

# Driver terapeutici per “piccole molecole” - apremilast

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## SINERGIE e PROSPETTIVE in DERMATOLOGIA

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Con il Patrocinio di

  
UNIVERSITÀ  
DEGLI STUDI  
DELL'AQUILA

  
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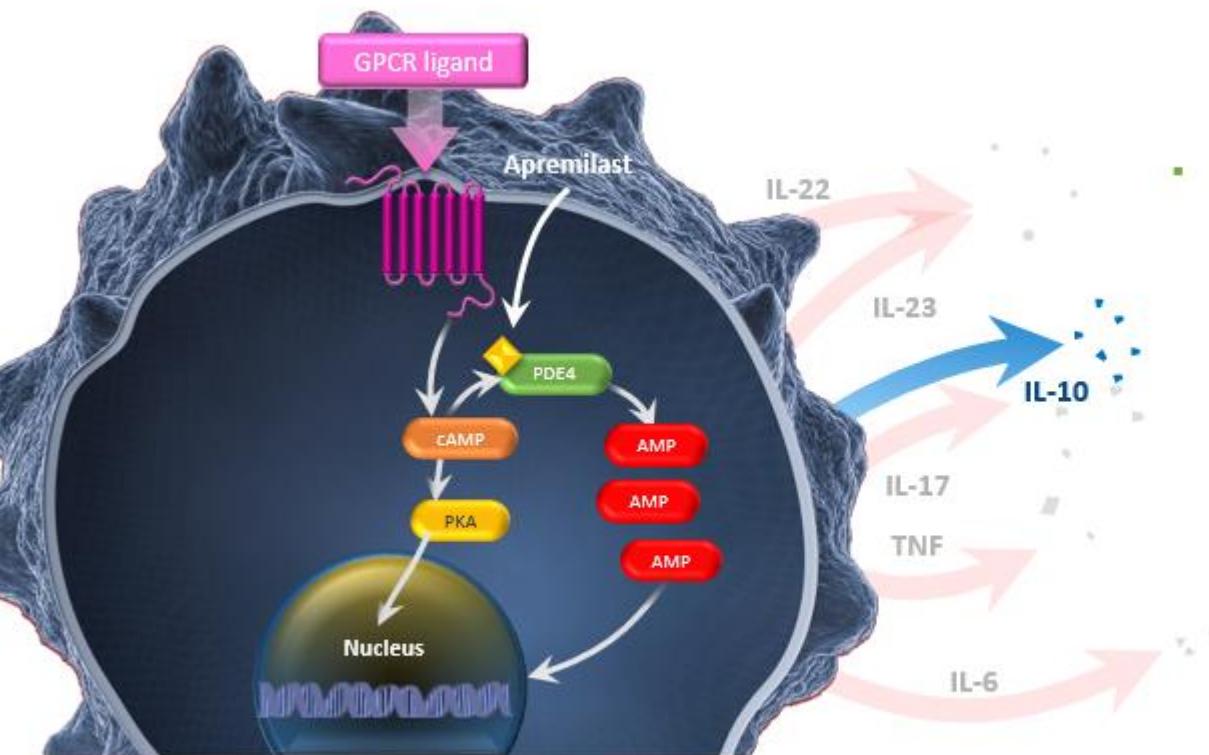


# Meccanismo d'azione

Apremilast, un inibitore orale a basso peso molecolare della fosfodiesterasi 4 (PDE4), agisce a livello intracellulare per modulare una rete di mediatori pro-infiammatori e antinfiammatori.

Inibizione della PDE4 → aumenta i livelli intracellulari di cAMP → sottoregolazione della risposta infiammatoria modulando l'espressione di TNF- $\alpha$ , IL-23, IL-17 e altre citochine infiammatorie. L'AMP ciclico modula inoltre i livelli di citochine antinfiammatorie, come IL-10.

# Meccanismo d'azione



CREB, cAMP-response element binding protein.

1. Schafer P. *Biochem Pharmacol* 2012;83:1583–90; 2. Li H, et al. *Front Pharmacol* 2018;9:1245;  
3. Pincelli et al. *J Drugs Dermatol* 2018;17:835–40.



- Psoriasi cronica a placche da moderata a grave nel paziente adulto che presenta tutte le caratteristiche di seguito indicate ai fini della rimborsabilità:

- PASI-BSA

- PASI > 10 o BSA > 10

- oppure

- PASI < 10 o BSA < 10, associati a lesioni:

- al viso       palmo/plantare       ungueale       genitale

- non ha risposto       oppure       ha una controindicazione       oppure       è intollerante

- ad altra terapia sistemica comprendente ciclosporina, metotrexato o psoralene e raggi ultravioletti di tipo A.

Terapia sistemica (specificare) \_\_\_\_\_

presenta controindicazioni o intolleranza agli *anti-TNF-α* e agli *inibitori delle interleuchine*

Anti-TNF-α (specificare): \_\_\_\_\_

Inibitore IL (specificare): \_\_\_\_\_



## APREMITAST: posologia

### Posologia

La dose raccomandata di Otezla è 30 mg due volte al giorno, assunta per via orale, alla mattina e alla sera, a distanza di circa 12 ore, senza limitazioni per quanto riguarda l'assunzione di cibo. È previsto uno schema di titolazione iniziale, come riportato nella Tabella 1 di seguito. Dopo la titolazione iniziale non è richiesta una nuova titolazione.

**Tabella 1: Schema di titolazione della dose**

Giorno 1	Giorno 2		Giorno 3		Giorno 4		Giorno 5		Giorno 6 e successivi	
mattina	mattina	pomeriggio	mattina	pomeriggio	mattina	pomeriggio	mattina	pomeriggio	mattina	pomeriggio
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg



[J Eur Acad Dermatol Venereol.](#) 2018 Jul;32(7):1173-1179. doi: 10.1111/jdv.14832. Epub 2018 Mar 30.

## Real-world data on the efficacy and safety of apremilast in patients with moderate-to-severe plaque psoriasis.

Papadavid E<sup>1</sup>, Rompoti N<sup>1</sup>, Theodoropoulos K<sup>1</sup>, Kokkalis G<sup>1</sup>, Rigopoulos D<sup>1</sup>.

### Author information

#### Abstract

**BACKGROUND:** Psoriasis is a chronic inflammatory skin disease, which requires long-term, safe and effective treatment. Apremilast, a small-molecule PDE4 inhibitor, has been introduced as psoriasis (and psoriatic arthritis) treatment in Europe in 2015.

**OBJECTIVE:** We analysed and report the efficacy and safety of apremilast in the first 51 patients with psoriasis that have undergone treatment with this novel small molecule in our outpatient clinic.

**METHOD:** Our primary endpoint was the evaluation of clinical response to apremilast according to the percentage of Psoriasis Area Severity Index (PASI) reduction ( $\Delta$ PASI) at 16 weeks after treatment initiation. Secondary endpoints were the evaluation at week 16 of (i) PASI; (ii) Dermatology Life Quality Index (DLQI); (iii) Physician Global Assessment (PGA); (iv) Psoriasis Scalp Severity Index (PSSI); and (v) the percentage of patients who achieved  $\Delta$ PASI50,  $\Delta$ PASI75,  $\Delta$ PASI90 and  $\Delta$ PASI100; (vi) adverse events (AE); (vii) reasons for drug discontinuation; and (viii) drug survival.

**RESULTS:** About 59.3% of the patients who remained on apremilast achieved at least  $\Delta$ PASI75 at week 16, while 11.1% achieved combined  $50\% \leq$  PASI < 75% and DLQI  $\leq$  5 (satisfactory response) adequate enough to maintain treatment. Five patients (18.5%) also achieved  $\Delta$ PASI100. Patients discontinued apremilast (28%), mostly during the first 4 weeks due to adverse events (12%) with gastrointestinal symptoms being the most common, and later due to lack of efficacy (16%). A statistically significant improvement of PASI, DLQI, PGA and PSSI scores was observed after 4 and 16 weeks of treatment relative to pretreatment measurements.

**CONCLUSION:** Apremilast is a safe and efficacious treatment for psoriasis patients as it produces  $\Delta$ PASI75 and  $\Delta$ PASI50 responses combined with DLQI  $\leq$  5 in 16 weeks in 70.4% of the patients. These results, from a real-world setting, confirm the efficacy and safety of apremilast which has been demonstrated in large phase III clinical trials.



J Am Acad Dermatol. 2017 Aug;77(2):310-317.e1. doi: 10.1016/j.jaad.2017.01.052. Epub 2017 Apr 14.

## **Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2).**

Crowley J<sup>1</sup>, Thaci D<sup>2</sup>, Joly P<sup>3</sup>, Peris K<sup>4</sup>, Papp KA<sup>5</sup>, Goncalves J<sup>6</sup>, Day RM<sup>6</sup>, Chen R<sup>6</sup>, Shah K<sup>6</sup>, Ferrández C<sup>7</sup>, Cather JC<sup>8</sup>.

### **+ Author information**

#### **Abstract**

**BACKGROUND:** Randomized, controlled trials demonstrated efficacy and safety of apremilast for moderate-to-severe plaque psoriasis and psoriatic arthritis.

**OBJECTIVE:** Assess long-term safety of oral apremilast in psoriasis patients.

**METHODS:** Safety findings are reported for 0 to ≥156 weeks from the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) 1 and 2.

**RESULTS:** The 0 to ≥156-week apremilast-exposure period included 1184 patients treated twice daily with apremilast 30 mg (1902.2 patient-years). During 0 to ≤52 weeks, the adverse events (AEs) that occurred in ≥5% of patients included diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, tension headache, and headache. From 0 to ≥156 weeks, no new AEs (affecting ≥5% of the population) were reported. AEs, serious AEs, and study drug discontinuations caused by AEs did not increase with long-term exposure. During the 0 to ≥156-week period, the rates of major cardiac events (exposure-adjusted incidence rate [EAIR] 0.5/100 patient-years), malignancies (EAIR 1.2/100 patient-years), depression (EAIR 1.8/100 patient-years), or suicide attempts (EAIR 0.1/100 patient-years) did not increase in comparison with the rates found during the 0 to ≤52-week period. No serious opportunistic infections, reactivation of tuberculosis, or clinically meaningful effects on laboratory measurements were reported.

**LIMITATIONS:** This study had a high dropout rate (21% of patients ongoing >156 weeks); most were unrelated to safety concerns.

**CONCLUSIONS:** Apremilast demonstrated an acceptable safety profile and was generally well tolerated for ≥156 weeks.

	Weeks 0 to 52 <sup>1</sup>	Weeks 52 to 104 <sup>1</sup>	Weeks 104 to 156 <sup>1</sup>	Weeks 0 to 156 <sup>1</sup>
	Apremilast 30 mg BID (n = 1184; pt-yrs = 915.7)	Apremilast 30 mg BID (n = 654; pt-yrs = 514.6)	Apremilast 30 mg BID (n = 401; pt-yrs = 339.0)	Apremilast 30 mg BID (n = 1184; pt-yrs = 1902.2)
<b>AEs occurring in &gt; 5% of patients, n (%)</b>				
Diarrhoea	205 (17.3)	15 (2.3)	7 (1.7)	221 (18.7)
Nausea	186 (15.7)	5 (0.8)	6 (1.5)	195 (16.5)
URTI	184 (15.5)	58 (8.9)	27 (6.7)	227 (19.2)
Nasopharyngitis	167 (14.1)	43 (6.6)	24 (6.0)	196 (16.6)
Tension headache	106 (9.0)	8 (1.2)	5 (1.2)	115 (9.7)
Headache	75 (6.3)	6 (0.9)	7 (1.7)	86 (7.3)

In the apremilast 30 mg BID treatment group, diarrhoea and nausea were predominantly mild to moderate in severity, occurred during the first weeks of dosing, and generally resolved within 1 month<sup>1,2</sup>. Apremilast has a favourable 5-year efficacy and safety profile<sup>2</sup>



# *Il paziente “moderato”*



# Paziente moderato

In letteratura non vi è una definizione univoca di quello che viene considerata come "psoriasi moderata", bensì si possono trovare diverse classificazioni a seconda delle varie linee guida.



# Paziente moderato

## EUROPEAN S3 GUIDELINES

- **Mild to moderate disease:** 'PASI > 10 or BSA > 10' or PASI 10 or more.
- **Mild psoriasis:** 'PASI ≤ 10 AND BSA ≤ 10 AND DLQI ≤ 10'.
- Taking into account the impact of important psoriasis characteristics from the patient's perspective criteria have been defined, which **upgrade mild disease to moderate-to-severe when present**. These include a major involvement of:
  - visible areas,
  - major involvement of the scalp,
  - involvement of genitals,
  - onycholysis or onychodystrophy of at least two fingernails, per hand,
  - presence of itch leading to scratching and the presence of recalcitrant plaques.
- **Severe psoriasis:** 'PASI > 20. Very severe psoriasis is considered to be present when PASI > 30 or BSA > 20 % or more.'
- **In addition:** 'Nast A, et al. J Eur Acad Dermatol Venereol. 2017 Dec;31(12):1951-1963'



# Paziente moderato

Patients presenting with disease manifestations not adequately controlled by topical therapy and with significant impairment in the quality of life may require systemic treatments. These manifestations include the involvement of visible areas (i.e. face, scalps and hands), genitals, palms and/or soles, nails, or the presence of intense pruritus. Consequently, in daily practice, a systemic therapy could be indicated even if PASI or BSA is lower than 10.

**Table 3** Indications for systemic treatments

- PASI  $\geq 10$
- PASI  $< 10$  but with involvement of sensitive area such as hands, palmoplantar, genital, scalp, face, and nails
- BSA  $\geq 5\%$  resistant to or in patients reluctant to topical therapy
- BSA  $< 5\%$  with disseminated lesions
- Subjective perception of disease severity (e.g. DLQI  $\geq 10$ )
- Active psoriatic arthritis
- Psoriasis associated with severe symptoms (e.g. itch, burning) that are not controlled by topical therapies



# Paziente moderato

[Drug Des Devel Ther.](#) 2016 May 25;10:1763-70. doi: 10.2147/DDDT.S108115. eCollection 2016.

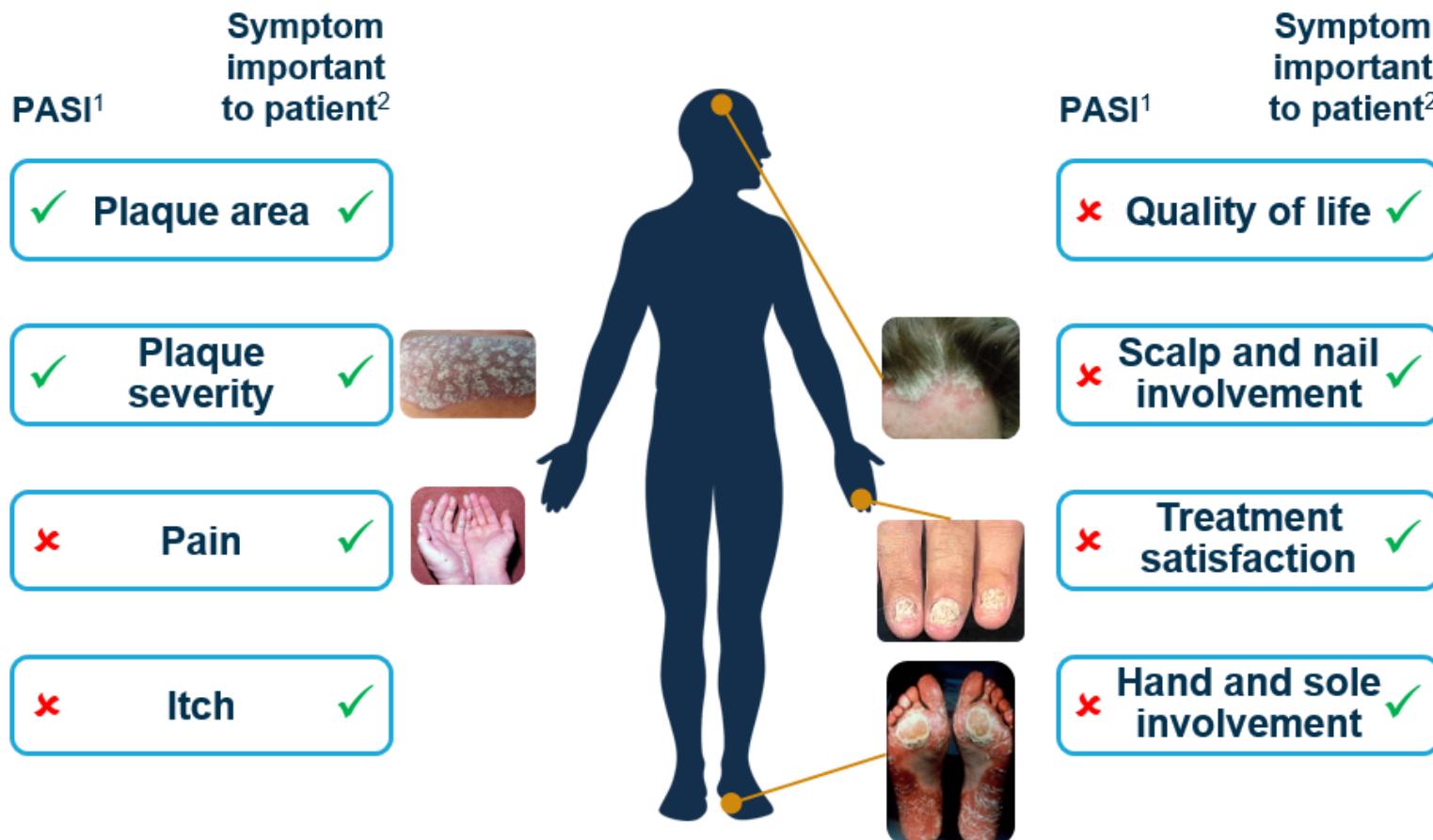
## **Apremilast in the therapy of moderate-to-severe chronic plaque psoriasis.**

[Gisondi P<sup>1</sup>](#), [Girolomoni G<sup>1</sup>](#).

"[...] psoriasis could be graded as moderate-to-severe also in cases of **BSA <10% and/or PASI <10 but DLQI >10** because of a significant impact on the quality of life and systemic therapy could be indicated [...]".

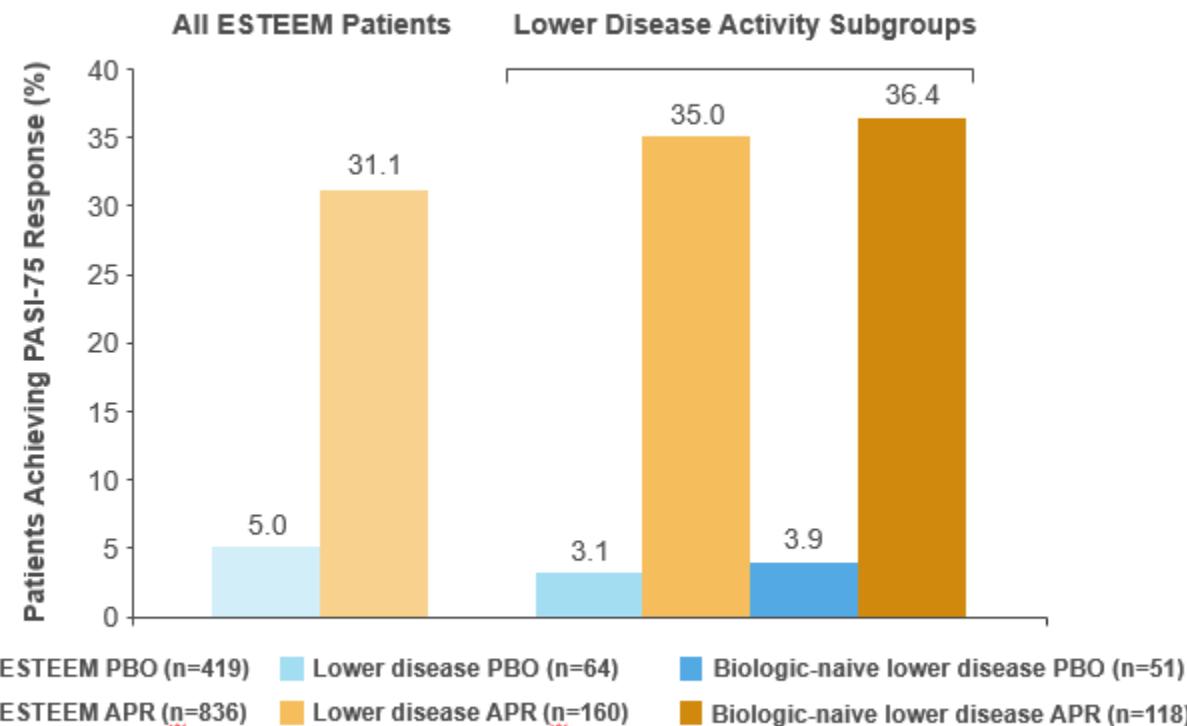
# Paziente moderato

## PASI: ASPECTS OF PSORIASIS THAT IT DOES AND DOESN'T CAPTURE



# ESTEEM 1&2

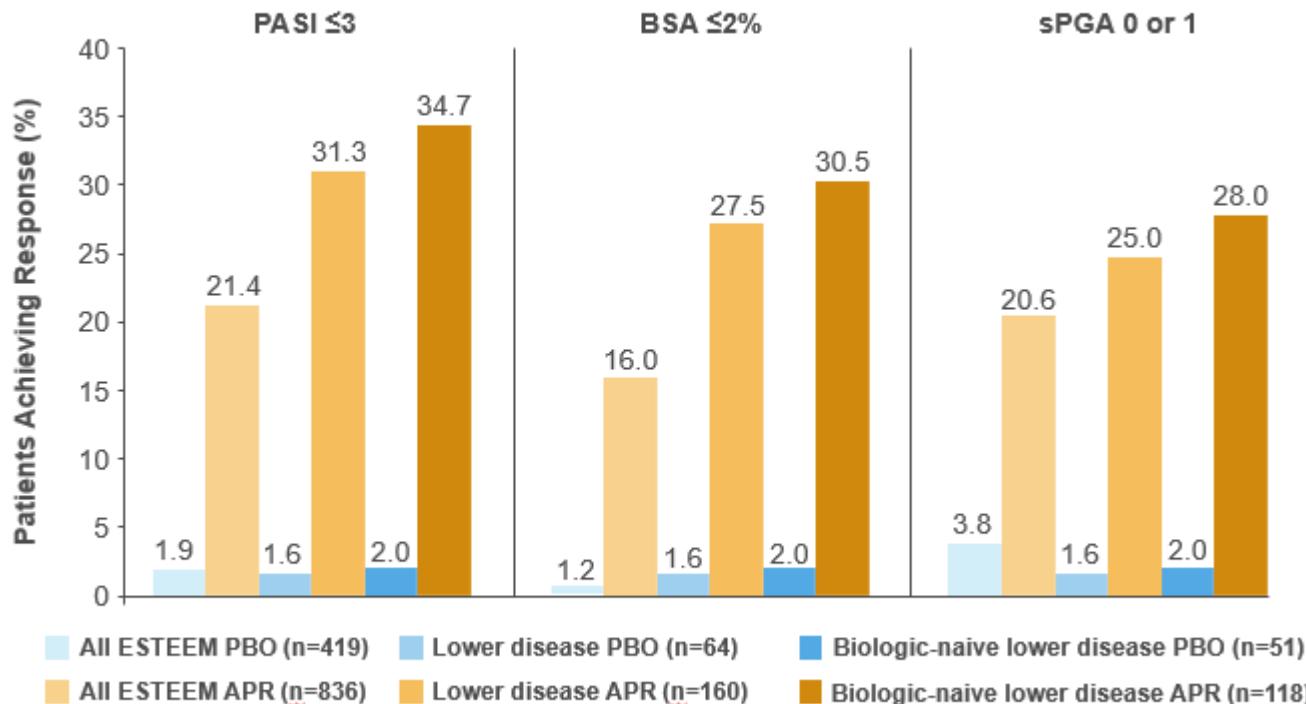
**Figure 1. PASI-75 Response at Week 16, All ESTEEM Patients vs. Lower Disease Activity Subgroups**



Includes all patients in each indicated group; patients with a missing value at Week 16 were considered non-responders.

# ESTEEM 1&2

**Figure 2. PASI ≤3, BSA ≤2%, and sPGA 0 or 1 at Week 16, All ESTEEM Patients vs. Lower Disease Activity Subgroups**



Includes all patients in each indicated group; patients with a missing value at Week 16 were considered non-responders.



# Studio UNVEIL

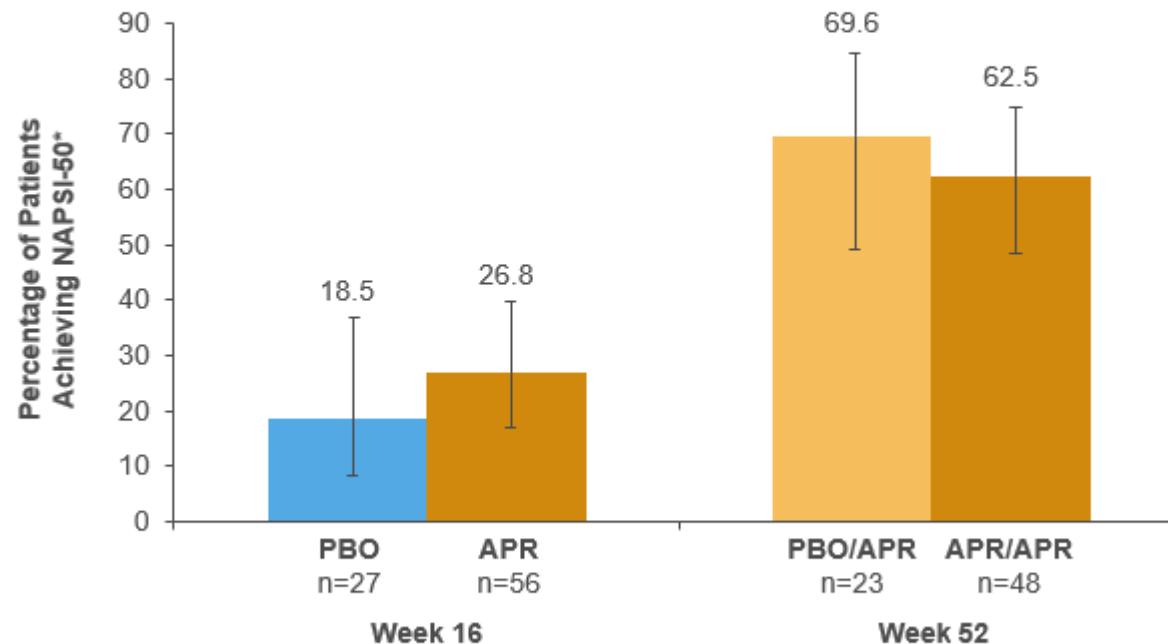
Characteristic	PBO n=73	APR n=148
Age, mean (SD), years	51.1 (13.7)	48.6 (15.4)
Male, n (%)	41 (56.2)	74 (50.0)
Body mass index, mean (SD), kg/m <sup>2</sup>	30.8 (6.5)	30.5 (7.4)
Duration of psoriasis, mean (SD), years	13.9 (12.6)	17.5 (13.9)
PGAxBSA score, mean (SD)	21.6 (5.9)	21.8 (5.3)
BSA, mean (SD), %	7.1 (1.8)	7.2 (1.6)
PASI score (0–72), mean (SD)	8.0 (3.2)	8.2 (4.0)
sPGA score=3 (moderate)*, n (%)	70 (95.9)	144 (97.3)
PtGA score=3 (moderate), n (%)	46 (63.0)	79 (53.4)
Pruritus VAS score, mean (SD), mm	60.0 (22.5)	55.0 (24.3)
DLQI total score, mean (SD)	11.1 (6.5)	11.0 (6.5)
Prior topical therapy, n (%)	59 (80.8)	122 (82.4)

\*Although the inclusion criterion was sPGA=3, patients with sPGA=4 were enrolled in error (n=6).  
PASI=Psoriasis Area and Severity Index.



# Studio UNVEIL

## PROPORTION OF PATIENTS ACHIEVING NAPSI-50 RESPONSE\* AT WEEK 16 AND WEEK 52



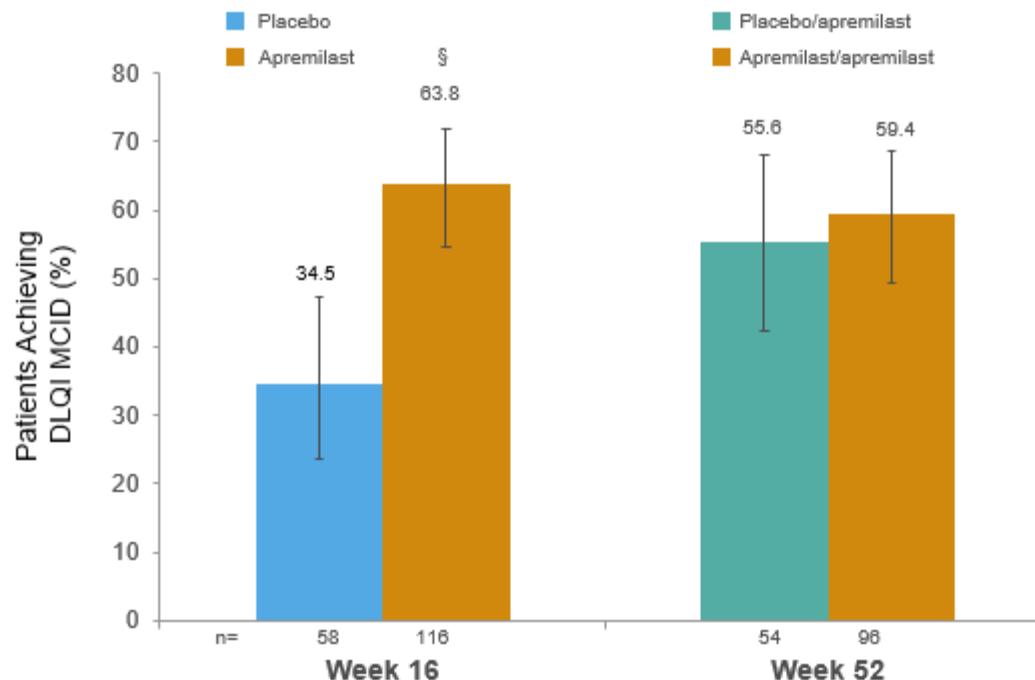
Adopted from Stein Gold L, et al. *J Drugs Dermatol*. 2018;17(2):221-228 UNVEIL

Adopted from Stein Gold L, et al. *J Drugs Dermatol*. 2018;17(2):221-228.

# Studio UNVEIL

## PROPORTION OF PATIENTS ACHIEVING DLQI MCID AT WEEK 16 AND WEEK 52 (LOCF)\*

- Significantly more patients with a baseline DLQI total score >5 who received apremilast vs. placebo achieved the DLQI MCID at Week 16
- Among patients who were initially randomized to apremilast at baseline, the percentages of patients who achieved DLQI MCID at Week 16 were maintained over 52 weeks



\*Post hoc analysis.

§ $P=0.0009$  vs. placebo. Includes patients with DLQI >5 at baseline. DLQI MCID =  $\geq 5$ -point decrease from baseline. Error bars indicate 95% confidence intervals.

Adopted from Stein Gold L, et al. J Drugs Dermatol. 2018;17(2):221-228.



[Acta Derm Venereol](#), 2016 May;96(4):514-20. doi: 10.2340/00015555-2360.

## Effects of Apremilast on Pruritus and Skin Discomfort/Pain Correlate With Improvements in Quality of Life in Patients With Moderate to Severe Plaque Psoriasis.

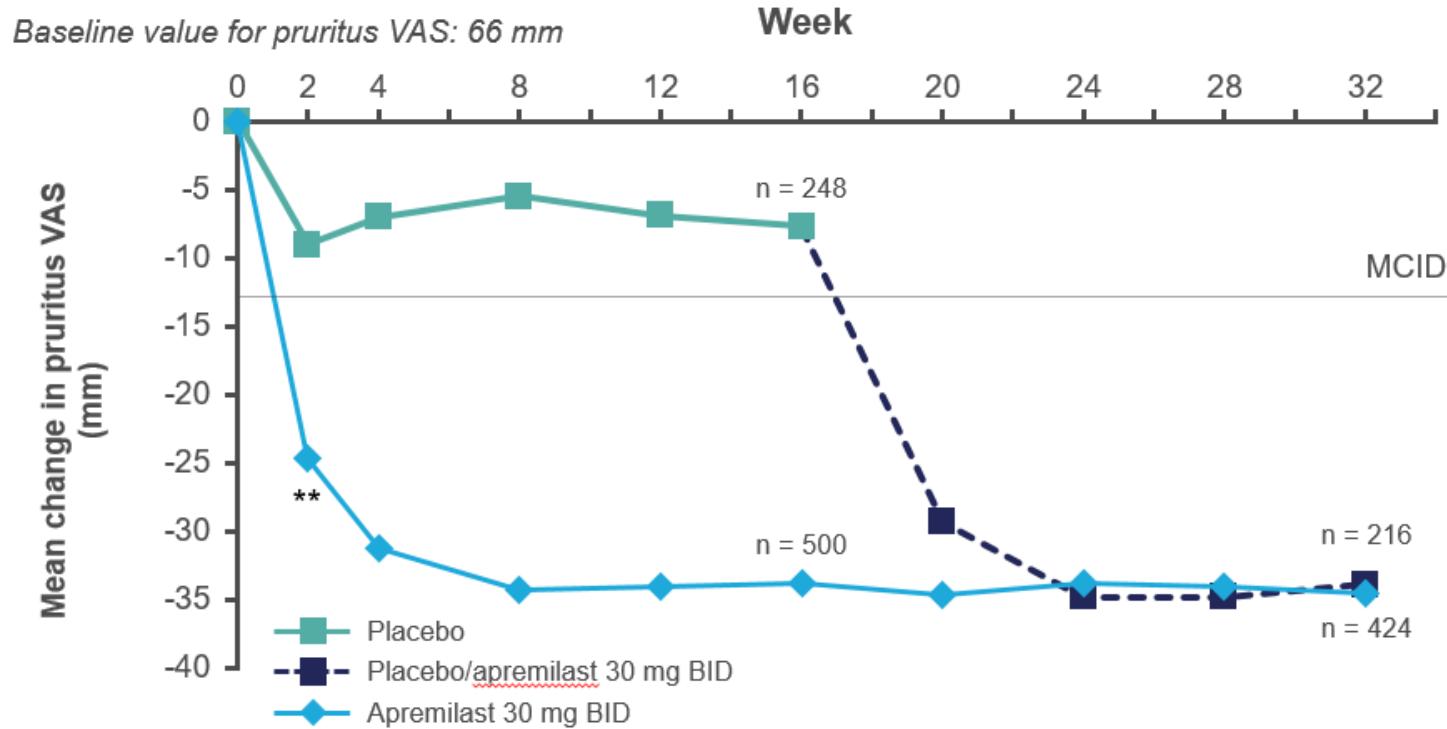
[Sobell JM<sup>1</sup>](#), [Foley P](#), [Toth D](#), [Mrowietz U](#), [Girolomoni G](#), [Goncalves J](#), [Day RM](#), [Chen R](#), [Yosipovitch G](#).

### Author information

#### Abstract

Pruritus and skin discomfort/pain negatively impact health-related quality of life (HRQoL). The effects of apremilast, an oral phosphodiesterase inhibitor, on pruritus, skin discomfort/pain, and patient global assessment of psoriasis disease activity (PgAPDA) were assessed in moderate/severe chronic plaque psoriasis patients in the phase 3 ESTEEM trials. Significant improvements in pruritus and skin discomfort/pain observed at Week 2 with apremilast versus placebo (both studies,  $p < 0.0001$ ) were sustained through Week 32. Among apremilast-treated patients, improvements in pruritus visual analog scale (VAS) scores correlated with Dermatology Life Quality Index scores ( $rs = 0.55$  [Week 16],  $rs \geq 0.51$  [Week 32]; both studies,  $p < 0.001$ ). PgAPDA correlated with improvements in pruritus ( $rs \geq 0.56$  [Week 16];  $rs \geq 0.53$  [Week 32]; both studies,  $p < 0.001$ ) and skin discomfort/pain ( $rs \geq 0.54$  [Week 16];  $rs \geq 0.53$  [Week 32]; both studies,  $p < 0.001$ ) VAS scores. Apremilast provided rapid and sustained improvement in pruritus and skin discomfort/pain, symptoms not typically captured in psoriasis assessments (e.g., PASI) that contribute significantly to patients' disease severity and HRQoL perceptions.

## Data from ESTEEM 1



Improvement in pruritus severity was correlated with an improvement in patient quality of life

\*\* P < 0.0001 vs. placebo (*post hoc* analysis); observed, full analysis set.

Week 16, n = 248 (placebo) and n = 500 (apremilast 30 mg BID); Week 32, n = 216 (placebo) and n = 424 (apremilast 30 mg BID).

BID, twice daily; MCID, minimal clinically important difference; VAS, visual analogue scale.

Sobell J, et al. Acta Derm Venereol 2016;96:514–520.



# Paziente moderato

Nel complesso, emerge come apremilast sia una opzione terapeutica valida e sicura in particolare nel paziente moderato, con scarsa estensione clinica della patologia ma coinvolgimento di aree "critiche" e/o scarsa qualità di vita (anche dovuta a sintomatologia pruriginosa)



	Psoriasis manifestation	Psa manifestation	Apremilast
Skin	✓		Significant reduction in psoriasis as early as Week 2; effects maintained longer term <sup>1-3</sup>
Scalp	✓		Significant reduction in scalp psoriasis <sup>4</sup>
Nails	✓		Significant reduction in nail psoriasis <sup>4</sup>
Palmoplantar	✓		Significant reduction in palmoplantar psoriasis <sup>3,5</sup>
Patient itch	✓		Rapid and significant reduction in itch as early as 2 weeks and effects maintained longer term <sup>6</sup>
Patient QoL (DLQI)	✓		Significant improvement in patient QoL and effects maintained longer term <sup>2,3,6,7</sup>
Tender and swollen joints		✓	~80% and ~90% reduction in tender and swollen joint counts respectively, at 5 years <sup>8</sup>
Enthesitis		✓	~60% patients with complete resolution at 5 years <sup>9</sup>
Dactylitis		✓	~80% patients with complete resolution at 5 years <sup>9</sup>

1. Otezla® (apremilast) SmPC. August 2018; 2. Papp K, et al. J Am Acad Dermatol 2015;73:37–49; 3. Paul C, et al. Br J Dermatol 2015;173:1387–99; 4. Rich P, et al. J Am Acad Dermatol 2018;74:134–42; 5. Bissonnette R, et al. J Am Acad Dermatol 2016;75:99–105;

6. Sobell J, et al. Acta Derm Venereol 2016;96:514–520; 7. Thaci D, et al. J Eur Acad Dermatol Venereol 2017;31:498–506;

DLQI, dermatology life quality index; QoL, quality of life.

8. Kavanaugh A, et al. Presented at: the 76th Annual Meeting of the AAD. 2018. Poster 6338;

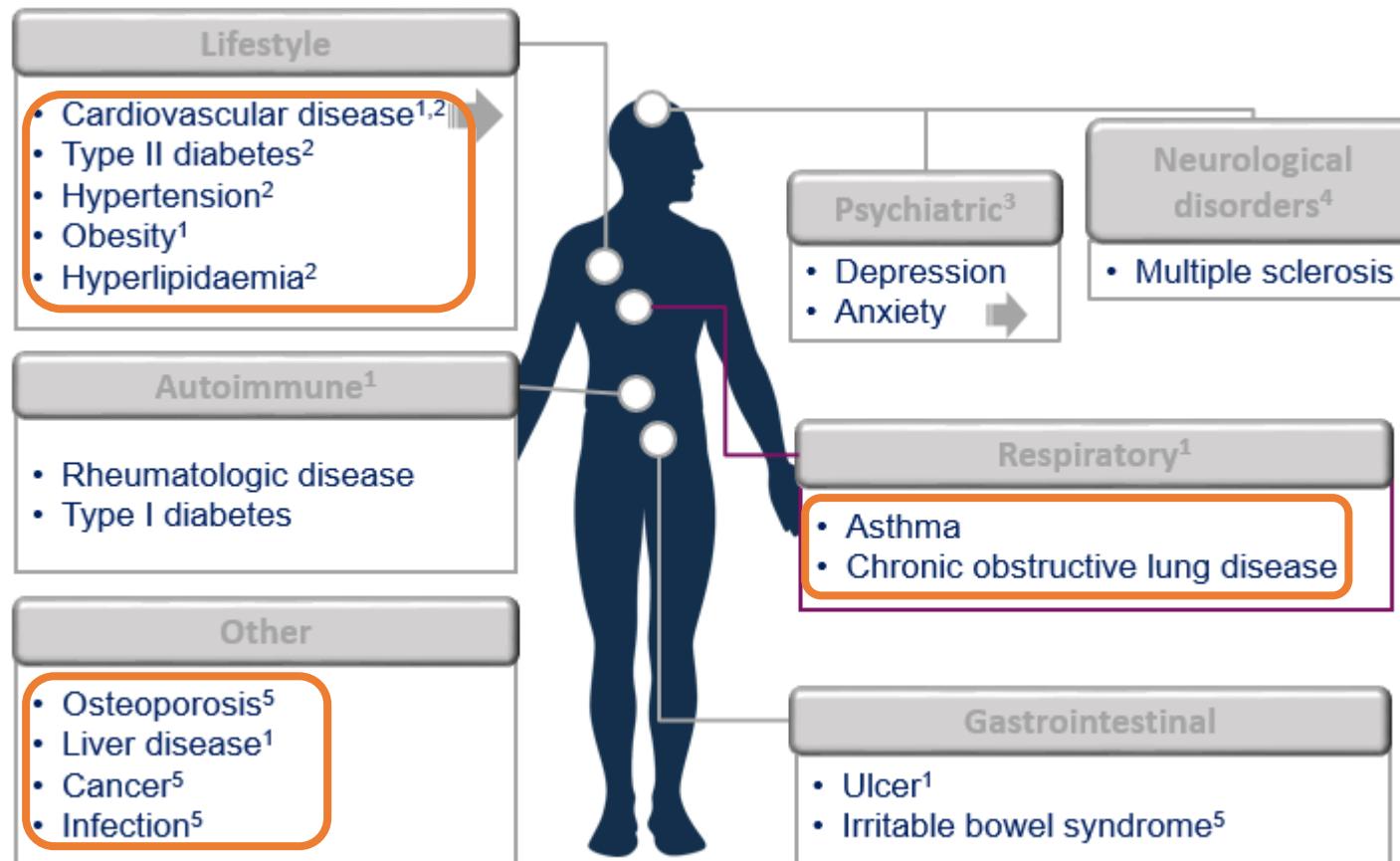
9. Kavanaugh A, et al. Presented at: the EULAR Annual Meeting. 2018. Poster THU0294.



# *Il paziente anziano con comorbidità*



# Paziente anziano



1. Yeung H et al. *JAMA Dermatol* 2013;149:1173–1179; 2. Kimball AB et al. *J Am Acad Dermatol* 2012;87:76–85; 3. Schmitt JM et al. *Dermatol* 2007;215:17–27.  
4. Dobson R et al. *J Neurol* 2013;260:1272–85; 5. Husted JA et al. *Arthritis Care Res (Hoboken)* 2011;63:1729.



# Paziente anziano

Oral DMARDs	Biologics
<b>Absolute contraindications<sup>a</sup></b>	
<ul style="list-style-type: none"><li>• Severe or serious infections<sup>1,11</sup></li><li>• Severe liver or kidney disorders<sup>1,11</sup></li><li>• Alcohol abuse<sup>1</sup></li><li>• Acute peptic ulcer<sup>1,11</sup></li><li>• History or current malignancy<sup>1,11</sup></li><li>• Significant anaemia, leukopenia, or thrombocytopenia<sup>2</sup></li><li>• Congestive heart failure<sup>1</sup></li><li>• Moderate to severe heart failure<sup>3</sup></li><li>• Sepsis<sup>4</sup></li><li>• History of or currently active infections (including tuberculosis and chronic hepatitis B)<sup>1,11</sup></li><li>• Systemic malignancy<sup>1</sup></li></ul>	
<b>Relative contraindications<sup>a</sup></b>	
<ul style="list-style-type: none"><li>• Kidney or liver disorders<sup>1,2,11</sup></li><li>• Diabetes<sup>2,11</sup></li><li>• Obesity<sup>2</sup></li><li>• Active infectious disease<sup>2</sup></li><li>• Live vaccine<sup>2,11</sup></li><li>• Concomitant treatment (e.g. SUP, nephrotoxic drugs)<sup>1,2,11</sup></li><li>• Compatibility with lifestyle<sup>5,6</sup><ul style="list-style-type: none"><li>• E.g. family planning<sup>7,8</sup> or burden of monitoring<sup>11</sup></li></ul></li></ul>	<ul style="list-style-type: none"><li>• Current, active, serious infections<sup>10</sup></li><li>• Severe liver disease<sup>11</sup></li><li>• History of tuberculosis<sup>10</sup></li><li>• Malignancy<sup>11</sup></li><li>• Hepatitis C<sup>1</sup></li><li>• Live vaccines<sup>1,10,11</sup></li><li>• Fear of needles/injections<sup>8</sup></li><li>• Concomitant treatment (e.g. PUVA &gt;200 treatments)</li><li>• Compatibility with lifestyle<sup>11</sup><ul style="list-style-type: none"><li>• E.g. burden of monitoring</li></ul></li></ul>

<sup>a</sup>List not exhaustive.

1. Pathirana D et al. JADAV. 2009;23(supple 2):1–70. 2. Kalb RE et al. J Am Acad Dermatol. 2009;60:824–837. 3. Remicade (infliximab) PI. 4. Enbrel (etanercept) PI. 5. Schaarschmidt ML et al. Arch Dermatol. 2011;147:1285–1295. 6. Chan SA et al. J Dermatolog Treat. 2013;24:64–69. 7. Tung JP and Maibach HI. Drugs. 1990; 40:697–712. 8. Landau JL et al. Skin Therapy Lett. 2011;16:1–3. 10. Cush. Ann Rheum Dis. 2005;64(suppl 4):iv18–iv23. 11. Nast A et al. JDDG. 2011;9(suppl 2):S1–S104.



Table 4 Continued

	Other label indications	Dosage	Duration	Efficacy	Safety	Contraindications	Important drug interactions	Drug screening	Drug monitoring
<b>Apremilast</b>									
Moderate-to-severe plaque psoriasis in adult patients who failed to respond to, or who have contraindications to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA	Psoriatic arthritis	Oral; 30 mg twice daily, morning and evening without regard to meals. Initial 5-day titration period	Approved for continuous treatment regimen	PASI75 in 28.8–33.1% and PASI90 in 8.8–9.8% of patients at week 16	Transient nausea and diarrhoea. Upper respiratory tract infections. Uncommon suicidal ideation and behaviour.	Pregnancy or breastfeeding. Active infections	None	None	None



**Apremilast summary table**

Approval of apremilast in Germany	2015 (moderate to severe psoriasis vulgaris and psoriatic arthritis)
Recommended initial dose	10 mg per day according to the dosing regimen below this table
Recommended maintenance dose	60 mg per day (30 mg twice a day) according to the dosing regimen (see long version)
Onset of clinical effect	PASI 75 response in 25 % of patients after 10.9 weeks with 30 mg twice a day [6]
Selection of main contraindications	<ul style="list-style-type: none"><li>– Pregnancy and breast-feeding</li></ul>
Selection of important ADRs	<ul style="list-style-type: none"><li>– Diarrhea</li><li>– Nausea</li><li>– Suicidal ideation</li></ul>
Selection of important drug interactions	Strong inducers of CYP3A4 (rifampicin, phenobarbital, carbamazepine, phenytoin and St. John's wort) may cause faster metabolism of apremilast
Miscellaneous	PDE-4 inhibitor



DOI: 10.1111/jdv.14114

GUIDELINES

## Italian guidelines on the systemic treatments of moderate-to-severe plaque psoriasis

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"Patients with a **history of neoplasm** require extreme caution in the prescription of immunosuppressive drugs. [...] Indeed, European guidelines recommended that **biological therapy should be avoided in patients with a current or recent past history of malignancy** (except for non-melanoma skin cancer) unless the malignancy has been diagnosed and treated more than **5 years** previously and the likelihood of cure is high [...]"



## MAJOR CARDIAC EVENTS, MALIGNANCIES, DEPRESSION AND SUICIDALITY – 3-YEAR POOLED ESTEEM DATA

Data from ESTEEM 1–2

	Apremilast-exposure period 0 to ≤ 52 weeks <sup>a</sup>		Apremilast-exposure period 0 to ≤ 182 weeks <sup>a</sup>	
	Apremilast n = 1184; pt-yrs = 915.7	Apremilast n = 1184; pt-yrs = 1902.2	n (%)	EAIR/100 pt-yrs
<b>Patients</b>				
Major cardiac events	4 (0.3)	0.4	10 (0.8)	0.5
Malignancies	15 (1.3)	1.6	23 (1.9)	1.2
Haematological	0	0	1 (0.1) <sup>b</sup>	0.1
Skin				
Basal cell carcinoma	9 (0.8)	1.0	11 (0.9)	0.6
Squamous cell carcinoma Keratoacanthoma	4 (0.3)	0.4	5 (0.4)	0.3
Malignant melanoma	3 (0.3)	0.3	4 (0.3)	0.2
Solid tumours	0	0	1 (0.1)	0.1
Breast cancer				
Lip and/or oral cavity cancer	2 (0.2)	0.2	3 (0.3)	0.2
Rectal cancer	0	0	1 (0.1)	0.1
Renal cell carcinoma	0	0	1 (0.1)	0.1
Thyroid neoplasm	1 (0.1)	0.1	2 (0.2)	0.1
Uterine cancer	0	0	1 (0.1)	0.1
Prostate cancer	1 (0.1)	0.1	1 (0.1)	0.1
Thyroid cancer	0	0	1 (0.1)	0.1
0	0	0	1 (0.1)	0.1
Depression as an AE	24 (2.0)	2.7	33 (2.8)	1.8
Depression as a serious AE	1 (0.1)	0.1	2 (0.2)	0.1
Suicide attempt	1 (0.1)	0.1	1 (0.1)	0.1
Completed suicide	0	0	0	0

- Rates of major cardiac events, malignancies, depression and suicidality were comparable across the APR-exposure periods

<sup>a</sup> The APR-exposure periods 0 to ≤ 52 weeks and 0 to ≤ 182 weeks include all patients who received APR regardless of when apremilast exposure started. APR exposure is based on each patient's total exposure to APR, defined as the time interval between the date of the first dose of apremilast and the date of the last dose of APR, inclusive; <sup>b</sup> diffuse large B-cell lymphoma. AE, adverse event; APR, apremilast 30 mg twice daily; EAIR/100 pt-yrs, 100 times the number (n) of patients reporting the event divided by pt-yrs (up to the first event start date for patients reporting the event); pt-yrs, patient-years.  
[JAAD](#). 2017 Aug;77(2):310-317.e1. doi: 10.1016/j.jaad.2017.01.052. Epub 2017 Apr 14.



# Paziente anziano

In questo contesto, apremilast:

- Non richiede un monitoraggio laboratoristico durante il trattamento
- Possiede scarse interazioni con altri farmaci (vantaggio in pazienti anziani spesso in terapia polifarmacologica cronica)
- Buon profilo di sicurezza in caso di scompenso cardiaco congestizio
- Possibilità di modulazione della dose in caso di insufficienza renale o di effetti collaterali
- Buon profilo di sicurezza in pazienti con comorbidità neoplastica recente e non aumento dell'incidenza di neoplasie



# Paziente anziano

Apremilast, grazie al suo favorevole profilo di sicurezza e tollerabilità, potrebbe rappresentare una valida opzione terapeutica in pazienti anziani, "fragili", con comorbidità multiple, laddove altre terapie sistemiche possono essere controindicate.



# ***Il paziente con comorbidità infettive***



# Comorbidità infettive

Nell'ambito degli effetti collaterali di apremilast, benché siano preponderanti gli effetti gastrointestinali, è riportato anche un lieve aumento del rischio di infezioni respiratorie delle vie aeree superiori.

Nonostante ciò, apremilast sembra possedere un buon profilo di sicurezza in presenza di comorbidità infettive.

Si ricorda, inoltre, come da scheda tecnica non sia previsto uno screening (markers HBV-HCV, quantiferon test...) pre-terapia.



J Am Acad Dermatol. 2017 Aug;77(2):310-317.e1. doi: 10.1016/j.jaad.2017.01.052. Epub 2017 Apr 14.

## Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥156 weeks from two phase 3 trials (EPOLEM 1 and 2)

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Abstract

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JCMS Case Report

SAGE Open Medical Case Reports

## Treatment of moderate to severe psoriasis with apremilast over 2 years in the context of long-term treated HIV infection: A case report

Misha Zarbaian<sup>1</sup>, Benoit Cote<sup>2</sup> and Vincent Richer<sup>1</sup>

SAGE Open Medical Case Reports

JCMS Case Reports

Volume 7: 1–2

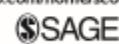
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**LIMITATIONS:** This study had a high dropout rate (21% of patients ongoing >156 weeks); most were unrelated to safety concerns.

**CONCLUSIONS:** Apremilast demonstrated an acceptable safety profile and was generally well tolerated for ≥156 weeks.

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SCUOLA DERMATOLOGICA  
SERGIO CHIMENTI

# Terapie di combinazione



# Terapie di combinazione

L'utilizzo combinato di Apremilast con altre terapie sistemiche è un'evenienza già riportata in letteratura sottoforma di case reports di associazione con adalimumab [1] e secukinumab [2]. Inoltre, vi è la possibilità di combinazione con altri farmaci sistematici come il methotrexate, l'acitretina, ciclosporina, fototerapia e altre terapie biologiche [3][4].

[1]. Danesh MJ, Beroukhim K, Nguyen C, Levin E, Koo J. Apremilast and adalimumab: A novel combination therapy for recalcitrant psoriasis. *Dermatol Online J.* 2015;21

[2]. Rothstein BE, McQuade B, Greb JE, Goldminz AM, Gottlieb AB. Apremilast and secukinumab combined therapy in a patient with recalcitrant plaque psoriasis. *J Drugs Dermatol.* 2016;15:648-9.

[3]. Abu Hilal M, Walsh S, Shear N. Use of apremilast in combination with other therapies for treatment of chronic plaque psoriasis: A retrospective study. *J Cutan Med Surg.* 2016;20:313-6.

[4]. Nast et al, European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol.* 2017 Dec;31(12):1951-1963



# Terapie di combinazione

Grazie all'assenza di interazioni farmacologiche con le altre terapie sistemiche si può sfruttare, ad esempio, l'effetto di apremilast sulla PsA in un paziente già in terapia biologico e non adeguatamente controllato sul versante articolare, ottenendo una risposta sinergica.

## Therapeutic combinations

Recommendation	Strength of consensus	Comment
Acitretin	○	Strong consensus No evidence available
Adalimumab	○	Strong consensus No evidence available
Ciclosporin	○	Strong consensus No evidence available
Etanercept	○	Strong consensus No evidence available
Fumaric acid esters	○	Strong consensus No evidence available
Infliximab	○	Strong consensus No evidence available
Methotrexate	○	Strong consensus No evidence available of the clinical benefit of this association in patients with chronic plaque psoriasis. A single pharmacokinetic study showed that methotrexate and apremilast can be co-administered without any effect on the pharmacokinetic exposure of either agent.
Secukinumab	○	Strong consensus No evidence available
Ustekinumab	○	Strong consensus No evidence available



# Terapie di combinazione

**Table 6**

Studies on combination therapy with apremilast

Combinations used	Evidence	Outcome
Methotrexate, etanercept, and ustekinumab	Multicenter, retrospective review[11]	Comparable long-term (52-week) efficacy and safety with monotherapy and combination therapy
NB-UVB, methotrexate, cyclosporine, acitretin, TNF inhibitors, ustekinumab	Retrospective chart review [66]	Apremilast is a relatively safe and effective treatment in combination with systemic, biologic, or phototherapy in the treatment of inadequately controlled chronic plaque psoriasis
NB-UVB	Open-label study[67]	A high treatment response (PASI 75 in 73% at week 12) without any unexpected safety signals in patients with moderate to severe plaque psoriasis
Adalimumab	Case report[68]	Plaque type psoriasis recalcitrant to topical, oral, and biologic medications attained almost complete remission
DMARDs	PALACE1 RCT (phase 3) [69]	Apremilast efficacious in psoriatic arthritis regardless of concomitant DMARD use
Secukinumab	Case report[70]	Significant skin improvement with minimal drug side effects in recalcitrant plaque psoriasis and psoriatic arthritis
Infliximab	Case report[71]	Maintenance of remission in generalised pustular psoriasis and acrodermatitis continua of Hallopeau after initial control with cyclosporine

RCT=Randomized controlled trial



# Ulteriori indicazioni

- Pazienti agofobici: la somministrazione orale è spesso un requisito chiesto dai pazienti
- Pazienti con scarsa compliance: la somministrazione orale e la mancanza di necessità di monitoraggio stretto con esami ematochimici può essere un vantaggio in questa tipologia di pazienti.



**GRAZIE PER L'ATTENZIONE!**