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DRUG EVALUATION

Pharmacodynamic assessment of apremilast for the treatment of moderate-to-severe plaque psoriasis

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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory skin disease affecting 2–3% of the population. Certain systemic drugs currently available for its treatment could be associated, in the long term, with organ toxicity and adverse events, thus, clinical monitoring throughout treatment is required. Moreover, tolerability issues, parenteral administration, and barriers to patient access, such as high cost and specialist management lead to treatment failure.

Areas covered: Apremilast is an oral small molecule inhibitor of phosphodiesterase 4 (PDE4i). PDE is the major enzyme class responsible for the hydrolysis of cyclic adenosine monophosphate in immune cells (cAMP). With PDE4 inhibition, apremilast works intracellularly to modulate pro-inflammatory and anti-inflammatory mediator production critically involved in psoriasis.

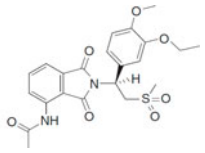
The aim of this paper is to focus the attention on apremilast pharmacodynamics effects, its efficacy and safety in treating moderate-to-severe plaque psoriasis.

Expert opinion: Apremilast is an effective and well-tolerated option in treating moderate-to-severe plaque psoriasis. Its safety profile and the oral administration offer significant advantages in prescribing apremilast for the treatment of psoriasis, particularly in some subsets of patients.

KEYWORDS: Apremilast, phosphodiesterase-4-inhibitor, psoriasis, oral therapy, small molecule.

adverse events **(AEs)**; arthropathic psoriasis **(PsA);** bis in die **(b.i.d.)**; Body Surface Area **(BSA)**; Cyclic adenosine monophosphate **(cAMP)**; cAMP responsive element binding protein (**CREB)**; Exchange protein directly activated by cAMP 1 **(Epac1)**; inducible NO synthase **(iNOS)**; Janus kinase **(JAK)**; Lipopolysaccharide **(LPS)**; Mieloid Dendritic Cells **(mDC); NAPSI** (Nail Psoriasis Severity Index); Natural Killer **(NK)**; Nuclear factor-κB **(NF-κB)**; Peripheral blood mononuclear cells **(PBMCs)**; Plasmacytoid Dendritic Cells **(pDCs)**; Phosphodiesterases **(PDEs)**; Phosphodiesterase 4 **(PDE4)**; Physician's Global Assessment **(sPGA)**; PDE4 inhibitors **(PDE4i)**; Protein Kinase A **(PKA)**; Psoriasis Area Severity Index **(PASI)**; Physician global assessment for lesions of the scalp **(ScPGA);** Signal transducer and activator of transcripton **(STAT)**; Suppressor of cytokine signaling 3 **(SOCS-3)**;

Box 1. Drug summary

Drug name	Apremilast
Phase: EMA approval	January 2015. for the treatment of adults with moderate-to-severe plaque psoriasis and psoriasic arthritis
Indication	Psoriasis; Psoriasic arthritis
Pharmacology description/mechanism of action	cAMP PDE4 inhibitor
Route of administration	Oral
Chemical structure	C22H24N2O7S 
Pivotal trial(s)	ESTEEM 1 and ESTEEM 2 [5,44]

1.INTRODUCTION

Psoriasis is a chronic, inflammatory skin disease, clinically characterized by erythematous and scaly plaques [1]. It affects approximately 2–3 % of the population worldwide. Although the pathogenesis is yet to be fully elucidated, psoriasis is associated with various genetic, immunological, psychological and environmental factors resulting in skin inflammation and keratinocyte proliferation [2,3]. Psoriatic skin lesions are characterized by hyperproliferation, aberrant differentiation and inflammation, with the psoriatic cytokine network maintained by the crosstalk between immune cells and keratinocytes. In normal skin, this acute inflammatory response signaling is typically down-regulated by negative feedback loops maintaining the homeostatic function of the skin immune system [4]. These feedbacks are altered in psoriatic patients resulting in chronic imbalance of pro- and anti-inflammatory cytokines [5].

The earliest trigger event seems to be the recruitment of plasmacytoid dendritic cells (pDCs) activated in response to several extracellular self-DNA fragments that get coupled to the endogenous cationic antimicrobial peptides such as LL-37, beta-defensin (hBD)2, hBD3, and lysozyme that are overexpressed in psoriatic skin. The aggregated and condensed structures formed by these peptides and self-DNA breaks innate tolerance via TLR9 activation which leads to IFN-α induction [6].

LL-37 could also be bound to self-RNA. This compound may activate pDCs through TLR8. Additionally, mDCs could also be activated directly through TLRs. LL-37 is also recognized as non-self antigen by autoreactive T cells. Alternatively, both pDCs and mDCs could be activated by chemerin, through chemr 23 receptor. IL-26 is a Th17 product that acts as antimicrobial peptide and bound to self DNA it activates TLR9 [7].

The increased concentration of IFN-α produced by activated pDCs stimulates mDCs and T cells to secrete several inflammatory and proliferative mediators (i.e., TNF-α, IL-23, IL-22, IL-21, IL-6, IL-

17, IL-20) that further promote the pathologic inflammatory cascade [8]. T cells proliferate and differentiate into different T cells subsets, particularly into IL-17-producing T cells [9]. The inflammatory cascade triggers tissue cell response leading to the activation of keratinocytes, fibroblasts, and endothelial cells [10,11]. The microenvironment within the psoriatic plaque is characterized by an elevated expression of pro-inflammatory and pro-proliferative mediators including cytokines and chemokines that create peculiar inflammatory circuits, which might be therapeutically inhibited, either neutralizing these mediators (i.e., TNF-α, IL-23, and IL-17) or inhibiting intracellular activating signals transduced by PDE4, for instance.

Blocking intracellular transducers that are highly expressed in activated inflammatory cells, such as PDE4 and janus kinase (JAK)-signal transducer and activator of transcription (STAT), it would be possible to inhibit a broader number of cells compared to biologic agents that target a single pro-inflammatory mediator (i.e., TNF-α). Potentially, interrupting the inflammatory cascade at multiple steps including the earliest phases, could be an effective modulation of the inflammatory gene expression.

2. OVERVIEW OF THE MARKET

Various topical medications, phototherapy, and systemic drugs are available to treat patients with psoriasis of varying disease severity.

The current gold standard is represented by biologic therapies targeting TNF-α and IL-12/23, which have dramatically improved clinical outcomes in patients with psoriasis. Despite the large number of drugs available, patients with psoriasis are often dissatisfied with those treatments.

Few studies estimated how many patients receive adequate treatments and fewer data is available about patients' satisfaction. Emerging data shows that a large proportion of patients with psoriasis are not receiving any treatment and almost 30% of patients with moderate-to-severe psoriasis are undertreated, receiving topical medication only [12]. Moreover, there are patients either non-

responding to currently available biological agents or have experienced diminishing therapeutic benefit over time [13, 14].

Although adverse effects and lack of effectiveness are primary reasons for discontinuing biological agents, route of administration, inability to reach specialized centers to obtain adequate assistance are mentioned among the top reasons for discontinuation. Thus, in spite of a range of options, effective treatment of psoriasis can be challenging. For this reason other new frontiers of medical and pharmaceutical research are explored to elucidate the immunopathogenesis of psoriasis and attempt to develop new therapeutic agents against different molecular pathways. In this landscape, small molecules including JAK and PDE4 inhibitors (PDE4i) could represent promising therapeutic targets for moderate-to-severe psoriasis.

3. INTRODUCTION TO THE COMPOUND

During the inflammatory process immune cells belonging to both innate and adaptive immunity are stimulated to produce pro-inflammatory and pro-proliferative mediators, which in turn, induce the activation of tissue cells, especially keratinocytes, fibroblasts and endothelial cells that participate to skin inflammation at lesional sites, secreting pro-inflammatory mediators and sustaining immune cell recruitment [15]. Both immune and tissue cells share a common key transducer for pro-inflammatory intracellular signaling, represented by the intracellular concentration of cAMP. cAMP is a second messenger involved in numerous cellular functions, including modulation of cytokine production in immune cells [16]. It plays a critical role in transducing extracellular stimuli into intracellular signals, and, thus, in controlling gene expression [17].

The inflammatory milieu induces G-protein-coupled receptors to bind and activate adenylyl cyclase, which determines increased production of cAMP [18]. High intracellular levels of cAMP increase anti-inflammatory cytokine production via activation of protein kinase A (PKA) and subsequent phosphorylation of transcription factors including CREB (cAMP responsive element binding

protein) which is a transcription factor capable of transcribing anti-inflammatory cytokine genes and ATF1 (activating transcription factor-1) [18, 19]. PKA activates CREB by phosphorylation as a result of high intracellular cAMP levels. On the other hand PKA activation leads to inhibition of other transcription factors like NF-κB [20, 21]. Nuclear factor-κB (NF-κB) is a transcription factor that contributes to the expression of proinflammatory cytokines, including TNF-α [10]. It is activated in response to low levels of intracellular cAMP due to decreased competition with CREB for transcriptional factor co-activators [22].

To summarize, increased level of inflammatory signals are related to low cAMP concentration and vice versa. This has been studied *in vitro* showing that stimulation of PKA by selective cAMP-derived agonists, decrease pro-inflammatory cytokine production from dendritic cells [23]. In most of the immune cell types, including those contributing to psoriasis pathogenesis, intracellular levels of cAMP are tightly controlled by cyclic nucleotide phosphodiesterases (PDEs), which are the only means of degrading cAMP, via enzymatic hydrolysis [22]. There are 11 known subtypes of PDEs that play a key role in degrading cyclic nucleotides (cAMP, cGMP), which are second messengers in intracellular signaling [24].

4. CHEMISTRY

Apremilast -(S)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3 dihydro-1H-isoindol-4-yl}acetamide- is an orally available PDE4 inhibitor and non-selective for PDE4 subtypes. With the exception of PDE4, apremilast did not significantly inhibit any of the kinases tested and had no significant activity against any of the cell surface receptors or enzymes tested [22]. Apremilast selectively binds and inhibits PDE4 through the dialkoxyphenyl pharmacophore [25]. This group is shared among several other PDE4i, which have been clinically tested or approved [26, 27].

5. PHARMACODYNAMIC ASSESSMENT

Apremilast modulates immune cell activation as PDE4 inhibition reduces the production of pro-inflammatory mediators like TNF-α, IFN-γ, IL-12/23p40, IL-23p19, IL-17A, and IL-22. On the other hand, apremilast has been reported to increase the production of IL-6, which shows both pro- and anti-inflammatory features [20, 2828]. Increasing intracellular cAMP levels, apremilast up-regulates CREB and down-regulates NF-κB-related genes [29]. It has been shown that apremilast influences the expression of both innate and adaptive immune cells modulating their proinflammatory cytokine production, including TNF-α [30] **(fig.1)**.

Apremilast pharmacodynamics was assessed in several studies. In early-stage and placebo-controlled studies in subjects with psoriasis, apremilast modulates the expression of inflammatory mediators, as well as demonstrated significant therapeutic activity, and an acceptable tolerability profile. It was estimated an epidermal thickness reduction by a mean of 20.5% from baseline at day 29, using apremilast 20 mg QD [31]. Among responders (subjects with at least 20% reduction in epidermal thickness) T cells were reduced by 28.8% in the dermis and 42.6% in the epidermis. Skin biopsies showed a reduction in the expression of inducible NO synthase (iNOS) mRNA after 2 or 4 weeks of treatment with apremilast. Similarly, in subjects with moderate to severe psoriasis, apremilast reduces keratinocyte responses to inflammation by the reduction in epidermal thickness [31].

Evaluating the effects of apremilast on LPS-stimulated human peripheral blood mononuclear cells (PBMCs), Schafer et al detected an attenuated expression of LPS-induced proinflammatory cytokines, including TNF-α, IFN-γ, IL-12A and IL-23A with apremilast treatment [32]. Apremilast inhibited expression of genes involved in immune-mediated pathways, including TNF-α, IFN-γ, IL-12A and IL-23A signaling [32]. Notably, also Natural Killer (NK)-derived TNF-α production was inhibited by apremilast. Moreover apremilast may also suppress cytokine signaling through: the

activation of exchange protein directly activated by cAMP 1 (Epac1), the expression of suppressor of cytokine signaling 3 (SOCS-3), and the inhibition of JAK-STAT signaling [33].

An open-label phase II study in recalcitrant psoriasis reported that apremilast suppresses MX1 mRNA expression (marker of the type 1 IFNs response in skin lesions) and reduces IFN-α secretion by activated pDCs [34].

Overall, apremilast seems to act mainly on the innate immune cell compartment (i.e., neutrophils, and NK cells) and, to a lesser extent, on adaptive immune cells. In particular, apremilast does not affect *in vivo* B-cell activation, as detected in an antigen-specific mouse B-cell transfer model [32]. Similarly, PDE4 inhibition has no significant effects on keratinocyte proliferation, as well as keratinocyte-derived TNF-α production. Thereby, the reduced cytokine expression derived from the adaptive immune compartment as well as the suppression of keratinocyte proliferation, seems to represent the downstream result of apremilast activity on innate immune cells that are primarily involved in the early stages of psoriasis pathogenesis [32,35].

Pharmacodynamic effects of apremilast on plasma biomarkers have been investigated in a phase III substudy, within the PALACE I study, correlating the decrease of inflammatory biomarkers with the clinical improvement in three groups of patients (20 mg b.i.d, 30 mg b.i.d., and placebo). Although PALACE I assessed apremilast efficacy in psoriatic arthritis, it provided relevant information regarding the plasma cytokine profile in response to apremilast. The pharmacodynamic assessment was evaluated on a panel of 47 inflammatory proteins. In both 20 mg and 30 mg arms of the study, after 16 and 24 weeks of treatment, significant differences of TNF-α, IL-8, IL-6, ferritin, MIP-1β, and MCP-1 serum concentrations were observed. Similarly, plasma concentrations of IL-6, IL-17, and IL-2 were decreased by both apremilast doses, after 40-week treatment, suggesting a long-term inhibition of the Th-17-driven inflammation. Notably, together with the reduced plasma concentration of pro-inflammatory products, apremilast was associated with a significant increase in anti-inflammatory mediator production, namely IL-10 and IL-1RA [36]. These outcomes are in line with another study showing the reduced expression of pro-inflammatory genes, namely 12/IL-

23p40, IL-17A, and IL-23p19, in lesional skin [34]. The evidence implicates that apremilast has a significant impact on the IL-17 pathway, both systemically (serum level) and locally (lesional skin). Since, in psoriatic disease, IL-17 is produced not only by T helper cells, but also neutrophils, mast cells, $\gamma\delta$ T cells, and innate lymphoid cells, it could be speculated that apremilast treatment may modulate the activity of several immune cells that, producing IL-17, contribute to the psoriatic inflammatory cascade [37].

6. PHARMACOKINETICS AND METABOLISM

Absorption: apremilast, orally administered, is absorbed with an absolute bioavailability of ~73%, with peak plasma concentrations (Cmax) occurring at a median time (tmax) of ~2.5 hours. Co-administration with food does not alter the extent of absorption of apremilast.

Distribution: Human plasma protein rate binding to apremilast, is approximately 68%. Mean apparent volume of distribution (Vd) is 87 liters.

Metabolism: After oral administration, apremilast is the major circulating component (45%) followed by its inactive metabolite M12 (39%). In humans, twenty-three apremilast metabolites have been identified and detected in plasma, urine and feces. Both cytochrome (CYP) oxidative metabolism, with subsequent glucuronidation, and non-CYP mediated hydrolysis metabolize apremilast. *In vitro*, CYP metabolism of apremilast is primarily mediated by CYP3A4, with minor contribution from CYP1A2 and CYP2A6 [38,39].

Elimination: The plasma clearance of apremilast is about 10 L/hr in healthy subjects, with a half-life of approximately 6-9 hours. About 58% and 39% is recovered in urine and feces, respectively [40].

Recommended dosage of apremilast is 30 mg b.i.d. approximately every 12 h with no food restriction. The dose should be reduced in patients with severe renal function impairment but no adjustment are needed for patients with hepatic disorders [41].

7. CLINICAL EFFICACY

7.1 Phase II studies

Clinical efficacy and safety of apremilast for the treatment of severe plaque-type psoriasis were firstly assessed by a phase II, multicenter, open-label, single-arm pilot study testing apremilast 20 mg b.i.d. [31] **(Tab.1**). This study consisted of three phases: screening, treatment and observational follow-up phase (28 days, 29 days and 28 days respectively). In a phase II, open-label multicenter study, Gottlieb et al. [34] evaluated the efficacy, tolerability and pharmacodynamics of apremilast in patients with recalcitrant plaque psoriasis. The study comprised four phases and each one showed a improvement in BSA and in static PGA. Pharmacodynamic assessment showed a significant reduction of the inflammatory infiltrate localized into the dermis and epidermis, mainly constituted by T cells, mDCs, and NK cells [37]. Papp et al. conducted a phase IIb, double-blind, placebo-controlled (in the first 16 weeks), randomized, dose-ranging study evaluating different apremilast dosages (10, 20 and 30 mg b.i.d.) for 24 weeks, with primary endpoint designed at Week 16. Although a dose response was demonstrated ranging from 10 to 30 mg b.i.d, 30 mg b.i.d. resulted the best performing dose and it was selected for phase III studies. Conversely to the 20 mg and 30 mg b.i.d. arms, apremilast 10 mg b.i.d. treatment did not obtain a higher response compared with placebo [42]. Currently, two more phase II studies in psoriasis are ongoing [43].

7.2 Phase III studies:

The efficacy and safety of apremilast have been widely evaluated in ESTEEM 1 and 2 studies. ESTEEM 1 and 2 are Phase III randomized studies testing apremilast 30 mg b.i.d. *versus* placebo in patients ≥18 years of age, with a ≥12 month history of chronic plaque psoriasis, who were candidates for treatment with phototherapy and/or systemic therapies. Additional including criteria were represented by: PASI score ≥12; BSA involvement ≥10%; and sPGA score of ≥3 [44, 5] (**Tab2)**.

Efficacy data, reported in ESTEEM 1 and 2, showed an improvement in all clinical parameters in patients treated with apremilast. In addition to its clinical efficacy, the overall rate of side effects was modest. The most commonly occurring adverse events (AEs) associated with apremilast were diarrhea, nausea, vomiting, headache and upper respiratory infections. These AEs were dose-dependent, mild or moderate, typically occurred in the first 14 days after starting apremilast, and generally resolved within 30 days without withdrawing treatment. Except for the most common AEs, no adverse events of special interest were observed [47] (**Tab3).**

The benefits brought by apremilast in the huge panorama of psoriasis therapies is above all in terms of safety: no dose adjustment is necessary in contrast with the conventional medications such as methotrexate or cyclosporine no apremilast-treated patients had TB reactivation, nor worsening of heart failure, no dose adjustment are needed for those subjects with moderate and severe hepatic impairment. Moreover, long-term studies conducted in mice and rats showed no increased risk of apremilast-induced tumors at oral doses up to 8.8 times the maximum recommended human dose [48]. In the latest years, long-term analysis over a 3.5-year- (182-week) period from ESTEEM 1 and 2 trials have been presented. The ESTEEM trials safety analysis was gathered from 1.184 patients treated with Apremilast 30mg b.i.d. for up to 182 weeks. The pooled data showed no new safety signals identified, no increase in exposure-adjusted incidence rates (EAIR) of adverse events, serious adverse events or drug discontinuations [49]. These results were in line with previous safety analyses on a 2-year period (104 weeks) of apremilast treatment [50-51].

8. REGULATORY AFFAIRS

Apremilast was approved by the FDA at the dosage of 30 mg b.i.d for the treatment of adult patients with active PsA in March 2014 and recently, in September 2014, for the treatment of adult patients affected by moderate-to-severe plaque psoriasis who may be eligible for phototherapy or systemic therapy. In January 2015 apremilast was approved by the EMA for both treatments of by moderate-to-severe plaque psoriasis and psoriatic arthritis. Clinical trial are ongoing in order to evaluate the

efficacy of apremilast in other autoimmune and auto-inflammatory diseases such as rheumatoid arthritis, dermatomyositis, Behc¸et disease, uveitis, ulcerative colitis, acute gout, erosive hand osteoarthritis and other cutaneous

diseases, including atopic dermatitis, acne, rosacea and contact dermatitis (**Tab 4)** [43].

9. CONCLUSION

Despite the impressive advancement in treating psoriasis over the past 15 years, there is still need for further improvement. Biologicals and DMARDs have several disadvantages in term of route of administrations and side effects. Moreover, biologicals show increased risks for infections and tumors. Consistent data has demonstrated that apremilast could represent an effective and safe therapeutic tool for the treatment for psoriasis [52]. The value that apremilast adds to the wide panorama of available drugs is represented by the satisfying management of the disease without incurring in severe side effects, the easier route of administration and the opportunity of an effective therapeutic option for those patients unresponsive to both other conventional and biological agents or whose treatment were contraindicated [53,54].

In September 2014, apremilast was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, and for the treatment of adult patients with active psoriatic arthritis.

10. EXPERT OPINION

Results from the aforementioned studies show that apremilast inhibits the production of multiple cytokines and chemokines in LPS-stimulated PBMCs such as IFN-γ, MIG, TNF-α, IL-12p70, MIP-1α, MCP-1 and GM-CSF, but not IL-8, IL-1β, promoting the increase of IL-6. The greatest potency was observed against the IFN-dependent chemokines IP-10 and MIG, and IFN-γ itself, suggesting a

general selectivity for the interferon responsive genes [55]. Based on the current pathogenic model that identifies the IL-23/IL-17 axis as the main pathway driving the psoriatic plaque formation, apremilast effects on IL-23- and IL-17- producing cells should be more deeply investigated [56,57]. Acting on plasmacytoid and myeloid dendritic cells, apremilast seems to interfere with the upstream steps of the IL-23/IL-17 axis, but it would be interesting to define apremilast ability in directly inhibiting IL-17 production.

The pharmacodynamic interaction of apremilast with the immune system cells lead to a broad, but not complete, inhibition of multiple pro-inflammatory mediators: polymorphonuclear leukocytes, mainly neutrophils, were blocked *in vitro* by apremilast, including the production of IL-8 and LTB4 by polymorphonuclear cells as previously reported for other PDE4 inhibitors [58]. In purified human NK cells, apremilast inhibited production of TNF-α and GM-CSF, and IFN-γ, induced by IL-2 and Fc receptor (FcRγ) cross-linking. Supernatants from psoriatic NK cells have been shown to produce large amounts of IFN-γ, and to induce expression of ICAM-1 and MHC class II in psoriatic keratinocytes [59].

Therapeutically, apremilast represent a promising option as it is well-tolerated and no blood test or imaging exam is mandatory during treatment. Another important advantage of apremilast is the route of administration and the possibility to be self-administered, the short half-life also makes apremilast convenient in case of sudden treatment interruption due, for example, to pregnancy or before major surgical intervention [60]. Nevertheless, no data o clinical reports are available regarding safety of apremilast during pregnancy and it is currently labeled as pregnancy category C drug.

Because of the effectiveness in modulating the inflammatory cascade in adaptive and innate immune system and the pharmacokinetic advantages, apremilast may offers an oral treatment option for those patients who discontinue treatments because of ineffectiveness, intolerability, or ineligibility to the currently available drugs.

According with the current armamentarium for the treatment of psoriasis and the efficacy profile, apremilast could be recommended for biologic-naïve patients and in subjects who are contraindicated for any conventional systemic or biologic therapy. Clinical and therapeutic aspects related to the apremilast use still need to be investigated: for instance, its benefits in childhood and adolescence psoriasis. The favorable safety profile leads to consider this drug a possible therapeutic option that could ease the management of these patients. No clinical studies testing apremilast in <18 year-old patients have been performed yet, but, recently, a case of successful treatment with apremilast in a adolescent psoriatic patient has been described, highlighting the noticeable and progressive improvement of the skin lesions and his quality of life associated with a satisfactory safety profile [61].

However, to place apremilast in the psoriasis therapeutic algorithm, head-to-head trials testing apremilast *versus* other therapeutics are necessary.

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Declaration of Interest

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.

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Figure 1: Mode of action of apremilast:

Apremilast specifically inhibits PDE4. Since PDE4 degrades cAMP to AMP, intracellular levels of cAMP increases during apremilast administration. This results in PKA activation and phosphorylation of transcription factors like CREB and ATF-1 and, conversely, in inhibition of NF-?B. This transcriptional regulation is responsible for the reduced production of pro-inflammatory mediators and the increased production of IL-6 and the anti-inflammatory mediator IL-10.

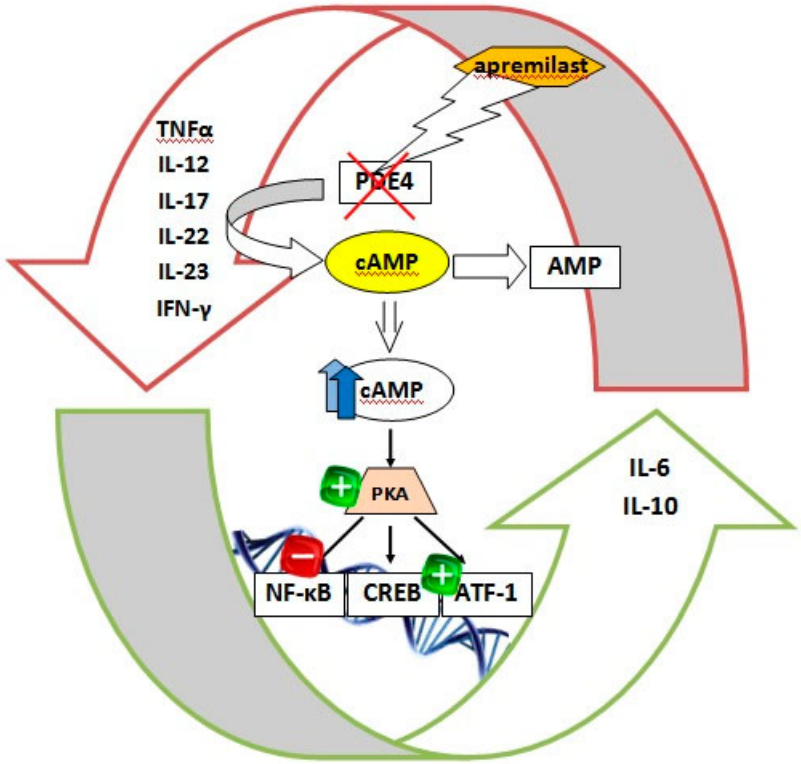

Table 1 : Clinical results in the pivot phase II study CC-10004- PSOR-001 [31]

	An open label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast [31] **CC-10004- PSOR-001**
N° Patients	**19 (17 compleeted the study and received apremilast 10mg b.i.d.)**
Baseline Characteristic (Mean) Apremilast 20 mg	**Age 40.8, Sex: 84.2% Male, Female, 15.8, PASI 18.6, BSA 30.5%**
PASI improvement	**day 29: 73.7%**
PASI 50	**day 29: 17.6%**
sPGA improvement	**day 29: 52.9%**
Epidermal quantitative total T cell count	**day 29: –18.6%**
Dermal quantitative total T cell count	**day 29: –23.4%**
epidermal thickness	**day 29: -20% (achieved by 53.3%)**

Table 2 : Clinical results in Phase III studies ESTEEMI and ESTEEMII [44, 5].

	ESTEEM I [44]	**ESTEEM II [5]**
N° Patients	**844 (1:2 placebo vs apremilast)**	**413 (1:2 placebo vs apremilast)**
Baseline Characteristic (Mean) Apremilast 30 mg	**Age 45.8, Sex 67.4% Males, BMI 31.2, PASI 18.7, BSA 24.4% VAS score pruritus 66.1, DLQI 12.7; ScPGA score ≥3 66.5% NAPSI score 4.2**	**Age 45.3, Sex: 64.2% Males, BMI 30.9, PASI 17.9, BSA 25.5% VAS score pruritus 67.7, DLQI 12.6; ScPGA score ≥3 64.2% NAPSI score 4.2**
PASI 75	**16 weeks: 33.1% vs 5.3% 32 w 28.3%**	**16w: 28.8% vs 5,8% 32w: 24.8%**
PASI 50	**16 w: 58,7% vs 17% 32 w : 53.6**	**16w: 55.5% vs 19.7% 32 w: 60%**
Nail: NAPSI 50	**16 w: 33.3% vs 14.9% 32w : 45.2 % 52 w: 70.7%**	**16w: 44.6% vs 18.7% 32w : 55.4% 52w: 68.6%**
Palms and soles: PPPGA 0-1	**16w. 38.6 vs 30.8% 32w: 42.1%**	**16w: 65.4 % vs 31.3% 32w: 53.8%**
Pruritus: VAS SCORE mm	**16 w: -31.5 vs -7.3 32w: -34.5**	**16w: -33.5 vs -12.2 32w: -34.7**
QoL: DLQI	**16 w: -6.6 vs -2.1 32w: -7.3**	**16w: -6.7 vs -2.8**

Table 3 : Summary of adverse events in Phase III clinical trials on psoriasis and/or psoriatic arthritis [36], [51], [44]. The frequence is defined as: very common(≥1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/10.000, < 1/1.000)

Organs and systems	**Frequency**	**Adverse event**
Infections and infestations	common	Bronchitis
		Upper respiratory infections
		Nasopharyngitis
Immune system disorders	uncommon	Hypersensitivity
Psychiatric disorders		Insomnia
Gastrointestinal disorders	very common	Nausea
		Diarrhea
	common	Vomiting
		Dyspepsia
		Upper abdomen pain
		Weight loss
		GERD
		Frequant bowel movements
Nervous and musculoskeletal system disorders	common	Headache
		Thension headache
		Back pain
		Fatigue
Respiratory disorders	common	Cough

Table 4: Currently ongoing clinical trials testing apremilast in psoriatic patients.

Study number	Study design	Population	Dosing	Subjects enrolled
Phase II trials				
CC-10004-PPSO-001 [43]	Multicenter, Open-Label Study to Assess the Safety, Tolerability and Pharmacokinetics of **APR** in Pediatric Subjects	Pediatric Subjects, male and female with Moderate to Severe **Plaque** Psoriasis	APR 10 mg b.i.d., APR 20 mg b.i.d., APR 30 mg b.i.d.	NA
CC-10004- PSOR-005 LTE [42]	Long-term safety extension study for subjects who completed the treatment phase of the extension study (CC-10004-PSOR-005E)	Male and female subjects who completed the treatment phase of the extension study (CC-10004-PSOR-005E)	APR 20 mg b.i.d., APR 30 mg b.i.d.	56
Phase III trials				
CC-10004-PSOR-008 (ESTEEM 1) [5]	Randomized, double-blind, placebo-controlled study	Male and female subjects with moderate-to-severe plaque psoriasis	Placebo, APR 30 mg b.i.d.	844
CC-10004-PSOR-009 (ESTEEM 2) [44]	Randomized, double-blind, placebo-controlled study	Male and female subjects with moderate-to-severe plaque psoriasis	Placebo, APR 30 mg b.i.d.	413
CC-10004-PSOR-010 [43]	Randomized, placebo-controlled, doubleblind, double-dummy study	Male and female subjects with moderate-to-severe plaque psoriasis	Placebo tablets + placebo injection, etanercept 50 mg QW + placebo tablets, APR 30 mg b.i.d. + placebo injection	250
Phase IV trials				
Inno-6040, AP-CL-PSORCARE-005313	A Double-blind, Placebo-controlled, Randomized Study on the Safety and Efficacy of APR	Male and female subjects with moderate-to-severe plaque psoriasis involving palms and/or soles	Apremilast, placebo	NA

AP-CL-PSOR-PI-004893 [43]	Randomized, Safety/Efficacy Study, Parallel Assignment, Double Blind	Male and female subjects with moderate-to-severe plaque psoriasis	Narrowband UVB and APR	NA
CC-10004- PSOR-012 [43]	Multicenter, Randomized, Placebo-controlled, Double-blind, Study of the Efficacy and Safety of APR	Male and female subjects with moderate-to-severe plaque psoriasis	Apremilast, placebo	NA