EXPERT OPINION

Apremilast as a treatment for psoriasis

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Introduction: Psoriasis is a common skin disorder characterized by chronic inflammatory lesions that are frequently vexing for patients and difficult for physicians to treat. Although multiple therapeutic options are available, all have limitations. Topical preparations have issues with patient adherence, as compared to oral routes of administration. Currently available oral medications, such as methotrexate, possess unfavorable toxicity profiles that limit use. There is a large unmet need for an effective, safe oral treatment for psoriasis. Apremilast is an oral medication that inhibits the activity of multiple inflammatory markers involved in the pathogenesis of psoriasis.

Areas covered: The present review article presents the pharmacokinetic properties of apremilast, as well as available preliminary pre-clinical and clinical trial data, and gives an overview of its safety and efficacy.

Expert opinion: Apremilast has been well tolerated in phase I and II clinical trials. It has favorable safety and toxicity profiles at doses that are also effective for the treatment of plaque psoriasis. Phase III clinical trials are currently underway and will better elucidate appropriate dosing of apremilast and further illuminate its side effect profile. In future studies, a comparison of apremilast to other psoriasis medications administered through different routes would be beneficial, to document whether patient adherence is better with an oral medication. Depending on the price of the agent, efficacy and perhaps most importantly its safety profile, apremilast may fill a key need as a safe, first-line oral treatment for patients with psoriasis.

Keywords: cytokines, PDE 4, phosphodiesterase type 4, psoriasis, TNF-alpha

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1. Introduction

Psoriasis is a chronic inflammatory disease, which affects 2–3% of American adults [1-3]. It is the most prevalent autoimmune disease in the US and adversely affects health due to its effects on psychological and emotional quality of life as well as links to comorbidites such as hypertension, metabolic syndrome and a heightened incidence of smoking [4-8]. The diagnosis is made clinically with the condition being characterized by well-demarcated erythematous plaques with a fine silvery scale [9]. There are several different subtypes based on morphologic appearance. Those subtypes are plaque, guttate, pustular, inverse and erythrodermic. Plaque psoriasis is diagnosed in 80–90% of patients and is commonly found in the scalp, trunk, buttocks and extensor surfaces of the limbs, but may occur on the face, hands, feet and genitalia [10].

The pathogenesis involves a complex set of interactions between environmental, immunologic and genetic factors [9]. The plaques in psoriasis are a result of epidermal hyperproliferation, whereas the erythema is caused by vascular proliferation and inflammation. Activated T cells and antigen-presenting cells cause the release of a variety of chemokines and cytokines, which are responsible for the hyperproliferation of

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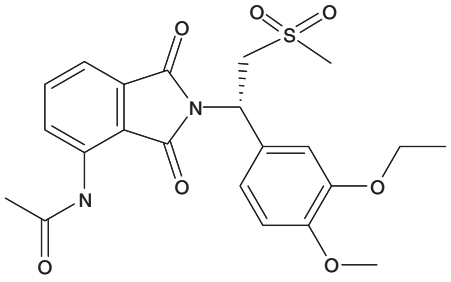
Box 1. Drug summary.

Drug name	Apremilast
Phase	Phase III
Indication	Psoriasis; psoriatic arthritis
Pharmacology description	Cyclic AMP phosphodiesterase-4 (PDE4) inhibitor
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	PSOR-005; ESTEEM 1

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keratinocytes resulting in a thickened epidermis [2]. Because of the multiple factors involved in the pathogenesis of psoriasis, there are many targets for drug therapy.

1.1 Current psoriasis treatment guidelines

Treatment of patients with psoriasis depends on the severity of the condition. The National Psoriasis Foundation characterizes severity of psoriasis based on the proportion of body surface area (BSA) affected [4]. Mild disease is defined as less than 3 or 5% BSA affected, whereas 3 or 5–10% BSA involvement is consistent with moderate disease and greater than 10% or involvement of the face, genitals, hands, feet, scalp and/or intertriginous areas affecting quality of life, is considered severe disease [1].

Most cases of psoriasis are categorized as mild to moderate disease and are highly responsive to topical therapy alone, whereas patients with moderate to severe disease require systemic medications in addition to topical therapy [11-13]. Although it is well recognized that topical therapeutics confer the best outcomes in mild to moderate psoriasis, Del Rosso found topical treatment best when lesions involve less than 20% of BSA [14-16].

A variety of topical therapies exist such as corticosteroids, vitamin D analogs, tazarotene, phototherapy and combination treatment regimens making use thereof [11,15,17-22]. Novel topical therapies are currently in development for psoriasis, including topical inhibitors of Janus Kinase, phosphodiesterase, the T-cell response and a topical non-steroidal derived from metabolites of bacterial symbionts of nematodes [23]. Although topical medications are the mainstay treatment option, especially for mild disease, compliance, patient satisfaction and injurious or unwanted consequences impede their usefulness, and are additionally limited by scant progress over the years in development of these topical agents [22-29].

Systemic options include oral agents – methotrexate, cyclosporine and retinoids such as acitretin – and injectable agents such as tumor necrosis factor-alpha (TNF-α) antagonists like adalimumab, etanercept and infliximab, as well as other biologics [1,4]. For some, the biologic agents revolutionized the treatment of moderate to severe psoriasis, but for others response rates were poor or incomplete with questionable safety and concerns over infection or malignancy. Acitretin is the only licensed oral retinoid available for the treatment of psoriasis but has decreased efficacy compared to systemic agents with approximately only 25% of patients achieving a PASI-75 response when used as monotherapy [30]. Therefore, an unmet need exists for a safe, effective oral medication for patients with moderate to severe psoriasis (particularly for the more moderate end of that spectrum).

2. Apremilast

Apremilast (**Box 1**) is an oral anti-inflammatory medication that specifically inhibits the activity of cyclic AMP phosphodiesterase-4 (PDE4) and the production of TNF-α, interleukin (IL)-8, IL-12, IL-23, chemokine CXC motifs CXCL9, CXCL10 and interferon (IFN)-γ *in vitro*, all inflammatory markers involved in the pathogenesis of psoriasis [31-35]. Four genes encode over 20 distinct isoforms of PDE4, which specifically hydrolyze the second messenger, cyclic adenosine monophosphate (cAMP) into AMP [36,37]. Different cell types express specific complements of PDE4 isoforms, which are each targeted to distinct signaling complexes [38,39]. Apremilast inhibits all PDE4 isoforms similarly, thereby increasing cAMP levels in cells and triggering signaling events controlled by cAMP [40]. The second messenger, cAMP, is involved in intracellular signal transduction pathways such as those regulating survival, proliferation, and inflammation [41]. Exchange protein

directly activated by cAMP (Epac) is a cAMP-activated guanine nucleotide exchange factor for Rap GTPases and therefore a novel cAMP effector in addition to protein kinase A that has been shown to regulate the inflammatory cascade through PI3K, Akt and GSK3-beta signaling [42-44]. The activation of protein kinase-A by cAMP allows this kinase to phosphorylate a variety of target proteins including the transcription factor CREB (cAMP response element binding protein), which alters the transcription of various genes, including those for IL-10 and IL-6, which play a key role in regulatory inflammation processes. Elevated cAMP inhibits nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB)-dependent transcription. Some cytokines that are NF-κB-dependent include TNF-α, IFN-γ, IL-12 and IL-23 [35]. TNF-α is a cytokine involved in inflammation in psoriasis, rheumatoid arthritis and inflammatory bowel disease [34]. The anti-inflammatory effects of apremilast are currently under investigation for many inflammatory conditions including psoriasis, psoriatic arthritis, ankylosing spondylitis, sarcoidosis, inflammatory bowel disease and rheumatoid arthritis [45-48]. This paper will focus on the use of apremilast in the treatment of psoriasis.

2.1 Preclinical studies

A study by Schafer *et al.* sought out to explore the action of apremilast. Normal human skin was first transplanted onto beige-colored severe combined immune-deficient (SCID) mice. Four weeks after the graft, the skin was triggered with natural killer (NK) cells from patients with psoriasis. Two weeks after the NK cell injections, the mice were divided into three groups of seven and given oral apremilast, cyclosporine or placebo. Four out of seven in the apremilast group underwent partial or complete recovery of histological features of psoriasis versus three out of seven in the cyclosporine group. Apremilast was found to be as effective in reducing the thickness of the epidermis as cyclosporine. Decreases in TNF-α, intracellular adhesion molecule one (ICAM-1) and human leukocyte antigen DR (HLA-DR) were found to be similar in both treatment groups in comparison to the control group [35].

2.2 Pharmacokinetics

Gottlieb *et al.* studied the pharmokinetics of 20 mg of apremilast given to patients for a period of 29 days and found it to have a mean half-life ($t_{1/2}$) of 8.2 hours, area under the curve at 24 hours (AUC_{24}) of 1799 ng·h/mL, maximum concentration in serum (T_{max}) at 2 hours, bioavailability (CL/F) of 10.4 L/h and volume of distribution (Vz/F) of 128 L [32]. A mean steady-state peak serum concentration (C_{max}) was found to be 207 ng/ml (450 nM). At this concentration, apremilast would inhibit about 70% of the TNF-α produced by lipopolysaccharide (LPS)-induced peripheral blood mononuclear cells (PBMC) [35]. Hoffman *et al.* also studied the pharmacokinetics in six healthy volunteers after a single dose of 20 mg of apremilast was given and found it to have a T_{max} of 1.5 hours, half-life of 6.8 hours, C_{max} of 333 ngEq/ml and an AUC of 1913 ngEq/mL [33]. Khobzaoui *et al.* describe apremilast as having a T_{max} of 1 hour after a 20 mg dose and 2 hours after a 10 mg dose and a $t_{1/2}$ of 5 hours. C_{max} was found to be 0.5 μg/ml after a dose of 20 mg [47]. The pharmacokinetics data are summarized (**Table 1**).

2.3 Phase I trials

A double-blind placebo controlled phase I study was done on 26 healthy volunteers divided into three groups and given placebo, 10 mg of apremilast or 20 mg of apremilast. Overall, apremilast was well tolerated. Out of the 12 subjects receiving apremilast, three reported headaches, and five reported symptoms of dizziness, dry skin and back pain [47].

The study by Hoffman *et al.* examined the pharmacokinetics of apremilast in an open-label, inpatient, single-dose study done on six healthy male volunteers between the ages of 19 and 55. Each subject fasted for 8 hours before and 4 hours after a single 20 mg dose of apremilast was given in an oral suspension with distilled water. Urine and feces samples were collected for 9 days after dose administration and blood was collected up to 7 days after taking the single dose of apremilast. This study found that apremilast was rapidly absorbed with plasma T_{max} values ≤ 2 hours. Only 4% of the dose was found unchanged in the feces, suggesting that most of the dose of apremilast was absorbed. Half-lives of apremilast and its metabolites ranged between 7 and 16 hours with the metabolites having longer half-lives than apremilast. The predominant metabolite was M12 (O-desmethyl apremilast glucuronide). Other metabolites were formed via pathways including O-demethylation, O-deethylation, N-deacetylation, hydrolysis, hydroxylation and glucuronidation. Most of the metabolites were tested for their PDE4 and TNF-α inhibitory activities and all were found to have greater than 50-fold less activity than apremilast except M7 and M17. However, these two metabolites were present in concentrations < 2% compared with apremilast. Clearance of apremilast is thought to be through multiple pathways including cytochrome p450 CYP3A4-mediated metabolism, nonenzymatic hydrolysis, non-CYP3A4-mediated metabolism and elimination of unchanged drug [33].

2.3.1 Phase II trials

Gottlieb *et al.* evaluated the efficacy of apremilast in patients with severe plaque psoriasis. This small study was an open-label, single arm study done at three different centers in the US. Nineteen patients between the ages of 22 and 59 were enrolled in the study and given 20 mg of apremilast once daily for 29 days. There were three phases in this study: a 28-day screening phase, 29-day treatment phase and a 28-day follow-up phase. Epidermal thickness was quantified by obtaining 6 mm skin punch biopsies at days 1, 15 and 29, with subsequent examination of sections under light microscopy, averaging epidermal thickness in three 10× fields. The primary endpoint was greater than or equal to a 20% decrease in the thickness of the epidermis after 29 days

Table 1. Pharmacokinetics of Apremilast.

	Gottlieb *et al.* [32]	Hoffman *et al.* [33]	Khobzaoui *et al.* [47]
Half-life (hours)	8.2	6.8	5
T_{max} (hours)	2	1.5	1
AUC_{24} (ng·h/mL)	1799	–	–
$AUC_{0\text{-}t}$ (ng·h/mL)	–	1913	–
C_{max} (ng/ml)	207	333	500

of treatment. Secondary endpoints included changes from baseline in the psoriasis area and severity index (PASI), static Physician's Global Assessment (sPGA) and BSA. Two patients withdrew early and four did not have a complete set of biopsy results from either days 1, 15 and/or 29. Eight of the 15 patients with skin biopsies that were fully analyzed achieved the primary endpoint and were considered responders. Among the responders, CD3+, CD83+ and CD11c+ cells were reduced within the epidermis and dermis. TNF-α production was also found to be reduced as determined by *ex vivo* blood samples taken after the first and last dose. The mRNA gene expression of the inflammatory marker nitric oxide synthase decreased. Activated nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1) often facilitate transcription of numerous genes, including nitric oxide synthase, resulting in inflammation. The acidic cytokeratin, K16+, which has been found to facilitate cell proliferation, also decreased [49]. Overall, 14 of the 19 patients enrolled in the study demonstrated improvement based on the PASI. Nine of 17 patients assessed on day 29 had an improvement in at least one category in the sPGA in comparison to baseline. Ten out of 17 patients assessed had less BSA involvement relative to baseline. Apremilast was well tolerated with few side effects including nausea, dizziness, headache and diarrhea. No patients discontinued the study due to adverse events. None of the 18 patients assessed during the 28-day follow-up phase of the study had a flare in the psoriasis but seven relapsed and required anti-psoriasis medication [32].

Papp *et al.* conducted a randomized, double-blind, multicenter, placebo-controlled dose comparison study of 260 patients with moderate to severe plaque psoriasis to test the safety and efficacy of apremilast. Patients were divided into three groups, treated for 12 weeks and observed in a follow-up phase of 4 weeks. One group received 20 mg of apremilast once a day for 12 weeks, another group received 20 mg of apremilast twice daily for 12 weeks and the third group received a placebo for 12 weeks. The primary endpoint was a PASI-75 by week 12 in comparison to baseline. A PASI-75 response denotes the percentage of patients with at least 75% improvement in their PASI score, and is the currently recognized benchmark endpoint used in clinical trials [50]. Twenty-four percent of patients receiving 20 mg twice daily achieved the primary endpoint versus 10% of patients in the placebo group (P = .023). No serious adverse effects were reported in this study. In the follow-up period, no subjects in the 20 mg twice-daily groups had a flare of their psoriasis symptoms. Overall, this study showed that apremilast was well tolerated and safe for the treatment of psoriasis [51,52].

Papp *et al.* recently published data on a phase IIb, 352-patient, multi-center study where patients received 10 mg, 20 mg or 30 mg of apremilast twice per day (BID) or placebo. Forty-one percent of patients treated with 30 mg of oral apremilast BID achieved PASI-75 after 16 weeks ($p < 0.001$) compared to the 5.7% receiving placebo. A dose-dependent effect was noted where 29% of patients receiving 20 mg BID of apremilast achieved a PASI-75 ($p < 0.001$), whereas 11% of patients receiving 10 mg BID of apremilast achieved a PASI-75. Adverse events were mild to moderate and included headache (32% of patients in the 30 mg BID apremilast arm versus 14% in the placebo group), nausea (18% versus 8%, respectively), upper respiratory tract infection (16% versus 6%, respectively) and diarrhea (14% versus 5%, respectively). No serious adverse events were linked to apremilast. Overall infections were 48% with 30 mg BID compared to 33% in the placebo group, with 1% of patients in both the 30 mg BID apremilast and placebo arms discontinuing treatment due to infection. In total, discontinuations due to adverse events were 14% for the 30 mg BID apremilast arm and 6% for placebo [53]. **Table 2** compares the features of selected phase II clinical trials.

There are seven ongoing phase 2 trials (**Table 3**) with no publishable results at this time. Six of the trials focus on the treatment of plaque psoriasis and one study follows the treatment of psoriatic arthritis. Two of the studies only have one treatment arm, focusing on primary outcomes of the safety and tolerability of apremilast. The other five studies compare variable doses of apremilast taken either once or twice a day with a placebo. Primary outcomes vary from PASI-75 from baseline, safety and efficacy [54].

2.3.2 *Phase III trials*

Currently, there are two ongoing phase III trials exploring the effects of apremilast on patients with psoriasis (**Table 4**). All studies are active with no results published at this time. ESTEEM 1 and ESTEEM 2 are assessing the efficacy of apremilast in the treatment of moderate to severe plaque psoriasis. The primary outcome being measured is achieving PASI-75 compared to baseline after 16 weeks of treatment of 30 mg of apremilast twice daily or placebo, with subsequent placebo-crossover and randomized withdrawal phases [54].

2.4 Safety

Phase I and phase II studies have shown that apremilast has been well tolerated with few side effects. The most common side effects reported are headache, nausea and pharyngitis or upper respiratory infection [32,47,53]. Results from phase III trials will give a better picture of the side effect profile of apremilast. Common side effects are summarized (**Table 5**).

Table 2. Summary of phase II clinical trial results from studies by Papp.

Papp *et al.* [53]		Papp *et al.* [51]	
Total number enrolled	352	Total number enrolled	260
Dose	10 mg once daily, 20 mg twice daily, 30 mg twice daily	Dose	20 mg once daily or 20 mg twice daily depending on group
Placebo group?	Yes	Placebo group?	Yes
Primary end point	PASI-75	Primary end point	PASI-75*
Duration of treatment	16 weeks	Duration of treatment	12 weeks
Follow-up	28 days	Follow-up	28 days
Percentage of 30 mg BID group achieving primary endpoint	41%	Percentage of 20 mg BID group achieving primary endpoint	24%
Percentage of placebo group achieving primary endpoint	5.7%	Percentage of placebo group achieving primary endpoint	10%
Percentage reporting adverse event of headache in 30 mg BID group	32%	Number with relapse at follow-up	0
Percentage reporting adverse event of headache in placebo group	14%	Percentage reporting adverse event in 20 mg BID group	54%
		Percentage reporting adverse event in placebo group	60%

*Defined as the percentage of patients with at least 75% improvement in their psoriasis area severity index (PASI) score, where PASI determines the severity of psoriasis by evaluation of erythema, induration, desquamation and body surface area involvement, and is scored from 0 (no disease) to 72 (maximum disease).

Table 3. Summary of ongoing phase II clinical trial results [32] (BID: twice daily).

NCT number	Condition	Acronym	Intervention	Sponsor	Primary endpoints
NCT00773734	Moderate to servere plaque psoriasis	PSOR-005 [53]	10 mg BID, 20 mg BID, 30 mg BID vs placebo	Celgene Corp.	PASI-75 at week 16
NCT01130116	Moderate to servere plaque psoriasis	PSOR-005LTE	20 mg BID, 30 mg BID vs placebo	Celgene Corp.	Long-term safety extension of PSOR-005E
NCT00953875	Moderate to servere plaque psoriasis	PSOR-005E	10 mg BID, 20 mg BID, 30 mg BID	Celgene Corp.	Clinical safety of up to 48 weeks therapy
NCT00521339	Recalcitrant psoriasis	PSOR-004	20 mg BID; 20 mg BID or 30 mg BID in optional treatment extension period	Celgene Corp.	Safety and tolerability of apremilast BID for 12 weeks
NCT01200264	Plaque psoriasis		30 mg BID	Duke University	Safety and efficacy of apremilast at 24 weeks in patients who have failed 1 course of biologic therapy
NCT00606450	Moderate to servere plaque psoriasis	PSOR-003 [51]	20 mg QD, 20 mg BID vs placebo	Celgene Corp.	PASI-75 at week 12
NCT00604682	Severe plaque psoriasis	PSOR-001	20 mg QD	Celgene Corp.	Pharmacodynamic effect of apremilast taken for 29 days

Because apremilast may be metabolized through multiple pathways including cytochrome p450 CYP3A4-mediated metabolism, there is potential for drug–drug interaction. A similar selective PDE4 inhibitor, roflumilast, which, as Daxas®, has received restricted approval for use in treating severe chronic obstructive pulmonary disease (COPD) and is dependent upon CYP3A4 for degradation and, in this instance, for formation of the N-oxide, which provides a more potent PDE4 inhibitor. Both drug inducers and inhibitors were found to affect the serum concentration of roflumilast and subsequent bioavailability [55].

Table 4. Summary of phase III clinical trial results [54] (BID: twice daily).

NCT number	Condition	Acronym	Intervention	Sponsor	Primary endpoint
NCT01194219	Moderate to severe plaque psoriasis	ESTEEM 1	30 mg BID vs placebo	Celgene Corp.	PASI-75 at week 16
NCT01232283	Moderate to severe plaque psoriasis	ESTEEM 2	30 mg BID vs placebo	Celgene Corp.	PASI-75 at week 16

Table 5. Common side effects of Apremilast reported per study.

	Gottlieb *et al.* [32]	Khobzaoui [47]	Papp [53]
Total number of subjects	17	12	352
Total number with side effect:	14	8	> 5%
Headache	5	3	32%‡
Nausea	3	0	18%‡
Dizziness	2	5*	0
Conversion to + ANA	2	0	0
Pharyngitis/URI	1	0	16%‡
Diarrhea	0	0	14%‡
Non-accidental injury	1	0	0
Dry skin	0	5*	0
Back pain	0	5*	0

*Dizziness, dry skin, and back pain experienced in the same patient.
‡Reported side effect in those treated with 30 mg BID dose.

3. Expert opinion

Although there are multiple effective psoriasis therapeutic options to choose from, many are associated with several disadvantages. Although topical corticosteroids are recognized as a mainstay treatment option for mild to moderate or localized psoriasis, a myriad of harmful outcomes may limit their use [16,22]. Local skin reactions such as striae, epidermal atrophy, hypopigmentation, acneiform eruption, as well as systemic side effects like hypothalamic–pituitary–adrenal axis suppression have been documented [12,14,16,22,56,57]. Adherence to topical medications is a barrier to effective treatment [24-26]. Patients tend to find topical treatment options unpleasant and time consuming, which could limit their usefulness for treating extensive disease; thus, phototherapy or systemic medications are generally required for moderate to severe psoriasis [27-29].

Biologics for psoriasis are given through intramuscular or subcutaneous injection or intravenous infusion, something most patients would like to avoid if they have not previously experienced injection treatment [58,59]. Methotrexate and cyclosporine represent oral medication for psoriasis, but have many limitations due to their hematologic, hepatic, pulmonary, and renal toxicities. Methotrexate requires folate supplementation and close follow-up monitoring such as liver function testing as well as complete blood counts [60]. Cyclosporine, due to its nephrotoxicity, can only be used for short-term therapy and there is concern with use in those with preexisting hypertension [61].

PDE4 inhibitors are in the midst of development as novel therapeutic options for inflammatory diseases, such as asthma, chronic obstructive pulmonary disease and psoriasis, as well as therapy for depression and cognitive enhancement. PDE4 is one of many phosphodiesterase isoforms that has a sole function to degrade the second messenger cAMP intracellularly; PDE4 inhibition will therefore suppress multiple responses immune and inflammatory mediators, including the production of interleukins, leukotrienes and superoxide anions, as well as degranulation, chemotaxis and adhesion of the myeloid cell line, and inhibition of T cell signaling [62].

PDE4 is found in leukocytes, airway and vascular smooth muscle, vascular endothelium and the brain. Although theophylline is regarded as the first non-selective PDE inhibitor, rolipram provided the paradigm of selective PDE4 inhibition, originally used for asthma, but limited by a narrow therapeutic index with emesis and nausea as side effects during phase II trials [63]. It is suggested that dose-limiting gastrointestinal side effects are due to PDE4 subtype selectivity and access to emetic centers of the brain [62]. Recently, roflumilast has been approved by the US Food and Drug Administration (FDA) for the treatment of severe COPD associated with chronic bronchitis and a history of exacerbations [64]. The most common adverse events gathered from clinical trials of roflumilast, in descending order of the rate of occurrence, are weight loss, diarrhea, nausea, headache and insomnia [56]. Placing this information in context, it appears that apremilast has a more favorable side effect profile than roflumilast, with headache and nausea as the most common adverse events. This potentially is due to the pharmacokinetic properties of the drugs, where apremilast has a comparably lower half-life (5.0 – 8.2 hours) and AUC0-t (1913 ng·h/mL) in contrast to that observed with roflumilast (half life 10.3 – 28.0 hours; $AUC_{0\text{-}t}$ 31 – 61 μg·h/mL) [56].

Apremilast offers patients another oral option for systemic treatment of psoriasis, which has been well tolerated in phase I and II clinical trials. It has favorable safety and toxicity profiles at doses that are also effective for the treatment of plaque psoriasis. Phase III clinical trials are currently underway and will better elucidate appropriate dosing of apremilast and further illuminate the side effect profile. In future studies, a comparison of apremilast to other psoriasis medications administered through different routes would be beneficial to document whether patient adherence is better with an oral medication. Depending on the price of the agent, efficacy, and perhaps most importantly its safety profile, apremilast may fill a key need as a safe, first-line oral treatment for patients with psoriasis.

Over the past two decades, Pharma has been struggling to bring PDE4 inhibitors to market, but has been thwarted to a large extent by side effects of emesis and nausea. However, we are starting to see glimpses of hope in achieving this with roflumilast (Daxas®) for COPD, albeit in a very restricted cohort of severe patients, and now here with regard to apremilast for psoriasis. This offers hope for further improvements in PDE4 inhibitors and use in the wide range of disease areas they have implied utility in from animal models.

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Declaration of interest

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