The results of these studies provide scientific evidence to support decisions regarding clinical therapy and further support the use of JAK inhibition as a novel mechanism for the treatment of PsA.

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