ORIGINAL RESEARCH

Articular and Extra-Articular Benefits in ACR20 Non-responders at Week 104 Treated With Apremilast: Pooled Analysis of Three Randomized Controlled Trials

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ABSTRACT

Introduction: PALACE 1, 2, and 3 were phase 3 studies aimed to evaluate apremilast efficacy and safety in patients with active psoriatic arthritis (PsA) despite prior treatment with conventional disease-modifying anti-rheumatic drugs and/or biologics. The pooled analysis reported here further characterized the clinical outcomes associated with long-term apremilast exposure in patients failing to achieve ≥ 20% improvement in the American College of Rheumatology response criteria (ACR20) at Week 104.

Methods: Patients randomized to apremilast 30 mg twice daily at baseline and classified as ACR20 non-responders (ACR20NRs) or ACR20 responders (ACR20Rs) at Week 104 were included. Efficacy outcomes included change from baseline to Week 104 in ACR core components and other endpoints.

Results: At Week 104, a total of 109 patients were ACR20NRs and 193 were ACR20Rs. As expected, the ACR20R group had improvements in all indices assessed. The ACR20NR group demonstrated substantial mean improvements from baseline in swollen joint count (SJC; − 58%), tender joint count (TJC; − 42%), and Physician's Global Assessment of Disease

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Activity (PhGA; − 44%); resolution of enthesitis (34%) and dactylitis (68%); and achievement of ≥ 75% reduction from baseline Psoriasis Area and Severity Index scores (among patients with psoriasis involving ≥ 3% of the body surface area) (36%).

Conclusion: Despite not fulfilling a formal ACR20 response at Week 104, ACR20NRs experienced sustained improvements in several PsA core domains, including SJC, TJC, enthesitis, dactylitis, and psoriasis, as well as the PhGA (visual analog scale) scores, with apremilast treatment.

Trial Registration: ClinicalTrials.gov identifier: NCT01172938, NCT01212757, and NCT01212770.

Key Summary Points

Why carry out this study?

In the PALACE 1, 2, and 3 phase 3 studies, significantly greater proportions of patients treated with apremilast achieved a ≥ 20% improvement in the American College of Rheumatology response criteria (ACR20) response at Week 16

Although not all patients who continued long-term apremilast treatment achieved an ACR20 response at Week 104, 61.4% receiving apremilast 30 mg twice daily completed Week 104 of the study

Despite not fulfilling a formal ACR20 response at Week 104, ACR20 non-responders experienced sustained improvements in several psoriatic arthritis core domains, including swollen joint count, tender joint count, enthesitis, dactylitis, and psoriasis, as well as the Physician's Global Assessment (visual analog scale) scores, with apremilast treatment, which may explain why these patients remained on long-term treatment

What was learned from the study?

Findings from this study identified key ACR components that may improve with apremilast treatment despite lack of achievement of ACR response, thus supporting the importance of evaluating clinical improvements using outcome assessments beyond ACR20 response

INTRODUCTION

Apremilast, a small molecule inhibitor of phosphodiesterase 4 specific for cyclic adenosine monophosphate [1, 2], was evaluated in three pivotal phase 3 studies of its Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) clinical development program [3–5]. These studies enrolled patients who had active psoriatic arthritis (PsA) despite prior treatment with a conventional synthetic disease-modifying anti-rheumatic drug and/or biologic therapy. Results from all three studies showed that apremilast improved signs and symptoms of PsA as well as physical function and severity of psoriasis. Apremilast had an acceptable safety profile and was generally well tolerated for up to 260 weeks [6].

Upon completion of the 52-week, double-blind phase in the PALACE 1, 2, and 3 studies, patients were eligible to enter into an open-label extension period to evaluate the effects of long-term exposure to apremilast. The objective of this post hoc analysis of the pooled PALACE 1, 2, and 3 study data was to further characterize the clinical benefits associated with long-term apremilast treatment in patients who did not achieve a ≥ 20% improvement in the American College of Rheumatology response criteria (ACR20) [7] at Week 104 but who stayed in the study, perhaps representing additional value in the medication not reflected in this arthritis-centered composite outcome. We examined ACR responses over time, as well as changes from baseline in individual PsA manifestations of arthritis, enthesitis and dactylitis, psoriasis, and patient-reported outcomes. Baseline and Week 16 data for patients who were classified

ACR20 non-responders (ACR20NRs) at Week 16 and discontinued from the study by Week 16 and those classified ACR20NRs at Week 104 were compared to assess potential difference between the two groups.

METHODS

Study Design

PALACE 1, 2, and 3 were phase 3, multicenter, randomized, double-blind, placebo-controlled clinical studies with similar designs (ClinicalTrials.gov: NCT01172938, NCT01212757, and NCT01212770, respectively) [3–5]. Briefly, these studies comprised a 24-week, randomized, double-blind, placebo-controlled period, a 28-week blinded active treatment period, and an open-label, long-term (4 years) treatment phase. At baseline, patients were randomized (1:1:1) to receive placebo, apremilast 30 mg twice daily (BID), or apremilast 20 mg BID for 24 weeks. At Week 16, patients who were considered ACR20NRs were eligible for early escape, and at Week 24, all remaining patients receiving placebo were switched to apremilast 30 mg BID or 20 mg BID and continued apremilast treatment for an additional 28 weeks (i.e., up to Week 52). Patients who completed 52 weeks of treatment were eligible to enroll in the long-term extension and receive apremilast treatment for an additional 4 years.

For each of the individual studies, the institutional review board (IRB)/ethics committee at each site approved the study protocol (main IRB center, PALACE 1 and PALACE 3: Schulman Associates IRB, Cincinnati, OH; PALACE 2: Western Institutional Review Board, Puyallup, WA), and all patients provided written informed consent before any study-related procedures were conducted. The three studies were conducted in compliance with the International Conference for Harmonisation Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki.

Patients

Detailed inclusion and exclusion criteria for the PALACE studies have been published previously [3–5]. Enrolled patients were adults with active PsA for at least 6 months who met the Classification Criteria for Psoriatic Arthritis (CASPAR) [8] and had at least three swollen joints and at least three tender joints despite prior exposure to a conventional synthetic disease-modifying anti-rheumatic drug or biologic therapy. Patients in PALACE 3 also had to have active skin disease with at least one plaque psoriasis lesion that was at least 2 cm in size. The current analysis includes patients who were randomized to apremilast 30 mg BID at baseline and classified as ACR20NRs or ACR20Rs at Week 104. In addition, baseline characteristics and efficacy were assessed in patients who were ACR20NRs at Week 16 and dropped out of the study by Week 16.

Study Outcomes

The proportion of ACR20NRs and ACR20Rs achieving non-overlapping ACR response categories (i.e., < 20, 20–49, 50–69, and ≥ 70% improvement), based on the minimum of percentage improvements in the swollen joint count (SJC) and tender joint count (TJC) and the three maximum improvements of the remaining five ACR components [9, 10], were assessed at baseline and at Weeks 16, 24, 40, 52, 65, 78, 91, and 104. Changes from baseline in the ACR core components were examined at the individual time points. These included SJC, TJC, the Physician's Global Assessment of Disease Activity (PhGA; visual analog scale [VAS]; 0–100 mm) score, the Patient's Global Assessment of Disease Activity (PtGA; VAS; 0–100 mm) score, the Patient's Assessment of Pain (VAS; 0–100 mm) score, and the Health Assessment Questionnaire-Disability Index (HAQ-DI) [11, 12] score as well as C-reactive protein (CRP). The proportion of patients achieving the Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) categories

Table 1 Baseline patient demographics and disease characteristics: Week 104 ACR20NRs and ACR20Rs (apremilast 30 mg twice daily from baseline)

Characteristics	Apremilast 30 mg BID[a]	
	ACR20NR (n = 109)	ACR20R (n = 193)
Age, mean (SD), years	51.6 (11.0)	50.1 (11.0)
Female, n (%)	64 (58.7)	105 (54.4)
BMI, mean (SD), kg/m^2	29.6 (6.4)	29.7 (6.0)
BMI $\geq$ 25 kg/m^2, n (%)	81 (74.3)	152 (78.8)
Duration of PsA, mean (SD), years	8.1 (7.9)	7.0 (7.6)
Duration of psoriasis, mean (SD), years	18.4 (14.3)	16.0 (12.1)
PASI score[b] (0–72), mean (SD)	7.8 (6.9)	9.4 (9.5)
Psoriasis BSA involvement $\geq$ 3%, n (%)	51 (46.8)	100 (51.8)
SJC (0–76), mean (SD)	10.5 (7.7)	11.6 (7.8)
TJC (0–78), mean (SD)	22.9 (16.0)	20.5 (13.2)
PhGA (VAS 0–100 mm), mean (SD)	55.5 (17.7)	56.8 (18.9)
PtGA (VAS 0–100 mm), mean (SD)	53.1 (19.7)	58.7 (22.0)
Patient's Assessment of Pain (VAS 0–100 mm), mean (SD)	55.0 (18.8)	58.9 (20.5)
HAQ-DI (0–3), mean (SD)	1.3 (0.6)	1.2 (0.6)
HAQ-DI $\leq$ 0.5, n (%)	14 (13.0)	34 (17.6)
CRP (normal range: 0–0.499), mean (SD), mg/dL	0.94 (1.7)	1.1 (1.2)
Normal CRP value ($\leq$ 0.499 mg/dL), n (%)	61 (56.0)	86 (44.6)
MASES[c] (0–13), mean (SD)	4.8 (3.1)	4.0 (2.8)
Dactylitis count[d] (0–20), mean (SD)	3.9 (4.1)	3.1 (3.1)
Prior use of conventional DMARDs only, n (%)	93 (85.3)	162 (83.9)
Prior use of biologics, n (%)	15 (13.8)	29 (15.0)
Prior biologic failures, n (%)	3 (2.8)	9 (4.7)
Baseline concomitant conventional DMARD use, n (%)	81 (74.3)	135 (69.9)
Baseline corticosteroid use, n (%)	11 (10.1)	22 (11.4)

Table 1 continued

Characteristics	Apremilast 30 mg BID[a]	
	ACR20NR (n = 109)	ACR20R (n = 193)
Baseline NSAID use, n (%)	81 (74.3)	142 (73.6)

ACR20 ≥ 20% improvement in American College of Rheumatology response criteria, *ACR20NR* ACR20 non-responder, *ACR20R* ACR20 responder, *BID* twice daily, *BMI* body mass index, *BSA* body surface area, *CRP* C-reactive protein, *DMARD* disease-modifying anti-rheumatic drug, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *MASES* Maastricht Ankylosing Spondylitis Enthesitis Score, *NSAID* non-steroidal anti-inflammatory drug, *PASI* Psoriasis Area and Severity index, *PhGA* Physician's Global Assessment of Disease Activity, *PsA* psoriatic arthritis, *PtGA* Patient's Global Assessment of Disease Activity, *SD* standard deviation, *SJC* swollen joint count, *TJC* tender joint count, *VAS* visual analog scale

[a] The n reflects the number of patients randomized to apremilast 30 mg BID at baseline who had ACR20 response data at Week 104; the actual number of patients available for each parameter may vary

[b] Patients with baseline psoriasis BSA involvement ≥ 3% and baseline PASI score (ACR20NR: n = 50; ACR20R: n = 100)

[c] Patients with enthesitis at baseline (ACR20NR: n = 74; ACR20R: n = 131)

[d] Patients with dactylitis at baseline (ACR20NR: n = 44; ACR20R: n = 91)

(remission ≤ 4; low disease activity > 4 to ≤ 13; moderate disease activity > 13 to ≤ 27; high disease activity > 27) was also assessed at baseline and study visits over 104 weeks.

Other efficacy endpoints included the proportions of patients who achieved a Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [13] of zero (among those with enthesitis at baseline) and the proportions of patients who achieved a dactylitis count of zero (among those with dactylitis at baseline). Dactylitis was assessed independently of SJC, with no double counting of the joints in the dactylitic digits as swollen or tender joints. The proportions of patients with a ≥ 75% reduction from baseline Psoriasis Area and Severity Index score (PASI-75) were evaluated among those with psoriasis involving ≥ 3% of the body surface area at baseline.

To assess how patients who were ACR20NRs at Week 16 and dropped out from the study by Week 16 differed from those who reached Week 104 and were classified ACR20NRs, baseline and Week 16 SJC, TJC, PtGA VAS scores, and Patient's Assessment of Pain VAS scores were compared between the two groups.

Statistical Analysis

Data from PALACE 1, 2, and 3 were pooled to permit a robust analysis of data. Efficacy data were analyzed descriptively by time point using all available data; analyses through Week 104 were based on observed data without imputation for missing data.

RESULTS

Patients

Of the 1493 total patients with PsA included in the PALACE 1–3 studies, 497 were randomized to receive apremilast 30 mg BID at baseline. Among these patients, 302 (60.8%) with data at Week 104 were included in this analysis, with 109 categorized as ACR20NRs and 193 categorized as ACR20Rs at Week 104. The mean (standard deviation) age at baseline was 51 (11) years and 56% were women (Table 1). Baseline patient demographics and disease characteristics were generally comparable between the two treatment groups. Patients who were ACR20NRs at Week 16 and dropped out by Week 16 had mean SJC, TJC, PtGA VAS scores, and Patient's Assessment of Pain VAS scores at baseline that

a ACR20NRs at Week 104

b ACR20Rs at Week 104

c ACR20NRs at Week 104

d ACR20Rs at Week 104
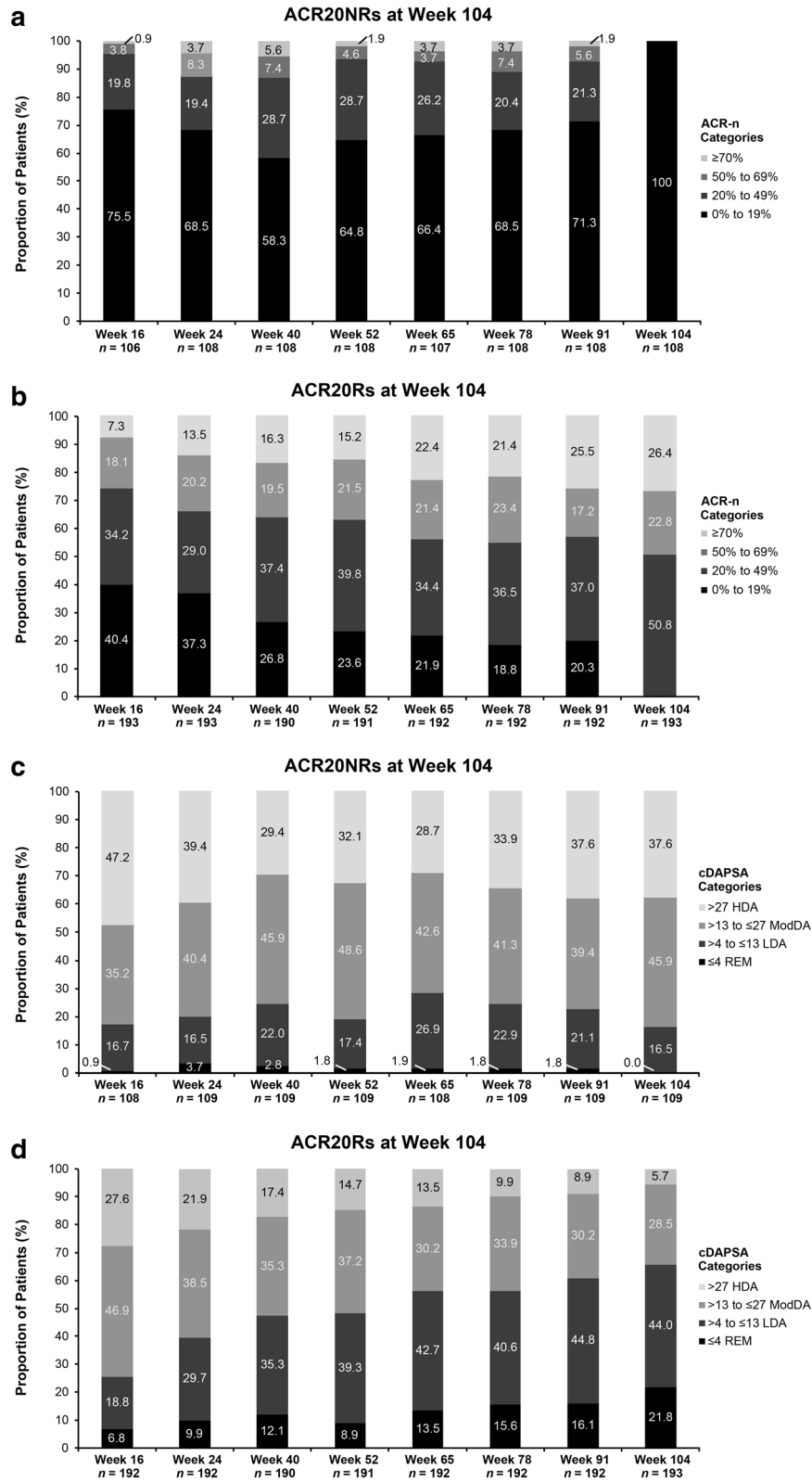
◄**Fig. 1** Proportion of ACR20NRs (**a**) and ACR20Rs (**b**) achieving ACR-n categories over 104 weeks and proportion of ACR20NRs (**c**) and ACR20Rs (**d**) achieving cDAPSA categories over 104 weeks. Data as observed. ACR20 is a composite measure defined as an improvement of 20% in swollen and tender joint counts and a 20% improvement in three of the five remaining ACR core set measures: Physician's Global Assessment of Disease Activity, Patient's Global Assessment of Disease Activity, Patient's Assessment of Pain, Patient's Assessment of Physical Function, and erythrocyte sedimentation rate or C-reactive protein [9]. *ACR20* ≥ 20% improvement in American College of Rheumatology response criteria, *ACR20NR* ACR20 non-responder, *ACR20R* ACR20 responder, *cDAPSA* Clinical Disease Activity Index for Psoriatic Arthritis, *HDA* high disease activity, *LDA* low disease activity, *ModDA* moderate disease activity, *REM* remission

were comparable to those of patients who remained in the study and were classified as ACR20NRs or ACR20Rs at Week 104.

Efficacy Results

Greater proportions of patients who were considered ACR20Rs versus ACR20NRs at Week 104 had consistently higher ACR responses or achieved better clinical outcomes throughout the 2-year period (Fig. 1a–d) [9]. Of the ACR20Rs at Week 104, a total of 40.4% had been classified as ACR20NRs at Week 16 (ie, gained responder status over time). This suggests that failing to achieve an ACR20 response with apremilast by Week 16 is not absolutely indicative of failing to achieve long-term ACR responses by Week 104, as maximal clinical improvements were observed after Week 16. Indeed, results indicate that the efficacy of apremilast does not plateau before Week 24, with continuous improvements observed over time (Figs. 1, 2).

In general, ACR20Rs who continued treatment with apremilast demonstrated greater improvements from baseline to Week 104 in several PsA core domains when compared to ACR20NRs. However, ACR20NRs demonstrated substantial improvements in SJC, TJC (Table 2; Fig. 2), dactylitis, enthesitis, and psoriasis

(Fig. 3). They also showed improvements in the PhGA (VAS) scores (Table 2). Half of patients who were ACR20R at Week 104 achieved 100% improvement (reduction) in SJC or ≥ 84.2% in TJC. Importantly, half of the patients who were ACR20NRs at Week 104 had improvements (reductions) in SJC and TJC that were ≥ 75.0% for SJC and ≥ 51.7% for TJC (Fig. 2). The mean percentage improvement in PhGA response was greater in Week 104 ACR20Rs than in Week 104 ACR20NRs (− 74.9% vs. − 44.3%). The PtGA responses improved in ACR20Rs (− 43.5%) but worsened in ACR20NRs (42.7%).

Of those Week 104 ACR20NRs treated with apremilast from baseline through 104 weeks who had enthesitis at baseline, 33.8% achieved resolution of enthesitis (i.e., achieved a MASES of 0) at Week 104, whereas this outcome was achieved by 50.4% of ACR20Rs at Week 104. A total of 68.2% versus 82.4% of ACR20NRs and ACR20Rs, respectively, with dactylitis at baseline achieved resolution of dactylitis based on the achievement of a dactylitis count of zero at Week 104 (Fig. 3). A comparable proportion of ACR20NRs and ACR20Rs (36.0 and 41.0%, respectively) with psoriasis involving ≥ 3% of the body surface area at baseline achieved a PASI-75 at Week 104. There were limited improvements recorded in Patient's Assessment of Pain, HAQ-DI, and CRP outcomes among ACR20NRs (Table 2).

The Week 16 responses by patients who were classified as ACR20NRs at Week 104 versus those who were ACR20NRs at Week 16 and dropped out of the study by Week 16 showed comparable improvements in SJC and TJC at Week 16; however, mean scores for the PtGA and Patient's Assessment of Pain were worse in patients who dropped out but improved in ACR20NRs who continued in the study (Table 3).

DISCUSSION

In this pooled analysis of data from the PALACE 1, 2, and 3 studies, a 36.1% of patients chose to remain in the study even though they were not classified as ACR20Rs at Week 104. As perhaps might have been expected by their choice to
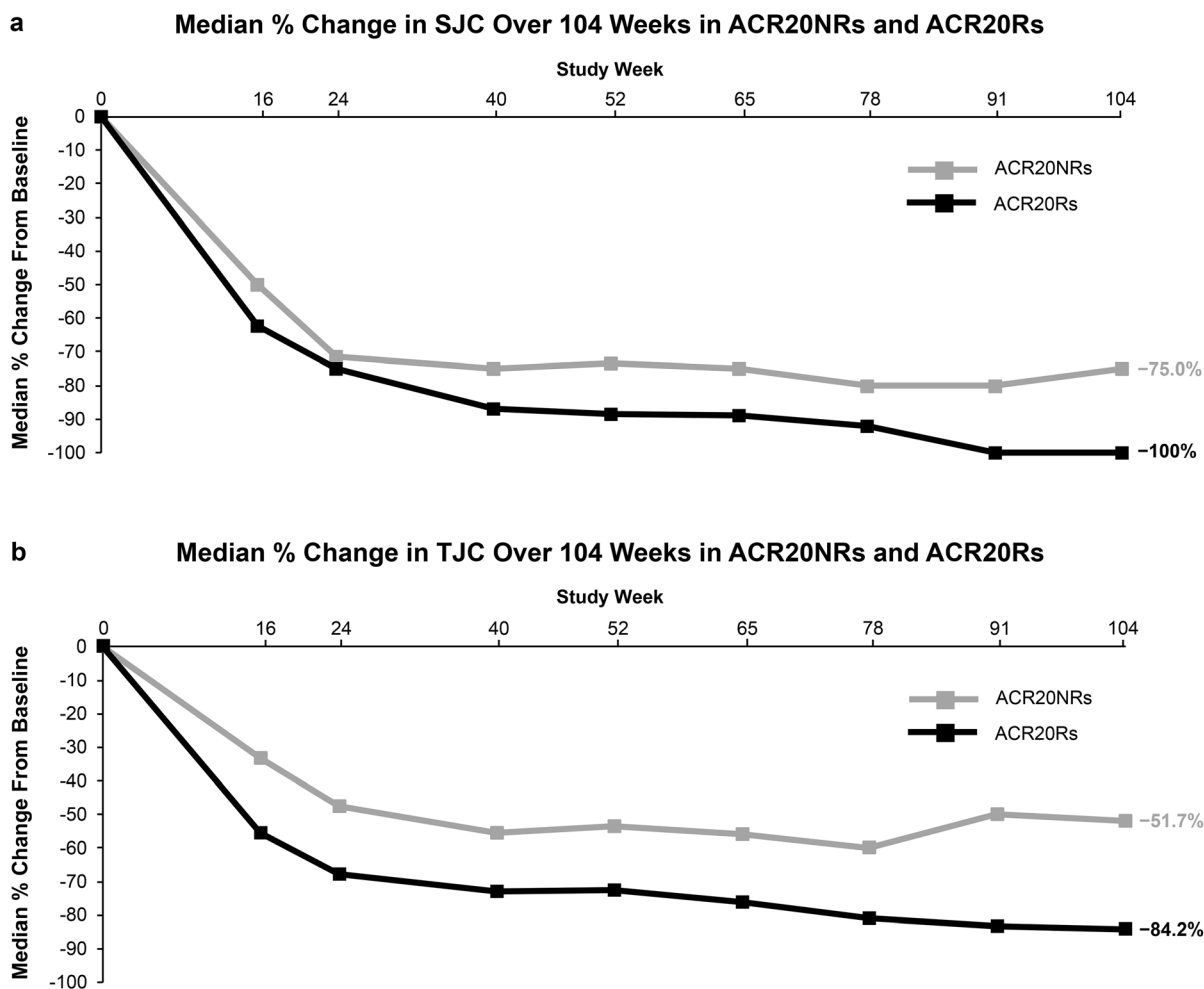
a

Median % Change in SJC Over 104 Weeks in ACR20NRs and ACR20Rs

b

Median % Change in TJC Over 104 Weeks in ACR20NRs and ACR20Rs

Fig. 2 Median percentage change in SJC (**a**) and TJC (**b**). Data as observed in patients randomized to apremilast 30 mg BID at baseline who were classified as ACR20Rs or ACR20NRs at Week 104. *BID* twice daily, *SJC* swollen joint count, *TJC* tender joint count

remain in the study, ACR20NRs who were treated with apremilast 30 mg BID from baseline through 104 weeks demonstrated sustained improvements in several PsA core domains, including SJC, TJC, enthesitis, dactylitis, and psoriasis, as well as the PhGA (VAS) scores. Among the ACR20NRs, the majority (68.2%) achieved a dactylitis count of zero and 33.8% achieved resolution of enthesitis at Week 104 versus 82.4 and 50.4%, respectively, in ACR20Rs at Week 104. Improvements in domains of PsA other than articular could be an important contributing factor to why patients who failed to achieve an ACR20 response at Week 104 remained on long-term apremilast treatment.

We also observed consistent improvements in PsA core domains after Week 24 among ACR20NRs and ACR20Rs, suggesting that the efficacy of apremilast does not plateau before Week 24 and that patients should remain on apremilast treatment longer than 24 weeks before considering treatment adjustments.

The composite measures in the ACR criteria were initially developed for measuring rheumatoid arthritis disease activity and define response as a binary outcome (achievement vs. non-achievement) [14]. Our data show that failure to achieve an ACR20 response does not necessarily mean lack of clinical benefit overall, and consideration of individual disease

Table 2 Summary of ACR core components and other efficacy endpoints at Week 104 for ACR20NRs and ACR20Rs

ACR core componets and other efficacy endpoints	Week 104	
	ACR20NR (*n* = 109)	ACR20R (*n* = 193)
SJC (0–76), mean (SD)	4.4 (6.4)	1.5 (2.8)
Change from baseline, mean (SD)	− 6.1 (7.2)	− 10.1 (7.1)
Change from baseline, median (Q1, Q3)	− 5.0 (− 9.0, − 3.0)	− 8.0 (− 12.0, − 5.0)
Percentage change from baseline, mean (SD)	− 58.0 (56.8)	− 87.5 (18.5)
Percentage change from baseline, median (Q1, Q3)	− 75.0 (− 100.0, − 46.2)	− 100.0 (− 100.0, − 81.8)
TJC (0–78), mean (SD)	12.9 (14.2)	4.3 (5.2)
Change from baseline, mean (SD)	− 10.0 (12.3)	− 16.3 (11.3)
Change from baseline, median (Q1, Q3)	− 9.0 (− 17.0, − 1.0)	− 14.0 (− 21.0, − 8.0)
Percentage change from baseline, mean (SD)	− 41.7 (44.2)	− 79.6 (19.4)
Percentage change from baseline, median (Q1, Q3)	− 51.7 (− 78.4, − 14.3)	− 84.2 (− 97.8, − 66.7)
PhGA (VAS 0–100 mm), mean (SD)	29.8 (20.5)	14.0 (13.8)
Change from baseline, mean (SD)	− 25.6 (21.8)	− 42.8 (20.4)
Change from baseline, median (Q1, Q3)	− 25.0 (− 40.0, − 10.0)	− 41.0 (− 58.0, − 28.5)
Percentage change from baseline, mean (SD)	− 44.3 (40.8)	− 74.9 (23.3)
Percentage change from baseline, median (Q1, Q3)	− 48.7 (− 74.1, − 20.0)	− 80.6 (− 93.5, − 61.6)
PtGA (VAS 0–100 mm), mean (SD)	54.7 (17.8)	28.7 (22.0)
Change from baseline, mean (SD)	1.6 (22.0)	− 30.1 (23.6)
Change from baseline, median (Q1, Q3)	2.0 (− 9.0, 12.0)	− 29.0 (− 46.0, − 15.0)
Percentage change from baseline, mean (SD)	42.7 (298.0)	− 43.5 (103.2)
Percentage change from baseline, median (Q1, Q3)	2.8 (− 16.2, 23.3)	− 55.1 (− 80.6, − 29.1)
Patient's Assessment of Pain (VAS 0–100 mm), mean (SD)	54.7 (18.0)	27.6 (21.3)
Change from baseline, mean (SD)	− 0.4 (19.9)	− 31.3 (23.1)
Change from baseline, median (Q1, Q3)	− 0.5 (− 8.5, 10.0)	− 32.0 (− 46.0, − 18.0)
Percentage change from baseline, mean (SD)	9.7 (55.6)	− 48.8 (51.7)
Percentage change from baseline, median (Q1, Q3)	− 0.7 (− 14.0, 21.9)	− 55.0 (− 78.7, − 33.8)
HAQ-DI (0–3), mean (SD)	1.2 (0.6)	0.7 (0.6)
Change from baseline, mean (SD)	− 0.1 (0.5)	− 0.5 (0.5)
Proportion of patients with HAQ-DI ≤ 0.5, n (%)	17 (15.6)	95 (49.2)
CRP (normal range: 0–0.499), mean (SD), mg/dL	0.87 (1.5)	0.60 (0.9)
Change from baseline, mean (SD)	− 0.07 (1.5)	− 0.45 (1.1)

Table 2 continued

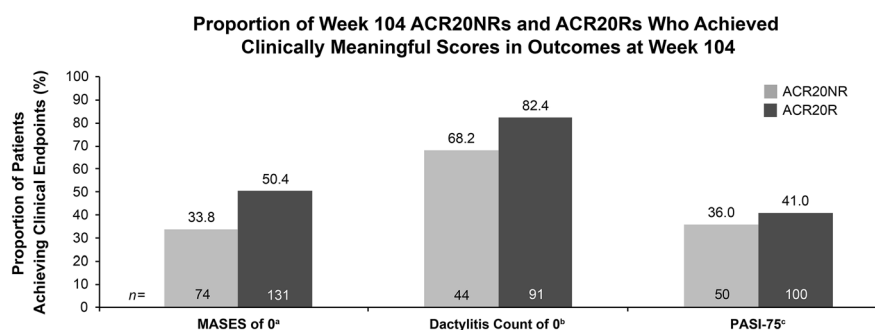| ACR core componets and other efficacy endpoints	Week 104	
	ACR20NR (n = 109)	ACR20R (n = 193)
Proportion of patients with normal CRP value ($\leq$ 0.499 mg/dL), n (%)	66 (60.6)	134 (69.4)

Data as observed

Q1, Q3 First and third quartile

Fig. 3 Achievement of clinically meaningful scores in categorical outcomes at Week 104. Data as observed in patients randomized to apremilast 30 mg BID at baseline. [a] Among patients with enthesitis at baseline. [b] Among patients with dactylitis at baseline. [c] Among patients with baseline psoriasis involvement $\geq$ 3% of the body surface area

domains is important to understand the full efficacy profile of PsA-specific treatments. The findings also highlight the need to define and optimize endpoints for PsA assessment in both clinical trials and daily practice. For example, ACR20NRs experienced substantial improvements in some measures of disease activity assessed in the PALACE 1–3 studies. The high prevalence of improvements in SJC and dactylitis resolution among ACR20NRs were among the most striking findings in this analysis. Resolution of dactylitis was an objective outcome that was likely accompanied by improvements in joint and entheseal tissue swelling and pain. Psoriasis was another objective outcome, and a substantial rate of PASI-75 responses (36.0%) may have contributed to the retention of ACR20NRs in this study.

Limited improvements in PtGA, Patient's Assessment of Pain, HAQ-DI, and CRP outcomes among ACR20NRs were commonly associated with ACR20 non-response at Week 104.

Interestingly, although improvement in HAQ-DI was limited, 15.6% of Week 104 ACR20NRs achieved a HAQ-DI score $\leq$ 0.5 at Week 104. The PtGA, Patient's Assessment of Pain, and HAQ-DI, which are components of minimal disease activity criteria, are easy to administer and commonly used to assess physical function in patients with PsA [12, 15–17]. While early (Week 16), limited improvements in patients' assessments of pain and disease were observed among those who continued therapy beyond Week 16 and were classified as ACR20NRs at Week 104, patients who were ACR20NRs at Week 16 and dropped out of the study by Week 16 had overall worse pain and self-assessment of disease, despite comparable improvements in SJC and TJC. Early improvements in PtGA and Patient's Assessment of Pain among ACR20NRs were not sustained, however, through Week 104. Of note, Eder et al. [18] observed high discordance between patient and physician assessments of joint disease (PtGA and PhGA) in

Table 3 ACR core components at Week 16 in Week 16 dropouts versus Week 104 ACR20NRs

ACR core components	Week 16 Dropouts[a]		Week 104 ACR20NR	
	Baseline ($n = 57$)	Week 16 ($n = 19$)	Baseline ($n = 109$)	Week 16 ($n = 109$)
SJC (0–76), mean (SD)	12.2 (7.8)	5.6 (4.6)	10.5 (7.7)	6.8 (8.3)
Change from baseline, mean (SD)	–	− 5.7 (7.3)	–	− 3.7 (5.7)
Change from baseline, median (Q1, Q3)	–	− 6.0 (− 10.0, − 2.0)	–	− 4.0 (− 7.0, − 1.0)
Percentage change from baseline, mean (SD)	–	− 35.8 (78.0)	–	− 39.4 (59.0)
Percentage change from baseline, median (Q1, Q3)	–	− 56.3 (− 83.3, − 22.2)	–	− 50.0 (− 85.7, − 6.7)
TJC (0–78), mean (SD)	24.7 (16.4)	15.5 (10.0)	22.9 (16.0)	17.1 (17.8)
Change from baseline, mean (SD)	–	− 6.5 (10.2)	–	− 5.8 (10.7)
Change from baseline, median (Q1, Q3)	–	− 5.0 (− 11.0, 0.0)	–	− 5.0 (− 11.0, 0.0)
Percentage change from baseline, mean (SD)	–	− 18.8 (44.8)	–	− 29.9 (48.0)
Percentage change from baseline, median (Q1, Q3)	–	− 25.7 (− 50.0, 0.0)	–	− 33.3 (− 64.3, 0.0)
PtGA (VAS 0–100 mm), mean (SD)	50.9 (25.3)	59.2 (19.6)	53.1 (19.7)	50.4 (21.4)
Change from baseline, mean (SD)	–	10.9 (23.3)	–	− 2.6 (24.3)
Change from baseline, median (Q1, Q3)	–	15.0 (− 3.0, 25.0)	–	0.0 (− 15.0, 11.0)
Percentage change from baseline, mean (SD)	–	244.7 (704.9)	–	19.8 (182.9)
Percentage change from baseline, median (Q1, Q3)	–	30.9 (− 3.4, 80.6)	–	0.0 (− 29.4, 20.0)
Patient's Assessment of Pain (VAS 0–100 mm), mean (SD)	53.4 (25.7)	52.0 (26.2)	55.0 (18.7)	51.8 (21.9)
Change from baseline, mean (SD)	–	4.8 (20.6)	–	− 3.1 (22.0)
Change from baseline, median (Q1, Q3)	–	3.0 (− 7.0, 20.0)	–	1.0 (− 17.0, 11.0)
Percentage change from baseline, mean (SD)	–	168.7 (497.1)	–	− 0.7 (48.7)

Table 3 continued

ACR core components	Week 16 Dropouts[a]		Week 104 ACR20NR	
	Baseline ($n = 57$)	Week 16 ($n = 19$)	Baseline ($n = 109$)	Week 16 ($n = 109$)
Percentage change from baseline, median (Q1, Q3)	–	13.0 (− 11.9, 48.8)	–	1.3 (− 32.3, 24.2)

Data as observed

[a] Patients who were ACR20NRs at Week 16 and discontinued from the study by Week 16

patients with PsA and that pain and fatigue were major contributors to this discordance. It is possible that early improvements in patient-reported pain and disease observed among Week 104 ACR20NRs in the current study may reflect differences between patient and physician ratings of pain and disease. Also, varying degrees of central sensitization or other factors, such as fibromyalgia, osteoarthritis, and musculoskeletal mechanical/degenerative lesions, may have led to these findings. In addition, while patient-reported outcomes such as PtGA and Patient's Assessment of Pain are a necessary complement to physician and laboratory assessments of disease, patients' perceptions of disease are subjective and may be influenced by psychological disorders and other sources of bias [19]. Also, although the HAQ-DI measure has demonstrated good internal consistency and structural validity, limitations of the HAQ-DI include ceiling and floor effects and conflicting validity across languages [12, 20].

A limitation of these analyses is that the data are from controlled clinical studies involving restricted eligibility criteria for patient enrollment. Thus, our study population may not completely represent the general population with PsA. Another limitation is the open-label design of this extension phase, which may lead to bias in reporting efficacy outcomes. Because all patients randomized to placebo were switched to apremilast by Week 24, the potential for PsA outcomes to improve over 104 weeks in the absence of systemic treatment cannot be ruled out.

CONCLUSIONS

Patients who did not achieve an ACR20 response at Week 104 upon treatment with apremilast 30 mg BID demonstrated significant improvements in some individual PsA core domains, which may explain why they remained on long-term treatment. These findings suggest that some patients with PsA may experience meaningful clinical benefits that are not completely captured or described by the ACR20 response criteria. Improvements in objective measures among ACR20NRs suggest that the ACR20 criterion should not be the sole determinant of efficacy or continuation of therapy in a multidimensional disease like PsA. Further study is required to completely understand the efficacy of therapeutics across the spectrum of PsA manifestations and the specific contributions that lead to ACR non-response and to determine which outcome measures specifically designed for PsA are more suitable to evaluate treatment response in this patient population.

ACKNOWLEDGMENTS

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REFERENCES

1. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. Biochem Pharmacol. 2012;83(12):1583–90.

2. Perez-Aso M, Montesinos MC, Mediero A, Wilder T, Schafer PH, Cronstein B. Apremilast, a novel phosphodiesterase 4 (PDE4) inhibitor, regulates inflammation through multiple cAMP downstream effectors. Arthritis Res Ther. 2015;17(1):249.

3. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomized, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014;73(6):1020–6.

4. Cutolo M, Myerson GE, Fleischmann R, et al. A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. J Rheumatol. 2016;43(9):1724–34.

5. Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Ann Rheum Dis. 2016;75(6):1065–73.

6. Kavanaugh A, Gladman DD, Edwards CJ, et al. Five-year efficacy and safety of apremilast treatment in subjects with PsA: a pooled analysis of the 3 phase III studies (abstract 686). 2018. https://acrabstracts.org/abstract/five-year-efficacy-and-safety-of-apremilast-treatment-in-subjects-with-psa-a-pooled-analysis-of-the-3-phase-iii-studies/. Accessed 22 Jun 2021.

7. 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.

8. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665–73.

9. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727–35.

10. El Miedany Y. Recent developments in management of psoriatic arthritis. Curr Rheumatol Rev. 2005;1(1):9–19.

11. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol. 1982;9(5):789–93.

12. Leung YY, Orbai AM, de Wit M, et al. Comparing the patient-reported physical function outcome measures in a real-life international cohort of patients with psoriatic arthritis. Arthritis Care Res (Hoboken). 2021;73(4):593–602.

13. Heuft-Dorenbosch L, Spoorenberg A, van-Tubergen A, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis. 2003;62(2):127–32.

14. Orbai AM, Ogdie A. Patient-reported outcomes in psoriatic arthritis. Rheum Dis Clin North Am. 2016;42(2):265–83.

15. Coates LC, Strand V, Wilson H, et al. Measurement properties of the minimal disease activity criteria for psoriatic arthritis. RMD Open. 2019;5(2): e001002.

16. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis. 2010;69(1):48–53.

17. Aouad K, Moysidou G, Rakotozafiarison A, Fautrel B, Gossec L. Outcome measures used in psoriatic arthritis registries and cohorts: a systematic literature review of 27 registries or 16,183 patients. Semin Arthritis Rheum. 2021;51(4):888–94.

18. Eder L, Thavaneswaran A, Chandran V, Cook R, Gladman DD. Factors explaining the discrepancy between physician and patient global assessment of joint and skin disease activity in psoriatic arthritis

patients. Arthritis Care Res (Hoboken). 2015;67(2): 264–72.

19. Cauli A, Gladman DD, Mathieu A, et al. Patient global assessment in psoriatic arthritis: a multicenter GRAPPA and OMERACT study. J Rheumatol. 2011;38(5):898–903.

20. Højgaard P, Klokker L, Orbai AM, et al. A systematic review of measurement properties of patient reported outcome measures in psoriatic arthritis: A GRAPPA-OMERACT initiative. Semin Arthritis Rheum. 2018;47(5):654–65.