

Patient-reported Health-related Quality of Life with Apremilast for Psoriatic Arthritis: A Phase II, Randomized, Controlled Study

Vibeke Strand, Georg Schett, ChiaChi Hu, and Randall M. Stevens

ABSTRACT. Objective. Apremilast, a specific inhibitor of phosphodiesterase 4, modulates proinflammatory and antiinflammatory cytokine production. A phase IIb randomized, controlled trial (RCT) evaluated the effect of apremilast on patient-reported outcomes (PRO) in psoriatic arthritis (PsA).

Methods. In this 12-week RCT, patients with active disease (duration > 6 mo, ≥ 3 swollen and ≥ 3 tender joints) received apremilast (20 mg BID or 40 mg QD) or placebo. PRO included pain and global assessment of disease activity [visual analog scale (VAS)], Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Medical Outcomes Study Short-Form 36 Health Survey (SF-36) assessing health-related quality of life (HRQOL). Percentages of patients reporting improvements \geq minimum clinically important differences (MCID) and correlations between SF-36 domains and pain VAS, HAQ-DI, and FACIT-F were determined.

Results. Among the 204 randomized patients (52.5% men; mean age 50.6 yrs), baseline SF-36 scores reflected large impairments in HRQOL. Apremilast 20 mg BID resulted in statistically significant and clinically meaningful improvements in physical and mental component summary scores and 7 and 6 SF-36 domains, respectively, compared with no change/deterioration in placebo group. Patients receiving apremilast 20 mg BID and 40 mg QD reported significant improvements \geq MCID in global VAS scores and FACIT-F versus placebo, and significant improvements in pain VAS scores. Moderate-high, significant correlations were evident between SF-36 domains and other PRO.

Conclusion. Apremilast resulted in statistically significant and clinically meaningful improvements in HRQOL, pain and global VAS, and FACIT-F scores. (J Rheumatol First Release April 15 2013; doi:10.3899/jrheum.121200)

Key Indexing Terms:

CLINICAL TRIALS
SPONDYLOARTHROPATHY

PSORIATIC ARTHRITIS

QUALITY OF LIFE
VISUAL ANALOG SCALE

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis¹. An estimated 40% of patients with psoriasis develop PsA^{1,2}, with a prevalence in the general US population between 0.3% and 1.0%¹. PsA is associated with poor health-related quality of life (HRQOL), including general health, bodily pain, and physical functioning, well below that of age- and sex-matched US norms^{3,4}, and longterm work disability^{4,5,6}. In a survey conducted by the National Psoriasis Foundation, 44% of patients with PsA who were not working reported

this was partially or entirely due to their PsA². The presence of both PsA and psoriasis may further influence HRQOL, with larger impairments than those seen with psoriasis alone^{7,8,9}.

Understanding the effect of new treatments on patient-reported outcomes (PRO) is important when assessing their overall clinical value. The effect on HRQOL may be influenced by treatment-related factors, such as efficacy, tolerability, adverse events, safety, and treatment regimen (e.g., dosing frequency, route of administration, cost). Effective treatment of patients with PsA, including use of disease-modifying antirheumatic drugs (DMARD), has been shown to significantly improve PRO, including HRQOL^{10,11}. However, these benefits differ among agents, with methotrexate (MTX) having a lesser effect on PRO than tumor necrosis factor (TNF) inhibitors^{9,12}. In addition, treatment of patients with traditional and biologic DMARD therapy may be compromised by adverse events, poor tolerability, inconvenient route of administration, and/or injection/infusion reactions^{13,14,15,16}. No oral DMARD therapy is currently approved by the US Food and Drug

From the Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, California, USA; University Erlangen-Nuremberg, Erlangen, Germany; and Celgene Corporation, Summit, New Jersey, USA.

Sponsored by Celgene Corporation.

V. Strand, MD, Adjunct Clinical Professor, Division of Immunology and Rheumatology, Stanford University School of Medicine; G. Schett, MD, University Erlangen-Nuremberg; C. Hu, EdM, MS; R.M. Stevens, MD, Celgene Corporation.

Address correspondence to Dr. V. Strand, Division of Immunology and Rheumatology, Stanford University School of Medicine, 306 Ramona Road, Portola Valley, CA 94028, USA. E-mail: vstrand@stanford.edu
Accepted for publication February 4, 2013.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2013. All rights reserved.

Administration for treatment of PsA, and there is only limited approval of leflunomide in Europe. Thus, efficacious, well tolerated, and easy-to-use treatment options are needed for patients with PsA.

During the past decade, the role of cyclic adenosine monophosphate (cAMP) in the pathophysiology of chronic inflammatory diseases has generated research interest. cAMP is a naturally occurring intracellular secondary messenger that helps to maintain immune homeostasis^{17,18}. Phosphodiesterase 4 (PDE4) is a cAMP-specific phosphodiesterase and the dominant phosphodiesterase in inflammatory cells^{19,20,21}. Inhibition of PDE4 increases the intracellular concentration of cAMP and modulates a network of proinflammatory and antiinflammatory mediators^{17,20,22,23}. Apremilast (Celgene Corporation), a specific inhibitor of PDE4, works intracellularly to reduce production of proinflammatory mediators, such as TNF- α , interleukin 23 (IL-23), and interferon- γ , and increase production of anti-inflammatory mediators, such as IL-10²⁰. Apremilast has been shown to be effective in the treatment of moderate to severe psoriasis and active PsA^{24,25,26}.

In a phase II, multicenter, randomized, controlled trial (RCT), apremilast 20 mg BID and 40 mg QD showed efficacy and a favorable benefit:risk profile in the management of patients with active PsA²⁵. After 12 weeks, 43.5% of patients receiving apremilast 20 mg BID ($p < 0.001$) and 35.8% receiving apremilast 40 mg QD ($p = 0.002$) exhibited $\geq 20\%$ improvements in American College of Rheumatology (ACR20) response criteria versus 11.8% receiving placebo. Improvements were generally maintained over 24 weeks of treatment²⁵. Our report summarizes the influence of apremilast treatment on PRO in this phase II RCT.

MATERIALS AND METHODS

Study design. This multicenter RCT enrolled men and women ≥ 18 years of age with active PsA (duration ≥ 6 months; ≥ 3 swollen joints; ≥ 3 tender joints) and negative rheumatoid factor (RF; titer ≤ 30 IU/ml). Patients must have discontinued systemic therapy for psoriasis and/or PsA, including but not limited to sulfasalazine, leflunomide, chloroquine, hydroxychloroquine, gold compounds, penicillamine, parenteral corticosteroids (including intraarticular), cyclosporine, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, tacrolimus, azathioprine, and fumaric acid esters within 28 days; phototherapy within 28 days; etanercept within 56 days; adalimumab, efalizumab, or infliximab within 84 days; and alefacept within 168 days of randomization. Patients using stable doses of nonsteroidal antiinflammatory drugs (≥ 2 weeks), oral corticosteroids (≥ 4 weeks), and/or MTX (≥ 8 weeks) before screening and throughout the study were eligible for study enrollment; those with erythrodermic, guttate, or pustular forms of psoriasis were excluded. Methods and results were as reported²⁵.

At baseline, eligible patients were randomized 1:1:1 to receive placebo or oral apremilast (20 mg BID or 40 mg QD) for 12 weeks, stratified by concomitant MTX use. At Week 12, placebo patients were rerandomized to receive apremilast 20 mg BID or 40 mg QD until Week 24 in a blinded fashion; all other patients continued to receive their assigned dose of apremilast. Throughout the trial, concomitant treatment with phototherapy or other systemic DMARD, other than MTX, was prohibited. In patients

with psoriasis, use of topical agents was prohibited, except coal tar shampoos, nonmedicated Eucerin cream, and low to moderate potency topical corticosteroids for treating psoriatic lesions. This report describes PRO, including HRQOL, at the primary 12-week endpoint.

PRO assessments. Changes from baseline to Week 12 and improvements \geq minimum clinically important differences (MCID) were determined for PRO, including 3 components of the ACR response criteria, patient-reported pain and global disease activity by visual analog scale (VAS), and Health Assessment Questionnaire Disability Index (HAQ-DI); Functional Assessment of Chronic Illness Therapy for Fatigue (FACIT-F); and the generic Medical Outcomes Study Short-Form 36 Health Survey version 2 (SF-36). Definitions of the MCID for each instrument are summarized in Table 1^{27,28,29,30,31,32}.

Statistical analysis. All analyses were performed in the intent-to-treat population who had baseline and ≥ 1 postbaseline assessments, with last-observation-carried-forward used for missing values. Changes from baseline in each score were summarized using descriptive statistics. For continuous measures, Week 12 changes from baseline within treatment groups (apremilast 20 mg BID and 40 mg QD) were compared with placebo using an analysis of covariance model (with treatment as the factor, baseline as the covariate, and blocking for MTX use). If either physical component summary (PCS) and/or mental component summary (MCS) scores of the SF-36 were statistically significant, significance was tested for individual domain scores. Mean changes from baseline in domain scores are displayed using spydergrams³³, with quantification of improvements by the health utility SF-6D after the method of Ara and Brazier, based on an algorithm using mean scores across all 8 domains of the SF-36^{34,35}. As a benchmark comparison, without statistical analyses, US normative data were calculated based on age and sex distribution of the protocol population, using published norm-based scoring algorithms based on the 1998 National Survey of Functional Health Status³⁶; no statistical analyses were conducted for differences between US normative data and study findings. Pearson correlations were determined for mean changes from baseline at Week 12 between the generic SF-36 Physical Function (PF), Bodily Pain (BP), and Vitality (VT) domain scores and disease-specific HAQ-DI, pain VAS, and FACIT-F, respectively. Correlations > 0.30 to ≤ 0.60 were considered moderate and > 0.60 high³⁷.

RESULTS

Patients. Of 204 patients randomized, 165 (80.9%) completed 12 weeks of treatment. Baseline demographic and disease characteristics are summarized in Table 2. The sample was composed of roughly equal proportions of men (52.5%) and women (47.5%) who were white (96.6%), overweight/obese (mean body mass index 30.2 kg/m², SD 5.94), and had had PsA for a mean of 7.8 (SD 8.5) years.

PRO assessments. Patient-reported pain and global assessments of disease activity were comparable among treatment groups at baseline and ranged between 54 and 60 mm on a 100-mm VAS scale (Table 3). At Week 12, mean changes in pain VAS scores were significantly greater in patients receiving apremilast 20 mg BID and 40 mg QD ($p < 0.05$ vs placebo for both doses). Global assessment scores worsened from baseline for placebo group but improved with apremilast 20 mg BID and 40 mg QD ($p < 0.05$ vs placebo for both doses). As shown in Figure 1, at Week 12, a significantly greater proportion of patients reported improvements \geq MCID in global assessments with apremilast 20 mg BID (44.9%; $p = 0.04$) and 40 mg QD (47.8%; $p = 0.02$) versus placebo. Numerically more patients reported clinically

Table 1. Overview of patient-reported health-related quality of life instruments^{27,28,29,30,31,32}.

| Instrument | Description | Assessment | MCID |
|--|---|---|---|
| Global disease activity and pain by VAS | Disease activity and pain scales | 0–100 mm, include “anchors” | Improvement: 10.0 points |
| HAQ-DI | Functional ability questionnaire | 0–3 (0 = no difficulty, 3 = unable to do) | Improvement: –0.13 points* and –0.3 points* |
| FACIT-F | Fatigue questionnaire; 13 questions evaluated on 5-point scale | 0–4 (0 = not at all, 4 = very much) | Improvement: 4.0 |
| SF-36 domains | Self-administered instrument assessing 8 health domains: (1) PF: limitations in physical activities; (2) RP: limitations in usual role activities; (3) BP: bodily pain; (4) GH: general health perceptions; (5) VT: vitality; (6) RE: limitations in usual role activities; (7) SF: limitations in social activities; (8) MH: general mental health | 0–100 points, worst to best | Improvement: 5.0 points Deterioration: –2.5 points |
| SF-36 physical and mental component summary scores (PCS and MCS) | Summarizes SF-36 subscale scores | 0–50 points (normative value = 50, SD 10) | Improvement: 2.5 points Deterioration: –0.8 points |
| SF-6D (utility-based measure) | Preference-based measure derived from the SF-36; yields a single score that qualifies changes across all 8 SF-36 domains | 0.296–1.0 (0 = death, 1.0 = perfect health) | MID ≥ 0.041 |

* MCID for HAQ-DI was analyzed using 2 different definitions based on 2 published MCID levels in PsA: –0.13³¹ and –0.3³². The present study population more closely resembles the population studied in Kwok, *et al*³¹ (MCID, –0.13); however, the more stringent level reported by Mease, *et al*³² (MCID, –0.3) was included for comparative purposes. FACIT-F: Functional Assessment of Chronic Illness Therapy for Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; MCID: minimum clinically important differences; MCS: mental component summary; MID: minimum important differences; PCS: physical component summary; SF-36: 36-Item Medical Outcomes Study Short-Form Health Survey, version 2; SF-6D: 6-Domain Short-Form Health Survey; VAS: visual analog scale.

Table 2. Patient demographic and baseline disease characteristics.

| Characteristic | Placebo, n = 68 | Apremilast 20 mg BID, n = 69 | Apremilast 40 mg QD, n = 67 |
|---|------------------|------------------------------|-----------------------------|
| Age, mean yrs | 51.1 | 50.9 | 49.9 |
| Male, n (%) | 32 (47.1) | 43 (62.3) | 32 (47.8) |
| Race, n (%) | | | |
| White | 68 (100.0) | 67 (97.1) | 62 (92.5) |
| Black | 0 | 0 | 1 (1.5) |
| Hispanic | 0 | 0 | 1 (1.5) |
| Asian/Pacific Islander | 0 | 1 (1.4) | 2 (3.0) |
| Other | 0 | 1 (1.4) | 1 (1.5) |
| Smokers, n (%) | 15 (22.1) | 14 (20.3) | 13 (19.4) |
| Weight, mean (SD), lb | 200.5 (39.2) | 184.4 (33.7) | 195.7 (44.2) |
| Body mass index, mean (SD), kg/m ² | 31.5 (5.52) | 28.2 (4.40) | 31.0 (7.14) |
| PsA disease category, n (%) | | | |
| Asymmetrical oligoarthritis | 20 (29.4) | 21 (30.4) | 26 (38.8) |
| Predominant spondylitis | 2 (2.9) | 3 (4.3) | 4 (6.0) |
| Symmetric polyarthritis | 39 (57.4) | 36 (52.2) | 32 (47.8) |
| Arthritis mutilans | 5 (7.4) | 0 | 2 (3.0) |
| Predominant DIP involvement | 2 (2.9) | 9 (13.0) | 2 (3.0) |
| PsA history, mean yrs* | 7.3 | 8.4 | 7.6 |
| Joint counts | | | |
| Pain/tender score | 21.3 | 20.6 | 23.2 |
| Swelling score | 9.5 | 10.6 | 8.4 |
| Psoriasis severity, n (%) | | | |
| None | 12 (17.6) | 7 (10.1) | 2 (3.0) |
| Mild | 40 (58.8) | 47 (68.1) | 41 (61.2) |
| Moderate | 11 (16.2) | 15 (21.7) | 20 (29.9) |
| Severe | 5 (7.4) | 0 | 4 (6.0) |
| Psoriasis history, mean yrs | 15.8 | 15.5 | 18.3 |
| Methotrexate use, n (%) | 29 (42.6) | 30 (43.5) | 30 (44.8) |
| CRP, mean (range), mg/l | 14.9 (3.0–237.0) | 10.4 (3.0–65.4) | 10.9 (3.0–95.0) |

* January was used for a missing month and 01 was used for a missing day to calculate the years of history. CRP: C-reactive protein; DIP: distal interphalangeal joints; PsA: psoriatic arthritis.

Table 3. Summary of pain and global VAS scores, FACIT-F, and HAQ-DI.

| Measure, mean (SD) | Placebo | Apremilast 20 mg BID | Apremilast 40 mg QD |
|----------------------|--------------|-------------------------|------------------------|
| Global VAS (0–100) | | | |
| Baseline | 58.3 (23.87) | 54.3 (19.53) | 55.7 (22.47) |
| Week 12/final visit | 59.4 (24.0) | 45.3 (25.9) | 45.0 (25.5) |
| Change from baseline | 1.0 (19.2) | –10.3 (24.6)* | –10.4 (23.6)* |
| Pain VAS (0–100) | | | |
| Baseline | 59.7 (22.64) | 55.7 (18.82) | 57.1 (23.77) |
| Week 12/final visit | 58.5 (24.4) | 44.9 (25.9) | 44.8 (26.1) |
| Change from baseline | –1.3 (19.7) | –11.2 (22.8)* | –11.5 (22.6)* |
| HAQ-DI (0–3) | | | |
| Baseline | 1.24 (0.77) | 0.96 (0.65) | 1.08 (0.71) |
| Week 12/final visit | 1.18 (0.78) | 0.80 (0.63) | 0.93 (0.71) |
| Change from baseline | –0.05 (0.39) | –0.16 (0.35) | –0.15 (0.39) |
| FACIT-F (0–52) | | | |
| Baseline | 28.8 (11.76) | 32.1 (11.92) | 27.7 (12.78) |
| Week 12/final visit | 29.5 (13.33) | 36.2 (11.80) | 32.0 (12.25) |
| Change from baseline | 0.5 (8.03) | 4.1 (8.78)* | 4.3 (9.46)* |
| SF-36 MCS | | | |
| Baseline | 43.6 | 45.0 | 43.5 |
| Week 12/final visit | 44.0 | 48.3 | 44.7 |
| Change from baseline | –0.8 | 3.4* | 1.1 |
| SF-36 PCS | | | |
| Baseline | 33.3 | 37.3 | 34.8 |
| Week 12/final visit | 34.1 | 40.2 | 36.9 |
| Change from baseline | 0.8 | 2.4* | 2.1 |

* $p < 0.05$ vs. placebo. FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; MCS: mental component summary; PCS: physical component summary; VAS: visual analog scale; SF-36: 36-item Medical Outcomes Study Short-Form Health Survey.

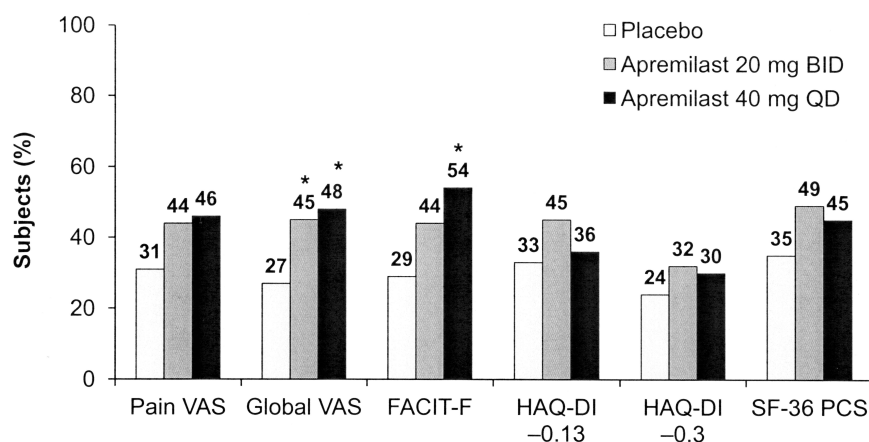


Figure 1. Percentage of patients reporting improvements above the respective MCID of the patient-reported outcomes pain (on VAS), global disease activity (VAS), fatigue (FACIT-F), function (HAQ-DI), and HRQOL (SF-36 PCS). *Significant differences, $p < 0.05$. FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; SF-36 PCS: 36-Item Medical Outcomes Study Short Form-36 Health Survey physical component summary; HRQOL: health-related quality of life; VAS: visual analog scale.

meaningful improvements in pain VAS scores with both apremilast doses versus placebo; however, differences versus placebo were not significant ($p \geq 0.10$).

Changes from baseline in HAQ-DI scores are sum-

marized in Table 3. Mean HAQ-DI scores were similar among treatment groups at baseline (range 0.96–1.24, SD 0.77–0.65). Mean changes from baseline in placebo were small (–0.05), but improved in both active treatment groups

(−0.16 and −0.15), which approached MCID. A numerically greater proportion of patients treated with apremilast reported improvements \geq MCID at Week 12 compared with placebo when MCID was defined as −0.13 or −0.3; however, differences versus placebo were not significant ($p \geq 0.16$; Figure 1).

Mean FACIT-F scores and changes from baseline observed at Week 12 in each treatment group are summarized in Table 3. Baseline mean FACIT-F scores were similar across all treatment groups (range 27.7–32.1, SD 12.8–11.9). At Week 12, mean changes in FACIT-F scores were significantly greater (vs placebo) with apremilast 20 mg BID ($p = 0.004$) and 40 mg QD ($p = 0.028$). Clinically meaningful improvements in FACIT-F scores were reported by 43.5% and 53.7%, respectively, of patients receiving apremilast 20 mg BID ($p = 0.07$) and 40 mg QD ($p < 0.01$; Figure 1).

At baseline, mean PCS and MCS scores were lower than US normative scores of 50 (SD 10), about 1.5 SD less in PCS scores (range 33.3–37.3) and 0.5 SD in MCS scores

(range 43.5–45.0). After 12 weeks of treatment, improvements in both PCS and MCS scores were statistically significant with apremilast 20 mg BID [2.4 ($p = 0.026$) and 3.4 ($p = 0.003$), respectively, vs placebo] and \geq MCID, compared with deterioration in placebo; there were numerical but not statistically significant changes with apremilast 40 mg QD. A greater proportion of patients receiving apremilast 20 mg BID and 40 mg QD reported improvements \geq MCID in PCS scores versus placebo, although differences were not statistically important (Figure 1).

At baseline, SF-36 domain scores in all groups were well below age- and sex-matched US normative values specific to this population by about 20 to 30 points in physical domains and > 10 points in mental domains, indicating large disease-associated impairments in HRQOL. At Week 12, patients receiving placebo reported little improvement in 5 and deterioration in 3 domains of the SF-36, with clinically meaningful worsening in the Role-Emotional (RE) domain (exceeding −2.5 for MCID for deterioration; Figure 2A). Patients treated with apremilast 20 mg BID reported statis-

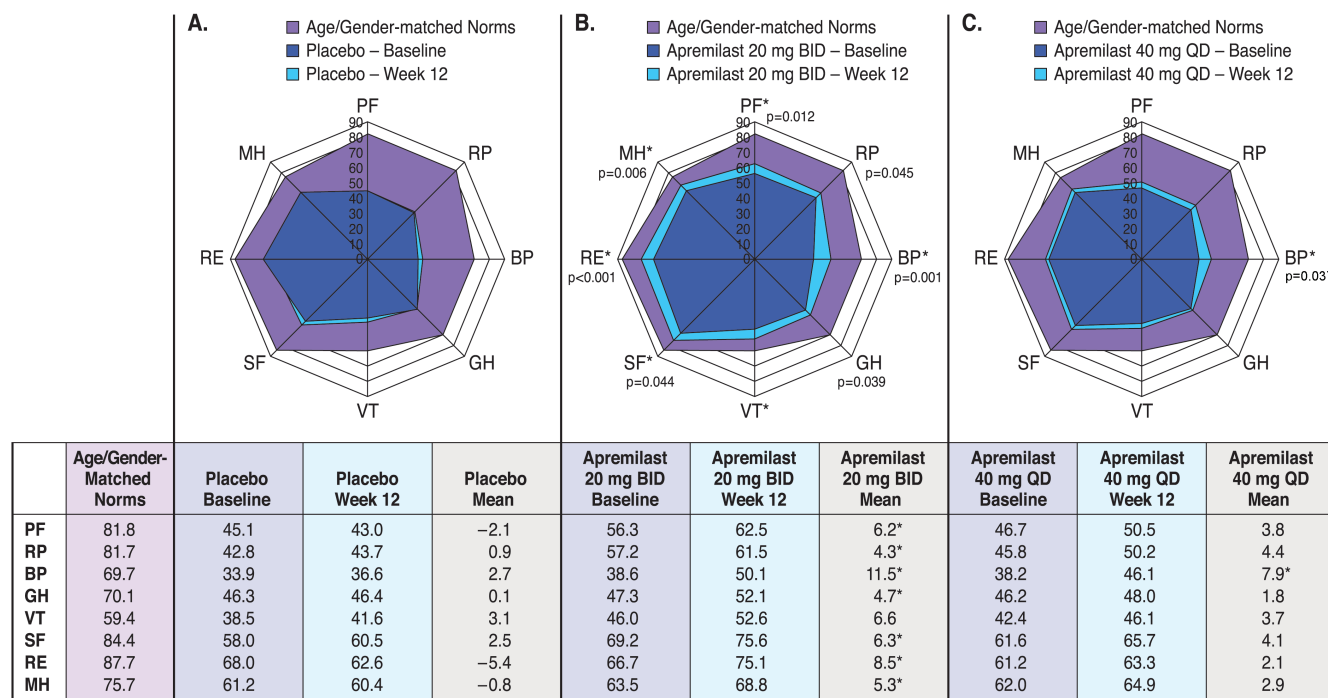


Figure 2. A. SF-36 domain scores at baseline and endpoint (Week 12) in patients receiving placebo versus age- and sex-matched norms. Gridlines represent changes of 10 points each, from minimum clinically important differences (MCID) to 2× MCID. An increase in score indicates improvement. Innermost polygon (dark blue): health-related quality of life (HRQOL) reported at baseline. Outer polygon (lavender): age- and sex-matched US normative values specific to this protocol population. Intermediate polygon (light blue): improvements in placebo at endpoint (Week 12). B. SF-36 domain scores at baseline and endpoint in patients receiving apremilast 20 mg BID versus age- and sex-matched norms. Gridlines represent changes of 10 points each (from MCID to 2× MCID). An increase in score indicates improvement. Innermost polygon (dark blue): HRQOL reported at baseline. Outer polygon (lavender): age- and sex-matched US normative values specific to this protocol population. Intermediate polygon (light blue): improvements in apremilast 20 mg BID at endpoint at Week 12, statistically significant in 7 of 8 domains and \geq MCID in 6. C. SF-36 domain scores at baseline and endpoint in patients receiving apremilast 40 mg QD versus age- and sex-matched norms. Gridlines represent changes of 10 points each (from MCID to 2× MCID). An increase in score indicates improvement. Innermost polygon (dark blue): HRQOL reported at baseline. Outer polygon (lavender): age- and sex-matched US normative values specific to this protocol population. Intermediate polygon (light blue): improvements in apremilast 40 mg QD at endpoint at Week 12, statistically significant and \geq MCID in the BP domain. * \geq MCID. SF-36: Medical Outcomes Study Short Form-36; BP: Bodily Pain; PF: Physical Function; MH: Mental Health; RE: Role-Emotional; RP: Role-Physical; SF: Social Function; VT: Vitality; GH: General Health.

tically significant ($p < 0.05$) mean improvements in 7 of 8 domains, which were clinically meaningful in 6 domains (Figure 2B). Among patients treated with apremilast 40 mg QD, statistically significant and clinically meaningful improvement was reported in the BP domain (Figure 2C). SF-6D baseline utility scores were 0.233 to 0.298 lower than age- and sex-matched US norms of 0.821. Treatment-associated improvements in the apremilast 20 mg BID and 40 mg QD groups resulted in mean increases of 0.076 and 0.047 in SF-6D utility scores, respectively, which exceeded the minimum important difference (MID).

DISCUSSION

As shown in other studies, improvements in physical functioning and pain appear prominent among overall

Administration of apremilast 20 mg BID was associated with broad improvements in patient-reported HRQOL at 12 weeks, statistically in PCS, MCS, and 7 of 8 domain scores of SF-36; clinically meaningful in MCS and 6 of 8 domain scores; and reflected by more patients receiving 20 mg BID reporting improvements \geq MCID. In contrast, SF-36 domain scores showed little change or even deterioration with placebo. Importantly, larger changes with both doses of apremilast were reported in the BP domain with the lowest scores at baseline, followed by RE, Social Function (SF), PF, and Mental Health (MH), indicating improvements in social and emotional well-being as well as pain and functioning. Clinically meaningful changes in VT (fatigue, energy, and pep) were not statistically significant, as the largest change in placebo occurred in this domain. While these results are encouraging, this was a relatively short study, and achievement of ACR20 over time indicates that improved response may be seen with longer treatment²⁵; it is hoped that continuing longer-term, phase III studies will better illustrate the effects of apremilast on HROOL.

Both active doses of apremilast were associated with statistically significant reductions in pain and global VAS scores and FACIT-F versus placebo, all clinically meaningful. These broad improvements across PRO are consistent with the reported changes in SF-36. Moderate to high, statistically significant correlations between SF-36 domains and pain VAS scores and HAQ-DI and FACIT-F demonstrate that the generic SF-36 measure of HRQOL offers sensitivity similar to the disease-specific instruments for detecting treatment-associated improvements. It also reflects the influence of disease and treatment-associated improvements in social and emotional functioning and mental health, which are not specifically assessed in other PRO.

A large proportion of individuals with PsA also have psoriasis, which adversely affects HRQOL, but to a different degree^{39,40,41}. Patients with PsA report an effect of disease on physical functioning: PF and RP domains, and BP and VT domains, which also affect RE and SF domains. In contrast, psoriasis has a relatively greater effect on mental rather than physical domains, particularly RE and SF, with a lesser degree of effect on RP and BP domains^{9,24}. In the current study population, 27% of patients had moderate to severe psoriasis at baseline. In a separate phase II RCT, apremilast was shown to be effective for treatment of moderate to severe plaque psoriasis, where 28.7% of patients treated with 20 mg BID and 40.9% with 30 mg BID

Table 4. Correlations between mean changes in SF-36 domains and pain VAS, HAO-DI, and FACIT-F*.

* Correlations $> 0.30 \leq 0.60$ are considered moderate; > 0.60 high. BP: Bodily Pain; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire Disability Index; NS: not significant; PF: Physical Function; SF-36: 36-Item Medical Outcomes Study Short-Form Health Survey; VAS: visual analog scale; VT: Vitality.

achieved $\geq 75\%$ reductions from baseline in Psoriasis Area and Severity Index scores²⁴. At baseline, SF-36 domain scores between the PsA and psoriasis populations were similar in SF and MH domains, but 16 to 21 points lower in the 4 physical domains and 9 to 10 points lower in the VT and RE domains. Apremilast 30 mg BID was also shown to significantly improve PRO, including HRQOL at 16 weeks in a population with moderate to severe plaque psoriasis, with similar magnitudes of change across physical and mental domain scores and endpoint values that approximated or met age- and sex-matched norms in the PF, RP, GH, VT, and SF domains⁴².

Limitations. Data in this report include posthoc analyses based on results from predefined secondary PRO. Nonetheless, they were designed to better characterize treatment-associated changes with active therapy and have further validated the utility of a generic instrument assessing HRQOL in PsA (the SF-36). The short duration of this trial — 12 weeks — limits the results, but nonetheless supports dose-related findings. The influence of longer-term apremilast treatment on patients' HRQOL will be assessed in ongoing, phase III trials that are expected to yield valuable information.

This trial used a rigorous design and provided strong evidence that apremilast is effective for the treatment of patients with active PsA²⁵. As described in a separate report, adverse events were predominantly mild or moderate in severity and generally did not lead to treatment discontinuation²⁵. Importantly, no opportunistic infections have been reported with use of apremilast. Based on these findings, the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) phase III study program, which consists of four 52-week RCT, followed by longterm open-label extensions (2–5 years), will evaluate the efficacy and safety of apremilast in active PsA, including a higher apremilast dose (30 mg BID), as studied in psoriasis²⁴.

Active PsA is associated with physical impairments and large decrements in patient-reported HRQOL. In our current study, apremilast 20 mg BID in patients with active PsA resulted in broad and statistically significant as well as clinically meaningful improvements in both disease-specific and generic measures of HRQOL and may become an important treatment option for this patient population.

ACKNOWLEDGMENT

The authors received editorial support in the preparation of this report from Peloton Advantage LLC, and Jennifer Schwinn, RPh.

REFERENCES

- Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: Epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005;64 Suppl 2:ii14-ii17.
- National Psoriasis Foundation. Report on the psycho-social impacts of psoriasis. Portland, OR: National Psoriasis Foundation; 2009 [Internet. Accessed March 7, 2012.] Available from: www.psoriasis.org/NetCommunity/Document.Doc?id=619
- Singh JA, Strand V. Spondyloarthritis is associated with poor function and physical health-related quality of life. *J Rheumatol* 2009;36:1012-20.
- Wallenius M, Skomsvoll JF, Koldingsnes W, Rodevand E, Mikkelsen K, Kaufmann C, et al. Work disability and health-related quality of life in males and females with psoriatic arthritis. *Ann Rheum Dis* 2009;68:685-9.
- Brodzsky V, Balint P, Geher P, Hodinka L, Horvath G, Koo E, et al. Disease burden of psoriatic arthritis compared to rheumatoid arthritis, Hungarian experiment. *Rheumatol Int* 2009;30:199-205.
- Zhu TY, Tam LS, Leung YY, Kwok LW, Wong KC, Yu T, et al. Socioeconomic burden of psoriatic arthritis in Hong Kong: Direct and indirect costs and the influence of disease pattern. *J Rheumatol* 2010;37:1214-20.
- Lundberg L, Johannesson M, Silverdahl M, Hermansson C, Lindberg M. Health-related quality of life in patients with psoriasis and atopic dermatitis measured with SF-36, DLQI and a subjective measure of disease activity. *Acta Dermatol Venereol* 2000;80:430-4.
- Rosen CF, Mussani F, Chandran V, Eder L, Thavaneswaran A, Gladman DD. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. *Rheumatology* 2012;51:571-6.
- Strand V, Sharp V, Koenig AS, Park G, Shi Y, Wang B, et al. Comparison of health-related quality of life in rheumatoid arthritis, psoriatic arthritis and psoriasis and effects of etanercept treatment. *Ann Rheum Dis* 2012;17:1143-50.
- Kavanaugh A, Antoni C, Krueger GG, Yan S, Bala M, Dooley LT, et al. Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis. *Ann Rheum Dis* 2006;65:471-7.
- Kavanaugh A, Menter A, Mendelsohn A, Shen YK, Lee S, Gottlieb AB. Effect of ustekinumab on physical function and health-related quality of life in patients with psoriatic arthritis: A randomized, placebo-controlled, phase II trial. *Curr Med Res Opin* 2010;26:2385-92.
- Heiberg MS, Kaufmann C, Rodevand E, Mikkelsen K, Koldingsnes W, Mowinkel P, et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. *Ann Rheum Dis* 2007;66:1038-42.
- Saurat JH, Guerin A, Yu AP, Latremouille-Viau D, Wu EQ, Gupta SR, et al. High prevalence of potential drug-drug interactions for psoriasis patients prescribed methotrexate or cyclosporine for psoriasis: Associated clinical and economic outcomes in real-world practice. *Dermatology* 2010;220:128-37.
- Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. *Ann Rheum Dis* 2008;67:855-9.
- New guidelines for managing psoriasis with systemic medications. *Dermatol Nurs* 2009;21:301-3.
- Brunasso AM, Puntoni M, Salvini C, Delfino C, Curcio P, Gulia A, et al. Tolerability and safety of biological therapies for psoriasis in daily clinical practice: A study of 103 Italian patients. *Acta Dermatol Venereol* 2011;91:44-9.
- Serezani CH, Ballinger MN, Aronoff DM, Peters-Golden M. Cyclic AMP: master regulator of innate immune cell function. *Am J Respir Cell Mol Biol* 2008;39:127-32.
- Tasken K, Aandahl EM. Localized effects of cAMP mediated by distinct routes of protein kinase A. *Physiol Rev* 2004;84:137-67.
- Baumer W, Hoppmann J, Rundfeldt C, Kietzmann M. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. *Inflamm Allergy Drug Targets* 2007;6:17-26.
- Schafer PH, Parton A, Gandhi AK, Capone L, Adams M, Wu L, et al. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates

- anti-inflammatory activity in vitro and in a model of psoriasis. *Br J Pharmacol* 2010;159:842-55.
21. Salari P, Abdollahi M. Phosphodiesterase inhibitors in inflammatory bowel disease. *Expert Opin Investig Drugs* 2012;21:261-4.
 22. Heystek HC, Thierry A-C, Soulard P, Moulon C. Phosphodiesterase 4 inhibitors reduce human dendritic cell inflammatory cytokine production and Th1-polarizing capacity. *Int Immunol* 2003; 15:827-35.
 23. Claveau D, Chen SL, O'Keefe S, Zaller DM, Styhler A, Liu S, et al. Preferential inhibition of T helper 1, but not T helper 2, cytokines in vitro by L-826,141 [4-[2-(3,4-Bisdifluoromethoxyphenyl)-2-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-phenyl]-ethyl]3-methylpyridine-1-oxide], a potent and selective phosphodiesterase 4 inhibitor. *J Pharmacol Exp Ther* 2004; 310:752-60.
 24. Papp K, Cather J, Rosoph L, Sofen H, Langley RG, Matheson RT, et al. The efficacy of apremilast, a phosphodiesterase-4 inhibitor, in the treatment of moderate to severe psoriasis: Results of a phase 2 randomised study. *Lancet* 2012;380:738-46.
 25. Schett G, Wollenhaupt J, Papp K, Joos R, DeVlam KL, Rodrigues JF, et al. Oral apremilast is effective in the treatment of subjects with active moderate to severe psoriatic arthritis: Results of a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2012;64:3156-67.
 26. Gottlieb AB, Strober B, Krueger JG, Rohane P, Zeldis JB, Hu CC, et al. An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast. *Curr Med Res Opin* 2008;24:1529-38.
 27. Hazes JM, Taylor P, Strand V, Purcaru O, Coteur G, Mease P. Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. *Rheumatology* 2010;49:1900-10.
 28. Strand V, Bombardier C, Maetzel A, Scott D, Crawford B. Use of minimum clinically important differences (MCID) in evaluating patient responses to treatment of rheumatoid arthritis (RA) [abstract]. *Arthritis Rheum* 2001;44 Suppl:S187.
 29. Strand V, Scott DL, Emery P, Kalden JR, Smolen JS, Cannon GW, et al. Physical function and health related quality of life: Analysis of 2-year data from randomized, controlled studies of leflunomide, sulfasalazine, or methotrexate in patients with active rheumatoid arthritis. *J Rheumatol* 2005;32:590-601.
 30. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:811-9.
 31. Kwok T, Pope JE. Minimally important difference for patient-reported outcomes in psoriatic arthritis: Health Assessment Questionnaire and pain, fatigue, and global visual analog scales. *J Rheumatol* 2010;37:1024-8.
 32. 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;38:2461-5.
 33. Strand V, Crawford B, Singh J, Choy E, Smolen JS, Khanna D. Use of "spydergrams" to present and interpret SF-36 health-related quality of life data across rheumatic diseases. *Ann Rheum Dis* 2009;68:1800-4.
 34. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). *Value Health* 2008;11:1131-43.
 35. Ara R, Brazier J. Predicting the Short Form-6D preference-based index using the eight mean Short Form-36 health dimension scores: Estimating preference-based health-related utilities when patient level data are not available. *Value Health* 2009;12:346-53.
 36. Ware J, Kosinski M, Dewey JE. How to score version 2 of the SF-36 health survey. Lincoln, RI: QualityMetric Inc.; 2000.
 37. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates Inc.; 1988.
 38. Salaffi F, Carotti M, Gasparini S, Intorcchia M, Grassi W. The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: A comparison with a selected sample of healthy people. *Health Qual Life Outcomes* 2009;7:25.
 39. Kimball AB, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. *Am J Clin Dermatol* 2005; 6:383-92.
 40. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JY, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol* 2008;58:851-64.
 41. Reich A, Hrehorow E, Szepietowski JC. Pruritus is an important factor negatively influencing the well-being of psoriatic patients. *Acta Derm Venereol* 2010;90:257-63.
 42. Strand V, Hu A, Day R, Sloan V. Improved quality of life with apremilast (APR) in the treatment of psoriasis: Results from a phase IIb randomized controlled study [abstract P3337]. *J Am Acad Dermatol* 2011;64 Suppl 1:AB154.