Psoriatic arthritis is a chronic inflammatory disease of the joints that occurs in patients with psoriasis. Nonbiologic disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and leflunomide, and biologic DMARDs such as TNF antagonists and ustekinumab, have been used in the treatment of this disease. Apremilast is a novel therapy that inhibits phosphodiesterase 4 and increases intracellular cAMP levels. It modulates the expression of proinflammatory and anti-inflammatory mediators in favor of anti-inflammatory activity. One Phase II and four Phase III clinical trials showed significant clinical efficacy and a good safety profile of apremilast compared with placebo in patients with active psoriatic arthritis.

**Keywords:** apremilast • phosphodiesterase 4 • psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that produces structural joint damage. It occurs in 0.1–1% of general population, and approximately one-third of all patients suffering from psoriasis. In 20–30% of PsA, arthritis appears prior to skin manifestations [1–3]. The systemic and articular symptoms of this chronic inflammatory disease are related to inflammatory mediators such as TNF, IL-17, IL-23, IFNγ and IL-2. In the long term, PsA has a significant adverse impact on health-related quality of life and physical function [1,4–9].

CAMP is a second messenger responsible for intracellular signal transduction and cytokine gene transcription involved in a variety of cellular and immune responses. Protein kinases activated by cAMP favor gene transcription of TNF and IL-12. Therefore, cAMP is a modulator of inflammatory responses critical to maintain immune homeostasis. Intracellular concentrations of cAMP result from the balance between the activity of adenyl cyclases (synthesis) and phosphodiesterases (degradation). Several families of phosphodiesterases are known; eight are able to hydrolyze cAMP to AMP. Phosphodiesterase 4 (PDE4) is a predominant cAMP-specific phosphodiesterase in inflammatory cells. It is expressed in myeloid and lymphoid cells as dendritic cells, T cells, macrophages and monocytes. It is also expressed in keratinocytes, smooth muscle cells, chondrocytes and endothelial cells. Four different PDE4 subtypes (A, B, C and D) and more than 20 isoforms have been identified. Inhibition of PDE4 activity increases the intracellular concentration of cAMP and enhances the subsequent activation of protein kinases. The final effect is the modulation of the expression of a network of proinflammatory and anti-inflammatory mediators (TNF, IFNγ, IL-10, IL-2, IL-17, IL-23 and IL-12), resulting in favorable anti-inflammatory activity [10–12].

The aim of this article is to review the information regarding the new therapeutic option apremilast for the treatment of PsA, its mechanism of action, and its efficacy and safety in randomized clinical trials (RCTs).

**Overview of the market**

**Nonbiologic disease-modifying anti-rheumatic drugs**

In PsA, methotrexate is the most widely used therapy, although evidence for its effective-
ness is limited. In the MIPA trial, tender and swollen joint count, function measured using the Health Assessment Questionnaire (HAQ), Psoriasis Area and Severity Index criteria for 75% improvement (PASI75), the composite response measures as Psoriatic Arthritis Response Criteria (PsARC), the American College of Rheumatology criteria for 20% improvement (ACR20 response) and the 28 joints-based Disease Activity Score (DAS28) were not significant better in the methotrexate-treated group than in placebo-treated group [18]. This trial has some important drawbacks as high dropout rate or inclusion of patients with milder disease that limit the relevance of the conclusions [14]. Also, previous reports showed no significant improvement in joint counts in patients treated with methotrexate [15,16]. Nevertheless, some open-label studies and observational studies showed substantial improvements in skin and joint domains [22–24]. Data on leflunomide in PsA are scanty. In a RCT, leflunomide was more efficacious than placebo in the primary outcome PsARC response (58.9% in leflunomide-treated and 29.7% in placebo-treated; p < 0.0001), and in ACR20 response, joint count, HAQ-digital index (DI) change and PASI75 score [19]. Data on efficacy of cyclosporine are also limited. One RCT showed significant improvement in ACR50 response, ACR70 response and joint count [20]. Another RCT showed significant improvement in joint count and PASI score but not in function (HAQ-DI change) or pain scores. There is no evidence that cyclosporin reduces progression of radiographic damage [21]. Efficacy of sulfasalazine is unproved. Some studies found mild significant improvement in joint score or skin involvement [22–24] while others found no significant differences [25,26]. Overall, evidence of the efficacy of nonbiologic DMARDs in PsA in RCTs is limited. Nevertheless, they are used as first-line treatment based on their efficacy in psoriasis and rheumatoid arthritis [13,16,27–28]. Although leflunomide is approved by the EMA for the treatment of PsA, oral DMARDs including leflunomide are currently not approved by the US FDA.

TNF antagonists
Infliximab, etanercept, adalimumab, golimumab and certolizumab are used as second-line therapy in PsA refractory to treatment with nonbiologic DMARDs. They have demonstrated significant efficacy and an adequate safety profile in RCTs compared with placebo. TNF antagonists improve many domains of PsA including skin, joints, entheses and axial involvement. The five TNF antagonists have demonstrated efficacy in joint (ACR20 responses ranging from 52 to 65%) and skin domains (PASI75 responses ranging from 38 to 68%), function (HAQ-DI), quality of life, work productivity and inhibition of radiographic progression of joint damage. Infliximab, golimumab and certolizumab have demonstrated also efficacy in enthesitis and dactylitis, and golimumab and certolizumab in nail involvement [29–33]. All have a good safety profile with similar incidence of adverse events (AEs), although infections (over all upper respiratory infections), tuberculosis reactivation, injection site reaction and infusion reactions have been described.

Ustekinumab
Ustekinumab is a fully human monoclonal antibody that binds the p40 subunit of IL-12 and IL-23. It has been recently approved for PsA. Ustekinumab significantly improved signs and symptoms of active PsA in RCTs compared with placebo. Active PsA was defined as ≥3 swollen joints and ≥3 tender joints and either CRP ≥15 mg/l or morning stiffness for at least 45 min. Clinical trials have showed improvement in ACR20 response, DAS28, HAQ-DI, BASDAI and PASI75, and a good safety profile in active PsA [34,35]. In the SUMMIT1 trial, 615 PsA patients were randomly allocated to receive ustekinumab 45 mg, ustekinumab 90 mg or placebo at week 0, week 4, and every 12 weeks thereafter. In total, 42.4% of patients treated with ustekinumab 45 mg group, 49.5% of patients treated with ustekinumab 90 mg group and 22.8% of patients of the placebo group (p < 0.0001) achieved ACR20 response at week 24. ACR50 response, ACR70 response, PASI28, PASI75, BASDAI, dactylitis and HAQ-DI were also significantly better in ustekinumab groups than in placebo.

Introduction to apremilast
Apremilast (CC-10004, Chemical Abstracts Service [CAS] registry number 608141-41-9) is a specific inhibitor of PDE4 that regulates proinflammatory and anti-inflammatory cytokine production. Its chemical name is (S)-N-{2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1H-isoidol-4-yl}acetamide. It has a molecular weight of 460.5 Da.

Apremilast binds in a partially competitive manner to the catalytic site of PDE4, thereby blocking cAMP degradation and resulting in increased levels of cAMP. Higher intracellular cAMP levels activates protein kinase A, which phosphorylates the transcription factors CREB, CREM and ATF-1, and inhibits the transcriptional activity of NF-kB. This modulates monocytes, neutrophils and T-cell function, and subsequent cytokine and chemokine production. PDE4 inhibition reduces the expression of the proinflammatory cytokines TNFα, IFNγ, IL-17 and IL-23 and increases the toll-like receptor 4-induced production of the anti-
inflammatory IL-10 \[10,11\]. Therefore, apremilast has the ability to regulate the inflammatory response at more than one point along the inflammatory cascade (see Figure 1).

**Pharmacodynamics, Pharmacokinetics & Metabolism**

Apremilast has an IC\textsubscript{50} of approximately 0.074 μM \[10,11\]. The affinity constant \(K_i\) of apremilast for PDE4 is 68 nM. Major apremilast metabolites are at least 50-fold less active than apremilast with regard to their ability to inhibit PDE4 and TNF\(\alpha\). Metabolites present at trace levels in plasma do retain some PDE4 and TNF\(\alpha\) inhibition activity with IC\textsubscript{50} values similar to those of apremilast, but do not contribute significantly to pharmacodynamic activity.

In one study, the oral absorption of apremilast was relatively fast with \(T_{\text{max}}\) of 1.5 h and plasma half-life of approximately 7 h. A Phase II study showed clinically relevant concentrations of apremilast, in patients with severe plaque-type psoriasis, based on the C\textsubscript{max} after the 20 mg dose, that were in the range of 207.07 ng/ml (450 nM), and \(T_{\text{max}}\) of 2 h and half-life of 8.2 h \[36\].

Apremilast is extensively metabolized via multiple pathways. Metabolic clearance of apremilast is the major route of elimination, while nonenzymatic hydrolysis and excretion of unchanged drug are involved to a lesser extent. Apremilast is usually not detected in plasma beyond the 48 h postdose, whereas metabolites are detected out to 168 h, having a \(T_{\text{max}}\) of 1–5 h and half-life of approximately 50 h. More than 90% of an oral dose of apremilast is excreted within 96 h postdose with approximately 58 and 39% of the dose excreted in urine and feces, respectively \[37\].

**Clinical Efficacy in PsA**

Efficacy and safety of apremilast was evaluated in patients with active PsA in spite of previous DMARD therapy compared with placebo through one Phase II study and four Phase III studies. Active PsA was defined as \(\geq 3\) swollen joints and \(\geq 3\) tender joints, at the time of screening and baseline. PALACE 1, 2, 3 and 4 are Phase III multicenter, double-blind, placebo-controlled, parallel-group studies with two active treatment groups (apremilast 20 or 30 mg orally twice a day). The primary end point of the PALACE 1, 2, 3 and 4 studies was the ACR20 response at week 16. Secondary end points included joint count, dactylitis, physical function (measured as HAQ-DI), skin involvement (PASI75) and patient-reported outcomes.

**Phase II Study (NCT00456092)**

A Phase II \[38,39\], multicenter, randomized, double-blind, placebo-controlled study included 204 patients...
with active PsA followed during 12 weeks (blind phase) and a 12-week extension phase. Patients were randomized to receive apremilast 20 mg twice per day, apremilast 40 mg once a day or placebo (stratified by baseline methotrexate use). In the long-term extension phase, the placebo group was re-randomized to one of the two doses of apremilast. At week 12, 43.5% of patients receiving apremilast 20 mg twice per day (p < 0.001) and 35.8% of those receiving 40 mg once per day (p = 0.002) achieved an ACR20 response, compared with 11.8% of those receiving placebo. At the end of the treatment extension phase (week 24), >40% of patients in the three groups treated with apremilast achieved an ACR20 response. A significantly greater proportion of patients receiving apremilast 20 mg twice per day achieved an ACR50 level of response at week 12 when compared with patients receiving placebo (17.4 vs 2.9%; p = 0.012). ACR50 response for patients receiving apremilast 40 mg once per day and ACR70 response were not statistically significant compared with those receiving placebo. The percentage of patients experiencing an improvement in the PsARC at week 12 was significantly higher in those receiving apremilast (p < 0.001) than those receiving placebo. Apremilast showed statistically significant and clinically meaningful improvements in health-related quality of life, pain scores and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores.

PALACE-1 (NCT01172938)
In PALACE-1 [40–43], 504 patients with active PsA were randomized to placebo, apremilast 20 mg twice per day or apremilast 30 mg twice per day through week 16 (stratified by baseline DMARD use). Patients with no improvement ≥20% in swollen and tender counts were considered nonresponders at week 16 and were required to enter the protocol-defined early escape; those on placebo were re-randomized to one of the apremilast doses and those on apremilast remained on their initial dose. At week 24, all remaining placebo patients were re-randomized to receive apremilast 20 or 30 mg through week 52. At week 16, there was significant improvement in ACR20 response in apremilast 20 mg (31.3%; p = 0.014) and apremilast 30 mg (41.0%; p < 0.0001) groups compared with placebo (19.4%). At week 16, median percentage reductions in swollen joint count were significantly higher in those receiving apremilast 20 mg (-39.3%; p = 0.0035) and apremilast 30 mg (-50.0%; p < 0.0001) than in those receiving placebo (-16.7%). Median percentage reductions in tender joint counts were significantly higher in those receiving apremilast 20 mg (-23.3%; p = 0.0007) and apremilast 30 mg (-42.9%; p < 0.0001) than in those receiving placebo (-7.0%). Significant improvement was observed also at week 24 in ACR50 and ACR70 response, HAQ-DI, DAS28, European League Against Rheumatism (EULAR) response, enthesitis, dactylitis, PsARC response, PASI50, PASI75 and SF-36 score. At week 52 improvements were sustained with 63.0% of patients receiving apremilast 20 mg twice a day and 54.6% of those receiving apremilast 30 mg twice a day achieved ACR20 response.

PALACE-2 (NCT01212757)
In PALACE-2 [41,44], 484 patients with active PsA were randomized to placebo, apremilast 20 mg and apremilast 30 mg orally twice per day (stratified by baseline DMARD use). Patients whose swollen and tender joint counts had not improved by ≥20% were considered nonresponders at week 16 and required to enter the protocol-defined early escape; those on placebo were re-randomized to one of the apremilast doses and those on apremilast remained on their initial dose. At week 24, all remaining placebo patients were re-randomized to receive apremilast 20 or 30 mg through week 52. At week 16, there was significantly greater proportion of patients achieved an ACR20 response in apremilast 20 mg (38.4%; p = 0.0002) and apremilast 30 mg (34.4%; p = 0.0024) than placebo (19.5%). At week 16, median percentage reductions in swollen joint count were significantly higher in those receiving apremilast 20 mg (-36.2%; p = 0.0001) and apremilast 30 mg (-33.3%; p = 0.0015) than in those receiving placebo (-33.3%). Median percentage reductions in tender joint counts were significantly higher in those receiving apremilast 20 mg (-36.2%; p < 0.0001) and apremilast 30 mg (-33.3%; p = 0.0015) than in those receiving placebo (-8.7%). Improvements in ACR20 response (52.9% for apremilast 20 mg and 52.6% for apremilast 30 mg), HAQ-DI mean change (-0.192 for apremilast 20 mg and -0.330 for apremilast 30 mg), PASI75 (27.1% for apremilast 20 mg and 39.3% for apremilast 30 mg), enthesitis, dactylitis and SF-36 were sustained through 52 weeks.

PALACE-3 (NCT01212770)
In PALACE-3 [41,45], 505 patients with active PsA, and at least one psoriatic lesion >2 cm at baseline despite prior DMARDs and/or biologics were randomized to placebo, apremilast 20 mg and apremilast 30 mg orally twice per day (stratified by baseline DMARD use). Patients whose swollen and tender joint counts had not improved by ≥20% were considered nonresponders at week 16 and required to enter the protocol-defined early escape; those on placebo were re-randomized to one of the apremilast doses and those on apremilast remained on their initial dose. At week 24, all remaining placebo patients were re-randomized to receive apremilast 20 or 30 mg through week 52. At week 16, there was significant improvement in ACR20 response in apremilast 20 mg (31.3%; p = 0.014) and apremilast 30 mg (41.0%; p < 0.0001) groups compared with placebo (19.4%). At week 16, median percentage reductions in swollen joint count were significantly higher in those receiving apremilast 20 mg (-39.3%; p = 0.0035) and apremilast 30 mg (-50.0%; p < 0.0001) than in those receiving placebo (-16.7%). Median percentage reductions in tender joint counts were significantly higher in those receiving apremilast 20 mg (-23.3%; p = 0.0007) and apremilast 30 mg (-42.9%; p < 0.0001) than in those receiving placebo (-7.0%). Significant improvement was observed also at week 24 in ACR50 and ACR70 response, HAQ-DI, DAS28, European League Against Rheumatism (EULAR) response, enthesitis, dactylitis, PsARC response, PASI50, PASI75 and SF-36 score. At week 52 improvements were sustained with 63.0% of patients receiving apremilast 20 mg twice a day and 54.6% of those receiving apremilast 30 mg twice a day achieved ACR20 response.
patients were re-randomized to receive apremilast 20 or 30 mg through week 52. At week 16, a significantly greater proportion of patients achieved an ACR20 response in apremilast 20 mg (29.5%; p = 0.0235) and apremilast 30 mg (42.8%; p < 0.0001) than in placebo (18.9%). At week 16, median percentage reductions in swollen joint count were significantly higher in those receiving apremilast 20 mg (-36.4%; p = 0.0301) and apremilast 30 mg (-50.0%; p = 0.0014) than in those receiving placebo (-20.0%). Median percentage reductions in tender joint counts were significantly higher in those receiving apremilast 20 mg (-30.0%; p = 0.0001) and in apremilast 30 mg (-43.7%; p < 0.0001) than in those receiving placebo (-8.6%). Improvements in ACR20 response (56.0% for apremilast 20 mg and 63.0% for apremilast 30 mg), HAQ-DI mean change (-0.332 for apremilast 20 mg and -0.350 for apremilast 30 mg), PASI75 (28.6% for apremilast 20 mg and 39.1% for apremilast 30 mg), enthesitis and dactylitis were sustained through 52 weeks.

PALACE-4 (NCT01307423)
In PALACE-4 [46], 527 patients with active PsA were randomized to receive placebo, apremilast 20 mg or apremilast 30 mg orally twice per day. Previous treatment with DMARDs was not allowed. Patients whose swollen and tender joint counts had not improved by ≥20% were considered nonresponders at week 16 and required to enter the protocol-defined early escape; those on placebo were re-randomized to one of the apremilast doses and those on apremilast remained on their initial dose. At week 24, all remaining placebo patients were re-randomized to receive apremilast 20 or 30 mg through week 52. At week 16, a significantly greater proportion of patients achieved an ACR20 response in apremilast 20 mg (29.2%; p = 0.0076) and apremilast 30 mg (32.3%; p < 0.0011) than in placebo (16.9%). Improvements in ACR20 response (53% for apremilast 20 mg and 59% for apremilast 30 mg), ACR50 response (27% for apremilast 20 mg and 32% for apremilast 30 mg), HAQ-DI mean change (-0.319 for apremilast 20 mg and -0.392 for apremilast 30 mg), PASI, enthesitis and dactylitis were sustained through 52 weeks.

Safety & tolerability
Treatment with apremilast was generally well tolerated in patients with active PsA in all studies (Phase II and III). In the Phase II study [38], the percentages of patients affected by ≥1 AE were similar in apremilast and placebo groups (80.9, 85.5 and 86.6 for placebo, apremilast 20 mg twice a day and apremilast 40 mg once a day, respectively). Percentages of patients suffering ≥1 serious AE were 10.9, 6.8 and 8.6% for placebo, apremilast 20 mg twice a day and apremilast 40 mg once a day, respectively. The most frequently reported AEs were diarrhea, headache, nausea, fatigue and nasopharyngitis. These AEs were mild or moderate in severity. No opportunistic infections, life-threatening disabling events or deaths were reported. Three malignancies were diagnosed; one oral neoplasm, one prostate neoplasm and one squamous cell carcinoma of the skin.

In the three Phase III clinical trials and 52-week long-term extension phases, apremilast was also generally well tolerated [47]. Patients treated with apremilast had 1535.4 patients-years of exposure. During the controlled phase (0–24 weeks), ≥1 AE was observed in 61.5% of patients treated with apremilast 20 mg, 60.8% with apremilast 30 mg, and 47.5% of patients placebo-treated. Percentage of patients suffering ≥1 severe AE effects were 3.8, 3.2 and 6.4% for placebo, apremilast 20 mg twice a day and apremilast 30 mg twice a day, respectively. During the treatment long-term phase (24–52 weeks) ≥1 AE effects were observed in 72.8% of patients treated with apremilast 20 mg and 74.1% of those treated with apremilast 30 mg; percentage of patients suffering ≥1 severe AE were 6.7 and 8.3% for apremilast 20 mg twice a day and 30 mg twice a day, respectively. Most frequent AEs were diarrhea (14.3%), nausea (12.6%), headache (10.1%), urticaria (10.3%) and nasopharyngitis (7.4%). Most AEs were mild or moderate in severity. Diarrhea, nausea and headache were dose-dependent, occurring primarily in first 2 weeks of treatment and frequently resolved within a month despite continued treatment. This is in contrast with early PDE4 inhibitors that failed in clinical trials due to the high prevalence of nausea and emesis [48]. One death occurred in an apremilast group due to multiorgan failure suspected to be nontreatment-related. Serious infections, opportunistic infections and malignancies were comparable to the placebo group. No cases of tuberculosis were observed. No clinically significant effects on laboratory parameters were reported. Most of the abnormal laboratory changes were similar between apremilast and placebo treated patients. They were mild, transient and asymptomatic.

Conclusion
Apremilast is a novel oral PDE4 inhibitor drug that regulates gene transcription of proinflammatory and anti-inflammatory cytokines. Apremilast decreases the proinflammatory cytokines TNFα, IFNγ, IL-17 or IL-23 and increases levels of the anti-inflammatory cytokine IL-10 under certain conditions. RCTs showed significant improvement in ACR20 response, tender and swollen joint count, dactylitis, enthesitis,
HAQ-DI change and PASI75 at week 16 with sustained efficacy up to week 52. Proportion of patients achieved an ACR20 response in apremilast RCTs seems numerically lower than in TNF-antagonist RCTs. However, no direct comparisons derived from head-to-head analyses are available. Future studies should assess the efficacy of apremilast compared with TNF antagonists and other biologics. Apremilast has a good safety profile and is generally well tolerated. AEs of mild or moderate diarrhea, headache, nausea, fatigue or nasopharyngitis occurred in patients treated with apremilast. In summary, apremilast seems numerically lower than in TNF-antagonist RCTs. However, no direct comparisons derived from head-to-head analyses are available. Future studies should assess the efficacy of apremilast compared with TNF antagonists and other biologics. Apremilast has a good safety profile and is generally well tolerated. AEs of mild or moderate diarrhea, headache, nausea, fatigue or nasopharyngitis occurred in patients treated with apremilast.

Company review disclosure
In addition to the peer-review process, with the authors consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made at the discretion of the author(s) and based on scientific or editorial merit only.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Executive summary

Mechanism of action
• Inhibition of phosphodiesterase 4 (PDE4) blocks cAMP degradation resulting in increased levels of cAMP and regulation of the inflammatory response, reduction of the expression of proinflammatory cytokines such as TNF or IL-23, and increased anti-inflammatory cytokines such as IL-10.

Pharmacokinetic properties
• Apremilast has a half-life of 7–8.2 h and Tmax of 1.5–2 h.
• The affinity constant Ki of apremilast for PDE4 is 68 nM.
• Major metabolites are inactive or 50-fold less active than apremilast.

Clinical efficacy
• Apremilast significantly reduces American College of Rheumatology criteria for 20% improvement response and other secondary outcomes such as swollen joint count, tender joint count, Health Assessment Questionnaire-Di mean change, enthesitis, dactylitis and Psoriasis Area and Severity Index criteria for 75% improvement.
• Efficacy is sustained over 52 weeks.

Safety & tolerability
• Apremilast is generally safe and well tolerated in clinical trials.
• The most frequent adverse events are diarrhea, nausea, headache and nasopharyngitis.

Dosage & administration
• In Phase III clinical trials apremilast was administered at dose of 20–30 mg twice a day orally.

References
9 Fiocco U EA, Sfriso P, Oliviero F, Lunardi F, Calabrese F. Blockade of intra-articular TNF in peripheral


14 Dousa G, Methotrexate in peripheral spondyloarthritis including psoriatic arthritis: a need for further evaluation. Rheumatology (Oxf) 51(8), 1343–1344 (2012).


