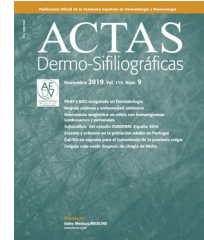




# ACTAS Derma-Sifiliográficas

Full English text available at  
[www.actasdermo.org](http://www.actasdermo.org)



## ORIGINAL ARTICLE

### The Use of Apremilast in Psoriasis: A Delphi Study<sup>☆</sup>



J.M. Carrascosa,<sup>a,\*</sup> I. Belinchón,<sup>b</sup> R. Rivera,<sup>c</sup> M. Ara,<sup>d</sup> M. Bustinduy,<sup>e</sup> P. Herranz<sup>f</sup>

<sup>a</sup> Servicio de Dermatología, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Barcelona, Spain

<sup>b</sup> Servicio de Dermatología, Hospital General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain

<sup>c</sup> Servicio de Dermatología, Hospital La Princesa, Madrid, Spain

<sup>d</sup> Servicio de Dermatología, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

<sup>e</sup> Servicio de Dermatología, Hospital Universitario de Canarias, La Laguna, Tenerife, Spain

<sup>f</sup> Servicio de Dermatología, Hospital Universitario La Paz, Madrid, Spain

Received 24 January 2019; accepted 22 July 2019

Available online 2 February 2020

#### KEYWORDS

Psoriasis;  
Apremilast;  
Treatment;  
Delphi;  
Recommendations;  
Small molecules

#### Abstract

**Background:** Experience in the use of apremilast in clinical practice complements the information available from pivotal clinical trials.

**Materials and methods:** Following a review of the literature, a panel of dermatologists with expertise in the management of psoriasis considered 5 scenarios in which the evidence supporting the use of apremilast to treat moderate psoriasis is insufficient or controversial. These scenarios were then assessed using a Delphi questionnaire.

**Results:** Consensus was reached on 96 (67%) of the 143 items (positive in 85 and negative in 11). The therapeutic goal for apremilast should be based on 4 outcomes: clinical response, symptoms, quality of life, and patient satisfaction. The scenario in which the use of apremilast was considered to have the greatest possibility of success was in patients with stable moderate psoriasis. Most of the clinicians considered apremilast to be an appropriate treatment when conventional therapies fail or are contraindicated, preferably before the prescription of biologic therapy. Consensus was reached that apremilast is an appropriate treatment for psoriasis in difficult locations, such as the scalp or the palms and soles. It was also agreed that apremilast requires less prescreening and monitoring than other conventional and biologic systemic therapies.

**Conclusions:** Apremilast could be a treatment option for patients with a different profile to that of clinical trial participants. The limitations of this proposal are the absence of consensus on the definition of moderate psoriasis, the lack of real-world evidence on the use of apremilast, and certain aspects related to tolerability.

© 2020 Published by Elsevier España, S.L.U. on behalf of AEDV. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<sup>☆</sup> Please cite this article as: Carrascosa JM, et al. Estudio Delphi para el uso de apremilast en la psoriasis. Actas Dermosifiliogr. 2020;111:115–134.

\* Corresponding author.

E-mail address: [jmcarrascosac@hotmail.com](mailto:jmcarrascosac@hotmail.com) (J.M. Carrascosa).

**PALABRAS CLAVE**

Psoriasis;  
Apremilast;  
Tratamiento;  
Delphi;  
Recomendaciones;  
Moléculas pequeñas

**Estudio Delphi para el uso de apremilast en psoriasis****Resumen**

**Antecedentes:** El manejo de apremilast en la práctica clínica complementa la información procedente de los ensayos clínicos pivotaes.

**Material y método:** Tras una revisión de la literatura se consideraron, por parte de un panel de dermatólogos expertos en el manejo de la psoriasis, 5 áreas donde la evidencia sobre el uso de apremilast en psoriasis moderada era insuficiente o controvertida que fueron evaluadas a través de un cuestionario diseñado según la metodología Delphi.

**Resultados:** Se alcanzó consenso en 96 de los 143 ítems planteados (67%) (85 en el acuerdo y 11 en el desacuerdo). El objetivo terapéutico con apremilast debería ponderarse entre la respuesta clínica, la sintomatología asociada, la calidad de vida y la satisfacción del paciente. El perfil en el que el uso de apremilast se considera con mayores posibilidades de éxito sería el de un paciente con psoriasis moderada estable. La mayoría de los clínicos consideraron que apremilast es adecuado para pacientes en los que hayan fracasado o estén contraindicados los tratamientos convencionales, preferentemente de forma previa a la indicación de terapia biológica. Hubo consenso en reconocer apremilast como una opción terapéutica adecuada para el tratamiento en localizaciones difíciles como la psoriasis palmoplantar y del cuero cabelludo. La necesidad de cribado, así como de su monitorización durante el seguimiento, se consideró menor que la de otros tratamientos sistémicos, convencionales y biológicos.

**Conclusiones:** Apremilast podría representar una opción terapéutica en un perfil de pacientes distinto al presentado en los ensayos clínicos. La ausencia de un consenso sobre la definición de psoriasis moderada, la escasa evidencia acerca del fármaco en vida real, así como algunos aspectos relacionados con la tolerabilidad representan limitaciones a estas propuestas.

© 2020 Publicado por Elsevier España, S.L.U. en nombre de AEDV. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Introduction**

Apremilast is an oral phosphodiesterase-4 inhibitor with immunomodulatory activity that partially blocks the expression of proinflammatory cytokines and induces the expression of anti-inflammatory cytokines with a pathogenic role in psoriasis. It is indicated for the treatment of moderate to severe psoriasis<sup>1</sup> and psoriatic arthritis and has acceptable short- and long-term safety and tolerability profiles. Nevertheless, because the patients studied in the pivotal clinical trials of apremilast had a very specific profile, similar to that of candidates for biologic therapy,<sup>2,3</sup> little is known about real-world usage, such as the identification of candidates for treatment or the correct positioning of the drug in relation to conventional and biologic therapies. Consensus-based recommendations based on expert opinions and developed using rigorous, validated methodologies serve as useful guidelines for such situations and provide experts with valuable information on the use of apremilast in everyday clinical practice.<sup>4</sup>

To complement the existing evidence on the use of apremilast, a group of experts came together to evaluate clinical scenarios and aspects of treatment for which the information in the literature was considered to be lacking.

**Material and Methods****Expert Panel**

The expert panel was formed by a national coordinator (J.M.C.) and 5 regional coordinators (R.R., I.B., M.G.B., M.A., P.H.). The regional members proposed and discussed

different clinical scenarios associated with the use of apremilast for which they considered it would be interesting to develop recommendations in light of the current lack of evidence or consensus. Five scenarios were chosen: *i*) effectiveness of apremilast in moderate psoriasis as an option prior to biologic therapy in this setting, *ii*) effectiveness in special locations: nails, scalp, and palms/soles; *iii*) effectiveness in psoriasis and psoriatic arthritis, *iv*) prescreening and management of comorbidities in psoriasis, and *v*) safety issues.

**Literature Search**

A literature search was performed in the MEDLINE and Cochrane Library databases to identify issues associated with the use of apremilast for which existing evidence was considered to be insufficient to answer questions that arise in routine clinical practice. A separate search strategy, complemented by a hand search, was designed for each scenario. For the evaluation of the different scenarios, priority was given to data from randomized clinical trials and real-world studies, although recent consensus documents, recommendation articles, and clinical guidelines were also included. The literature search was performed in February 2018 and targeted articles originally published in English or Spanish. No time restrictions were placed on clinical trials or real-world studies (Table 1). When this article was finished, additional searches of the same databases were performed to identify new information on the real-world use of apremilast (literature search updated in May 2019).

**Table 1** Literature Search Strategy.

The search strategies used for each scenario are detailed below: i) Scenario #1: "(Apremilast OR otezla) AND (psoriasis OR moderate psoriasis OR severe to moderate psoriasis) AND efficacy NOT psoriatic arthritis" (45 references/12 clinical trials); ii) Scenario #2: "(Apremilast OR otezla) AND (psoriasis OR moderate psoriasis OR severe to moderate psoriasis) AND efficacy AND (scalp OR nail OR palmoplantar OR difficult to treat) NOT psoriatic arthritis" (9 references/2 clinical trials); iii) Scenario #3: "(Apremilast OR otezla) AND (psoriasis OR moderate psoriasis OR severe to moderate psoriasis) AND psoriatic arthritis AND efficacy" (214 references/2 clinical trials); iv) Scenario #4: "psoriasis AND comorbid\* AND (screening OR management) NOT psoriatic arthritis" (513 references/8 clinical trials); v) Scenario #5: "(Apremilast OR otezla) AND (psoriasis OR moderate psoriasis OR severe to moderate psoriasis) AND safety NOT psoriatic arthritis" (27 references/11 clinical trials)

## Development of the Delphi Questionnaire

Appendix B Annex SI. See supplementary material.<sup>5-7</sup>

## Results

### Effectiveness of Apremilast in Moderate Psoriasis: Use Before Biologic Therapy in Patients With Moderate Psoriasis

Positive consensus was reached for 30 (55.6%) of the 54 items (24 in the first round and 6 in the second round) on the use of apremilast before biologic therapy in patients with moderate psoriasis. Negative consensus was achieved for 3 items (5.6%): 2 in the first round and 1 in the second. Absolute Psoriasis and Area Severity Index (PASI) scores and overall patient-reported satisfaction were considered to be the most appropriate variables for evaluating apremilast in clinical practice. The panel agreed that it was appropriate to maintain apremilast up to 24 weeks in patients with a partial response at week 16 (< 50% reduction in PASI or absolute PASI score > 5), as long as they were satisfied with the treatment and had not experienced significant impairment in quality of life (Dermatology Life Quality Index [DLQI] score < 1). It was even considered justifiable to maintain apremilast beyond week 24 in patients who had not achieved PASI-75 if they were satisfied with their treatment.

Apremilast was considered to be an appropriate treatment for patients with moderate psoriasis when conventional systemic treatments fail or are contraindicated and for patients who are not yet candidates for biologic therapy or who do not respond to or have a contraindication to biologic agents. The following factors were identified as having the greatest influence on the decision to prescribe apremilast: *i*) moderate skin involvement, *ii*) clinical stability, *iii*) associated symptoms, *iv*) presence of palmoplantar psoriasis, *v*) presence of comorbidities, *vi*) polymedication, *vii*) young patients expected to need treatment for a long time, and *viii*) patients with injection phobia. By contrast, apremilast was not considered appropriate for patients with extensive, unstable psoriasis or for patients requiring rapid clearance.

The combined use of apremilast and phototherapy (particularly narrowband UV-B therapy) was considered appropriate in the following circumstances: *i*) as a treatment initiation strategy in patients requiring rapid clearance, *ii*) in patients who fail to achieve an optimal response after 16 to 24 weeks but who are satisfied with their treatment, and *iii*) in patients who start to show loss of effectiveness (Table 2).

## Effectiveness of Apremilast in Special Locations

The expert panel agreed in the first round that apremilast was an appropriate treatment for patients with psoriasis affecting special locations, such as the nails, the scalp, and the palms and soles (Table 3).

### Effectiveness of Apremilast in Patients With Concomitant Psoriasis and Psoriatic Arthritis

Positive consensus was reached for 3 (42.9%) of the 7 items (2 in the first round and 1 in the second) on the use of psoriasis in patients with concomitant psoriasis and psoriatic arthritis. It was agreed that it was appropriate to use apremilast before biologic therapy in patients with moderate to severe psoriasis and concomitant psoriatic arthritis who have peripheral disease with moderate inflammatory activity (few joints affected) or dactylitis (Table 4).

### Prescreening and Management of Comorbidities in Psoriasis

Positive consensus was reached for 26 (59.1%) of the 44 items (20 in the first round and 6 in the second round) in the section on apremilast and comorbidities in psoriasis. Negative consensus was reached for 4 items (9.1%): 2 in the first round and 1 in the second. It was agreed that apremilast offered advantages over other conventional systemic treatments and biologic therapies in terms of its impact on comorbidities in patients with recurrent, chronic, or active infections, a recent history of cancer (< 5 years), active cancer, other immunosuppressive states, or metabolic disorders. The panel also agreed that apremilast was safer than biologic agents for patients with congestive heart disease or demyelinating disorders. By contrast, apremilast was not considered to be an appropriate treatment for patients with mood disorders (Table 5).

Prescreening and follow-up requirements were considered to be less stringent with apremilast than with conventional systemic or biologic therapies. The panel agreed, however, that blood tests and a pregnancy test in women of childbearing potential were advisable before treatment initiation. They did not, however, consider it necessary to perform a chest radiograph or to test for latent tuberculosis before starting treatment. It was also considered unnecessary to modify vaccine schedules once treatment had started (Table 5).

**Table 2** Effectiveness of Apremilast in Moderate Psoriasis: Use Before Biologic Therapy in Patients With Moderate Disease.

	Item	Median	MAD-M	Appropriateness	Agreement	Result
1	Moderate plaque psoriasis must be differentiated from severe psoriasis and the different treatment options available for both conditions should be considered.	8	0.94	Appropriate	Agree	Consensus in first round
2	The criteria for classifying moderate plaque psoriasis need to be better defined.	9	0.47	Appropriate	Agree	Consensus in first round
3	Treatment response criteria in moderate plaque psoriasis need to be better defined.	8	0.76	Appropriate	Agree	Consensus in first round
4	The most appropriate indices for evaluating response in moderate psoriasis are					
	PASI-75/PASI-90/PASI-100	6	1.18	Not true	Neutral	No consensus
	Relative PASI (percent improvement)	7	0.94	Appropriate	Neutral	No consensus
	PASI (absolute value)	8	1.06	Appropriate	Agree	Consensus in first round
	BSA	5	1.18	Not true	Neutral	No consensus
	PGA	8	0.71	Appropriate	Agree	Consensus in first round
	DLQI	8	0.94	Appropriate	Neutral	No consensus
	Overall patient-reported satisfaction	8	1.06	Appropriate	Agree	Consensus in first round
	Self-reported satisfaction questionnaires (patient-reported outcomes)	7	0.76	Appropriate	Neutral	No consensus
7	The most appropriate measures for evaluating the therapeutic effect of apremilast are					
	PASI-75	6	1.35	Not true	Neutral	No consensus
	Relative PASI (percent improvement)	7	1.00	Appropriate	Neutral	No consensus
	PASI (absolute value)	8	0.71	Appropriate	Agree	Consensus in first round
	PGA	7	1.29	Appropriate	Neutral	No consensus
	BSA	6	1.35	Not true	Neutral	No consensus
	PGA × BSA	5	1.18	Not true	Neutral	No consensus
	Improvement in quality of life (DLQI)	6	0.94	Not true	Neutral	No consensus
	Visual analog scales (pruritus/pain)	7	1.24	Appropriate	Neutral	No consensus
	Safety	9	1.06	Appropriate	Agree	Consensus in first round
	Tolerability	7	1.18	Appropriate	Agree	Consensus in first round
	Overall patient-reported satisfaction	8	0.88	Appropriate	Agree	Consensus in first round

Table 2 (Continued)

	Item	Median	MAD-M	Appropriateness	Agreement	Result
8	The treatment goal for apremilast should be based on clinical response, associated symptoms, and quality of life assessed on a case-by-case basis.	9	0.71	Appropriate	Agree	Consensus in first round
9	Patient satisfaction with treatment is an important factor to consider when assessing the therapeutic effect of apremilast.	8	1.12	Appropriate	Agree	Consensus in first round
10	It is appropriate to switch from apremilast to another treatment in the following situations:					
	Failure to achieve PASI-50 during the first 16 weeks of treatment	7	1.29	Appropriate	Neutral	No consensus
	Failure to achieve PASI-75 during the first 16 weeks of treatment	4	1.35	Not true	Neutral	No consensus
	Absolute PASI score > 7 during the first 16 weeks of treatment	7	1.47	Appropriate	Neutral	No consensus
	Absolute PASI score > 5 during the first 16 weeks of treatment	7	1.29	Appropriate	Neutral	No consensus
	Absolute PASI score > 3 during the first 16 weeks of treatment	3	1.18	Inappropriate	Agree	Consensus in first round
11	It is appropriate to maintain treatment with apremilast in a patient who does not achieve PASI-50 or has an absolute PASI score > 5 after 16 weeks of treatment if the effects on the patient's quality of life are satisfactory (DLQI < 5) and/or if the patient is satisfied with the treatment.	6	1.29	Not true	Neutral	No consensus
12	It is appropriate to maintain treatment with apremilast in a patient who does not achieve PASI-50 or has an absolute PASI score > 5 after 16 weeks of treatment if the effects on the patient's quality of life are satisfactory (DLQI < 1) and/or if the patient is satisfied with the treatment.	7	1.29	Appropriate	Agree	Consensus in first round

Table 2 (Continued)

Item	Median	MAD-M	Appropriateness	Agreement	Result	
13	In patients who achieve a partial response to apremilast (PASI $\geq$ 50% < 75%) during the first 16 weeks of treatment, it is appropriate to maintain treatment up to week 24 and then re-evaluate response.	8	0.59	Appropriate	Agree	Consensus in first round
14	It is appropriate to maintain treatment with apremilast in patients who express satisfaction with treatment even if they do not achieve PASI-75 by week 24.	8	1.53	Appropriate	Agree	Consensus in first round
19	It is appropriate to combine apremilast with phototherapy (narrowband UV-B therapy) in the following patients:					
	Patients who require faster clearance on treatment initiation	9	0.94	Appropriate	Agree	Consensus in first round
	Patients who do not achieve an optimal response after 16 to 24 weeks but who express satisfaction with their treatment	8	1.53	Appropriate	Agree	Consensus in first round
	Patients who experience loss of effectiveness during continued treatment with apremilast	8	1.29	Appropriate	Agree	Consensus in first round
22	The fact that drug effectiveness is restored during retreatment is a quality that makes apremilast an appropriate option for patients who require temporary treatment interruption.	8	0.76	Appropriate	Agree	Consensus in first round
5	Apremilast is a particularly appropriate option for the treatment of moderate psoriasis in patients who fail to respond to or have a contraindication to conventional systemic therapies but are not yet candidates for biologic therapy.	9	0.47	Appropriate	Agree	Consensus in first round
20	Apremilast is an appropriate option for patients with plaque psoriasis in whom biologic therapy has failed.	5	2.24	Not true	Disagree	No consensus

Table 2 (Continued)

	Item	Median	MAD-M	Appropriateness	Agreement	Result
21	Apremilast is an appropriate option for patients with plaque psoriasis in whom biologic therapy is contraindicated.	8	0.76	Appropriate	Agree	Consensus in second round
6	The variables that most influence the decision to use apremilast are					
	Moderate skin involvement	8	0.88	Appropriate	Agree	Consensus in first round
	Clinical stability	7	0.94	Appropriate	Agree	Consensus in first round
	Presence of associated symptoms (pruritus/pain)	8	0.88	Appropriate	Agree	Consensus in first round
	Presence of nail psoriasis	6	1.18	Not true	Neutral	No consensus
	Presence of scalp psoriasis	7	1.12	Appropriate	Neutral	No consensus
	Presence of palmoplantar psoriasis	8	0.82	Appropriate	Agree	Consensus in first round
	Presence of concomitant psoriatic arthritis	7	1.18	Appropriate	Neutral	No consensus
	Presence of comorbidities	9	1.06	Appropriate	Agree	Consensus in first round
	Polymedication	8	1.18	Appropriate	Agree	Consensus in first round
	A young patient who is expected to require specific treatments for psoriasis for a long time	7	0.71	Appropriate	Agree	Consensus in first round
	Elderly patients with multiple comorbidities	8	0.71	Appropriate	Agree	Consensus in first round
	Unstable forms of psoriasis with extensive skin involvement	1	1.24	Inappropriate	Agree	Consensus in first round
	Patients who require rapid clearance of skin lesions	1	1.18	Inappropriate	Agree	Consensus in first round
	Patients who prefer oral medication	9	0.94	Appropriate	Agree	Consensus in first round

Abbreviations: BSA, body surface area affected; DLQI, Dermatology Life Quality Index; MAD-M, mean absolute deviation from the median; PASI, Psoriasis Area Severity Index; PASI-75/90/100, reduction of  $\geq 75\%$ / $\geq 90\%$ / $\geq 100\%$  in PASI; PGA, physician global assessment.

**Table 3** Effectiveness of Apremilast in Special Locations: Nails, Scalp, and Palms and Soles.

Item	Median	MAD-M	Appropriateness	Agreement	Result
15 Psoriasis in special locations (scalp, nails, palms/soles) has a considerable impact on patient quality of life and is difficult to treat with available systemic treatments.	8	0.65	Appropriate	Agree	Consensus in first round
16 Apremilast is an appropriate option for treating psoriasis in special locations (nails, scalp, and palms/soles) before the use of biologic therapy.	8	0.76	Appropriate	Agree	Consensus in first round

Abbreviation: MAD-M, mean absolute deviation from the median.

**Table 4** Effectiveness of Apremilast in Patients With Concomitant Psoriasis and Psoriatic Arthritis.

Item	Median	MAD-M	Appropriateness	Agreement	Result
17 Apremilast is an appropriate option for treating patients with moderate psoriasis and concomitant psoriatic arthritis before the use of biologic therapy.	8	1.29	Appropriate	Agree	Consensus in second round
18 The factors that most influence the decision to start apremilast in patients with moderate psoriasis and concomitant psoriatic arthritis are					
Peripheral forms of disease with moderate inflammatory activity (few affected joints)	8	1.12	Appropriate	Agree	Consensus in first round
Peripheral forms of disease with severe inflammatory activity (generally multiple joint involvement)	3	1.18	Inappropriate	Neutral	No consensus
Axillary forms of disease	3	1.24	Inappropriate	Neutral	No consensus
Mixed forms of disease with moderate inflammatory activity	6	1.59	Not true	Neutral	No consensus
Presence of enthesitis	7	0.82	Appropriate	Neutral	No consensus
Presence of dactylitis	7	1.06	Appropriate	Agree	Consensus in first round

Abbreviation: MAD-M, mean absolute deviation from the median.

## Safety Issues

Positive consensus was reached for 24 (66.7%) of the 36 items (17 in the first round and 7 in the second ) on safety issues associated with the use of apremilast. Negative consensus was achieved for 4 items (11.1%), all in the first round. Monitoring was considered less necessary during treatment with apremilast than with conventional systemic treatment (consensus reached in the first round) or biologic therapy (consensus reached in the second round). It was agreed that a complete blood test was advisable once or twice a year and that additional tests should be ordered in accordance with the patient's underlying disease. The

panel also agreed that apremilast was an appropriate option for polymedicated patients and patients with injection phobia.

Weight loss, mood changes, and gastrointestinal disorders were all considered to be important adverse effects that should be contemplated before starting treatment with apremilast and monitored periodically thereafter. The panel also recommended monitoring weight changes in underweight patients and stressed the need to consider the risk of mood changes before starting a patient on apremilast and to monitor for such changes during treatment. The recommendations for minimizing and managing adverse effects are summarized in [Table 6](#) .



**Table 5** Prescreening and Management of Comorbidities in Psoriasis.

	Item	Median	MAD-M	Appropriateness	Agreement	Result
37	Comorbidities must be taken into account when treating patients with psoriasis.	9	0.29	Appropriate	Agree	Consensus in first round
38	Apremilast has advantages over other conventional systemic therapies in patients with psoriasis with					
	Cardiovascular disease	8	1.12	Appropriate	Agree	Consensus in first round
	Congestive heart failure	8	1.18	Appropriate	Agree	Consensus in first round
	Dyslipidemia	8	1.29	Appropriate	Agree	Consensus in first round
	Type 2 diabetes mellitus	8	1.35	Appropriate	Agree	Consensus in first round
	Obesity	8	1.00	Appropriate	Agree	Consensus in first round
	Metabolic syndrome	8	1.12	Appropriate	Agree	Consensus in first round
	Liver disease	8	1.12	Appropriate	Agree	Consensus in first round
	Chronic kidney failure	6	1.59	Not true	Neutral	No consensus
	Demyelinating disorders	8	1.88	Appropriate	Neutral	No consensus
	Inflammatory bowel disease	5	1.71	Not true	Neutral	No consensus
	Mood disorders	2	1.35	Inappropriate	Agree	Consensus in first round
	Multiple comorbidities	8	0.88	Appropriate	Agree	Consensus in first round
	Recurrent or chronic infections including HIV, HVB, and HVC infections and tuberculosis	8	1.18	Appropriate	Agree	Consensus in first round
	Active infections including HIV, HVB, HVC infections and tuberculosis	8	1.65	Appropriate	Agree	Consensus in first round
	A recent history of cancer (< 5 y)	9	1.24	Appropriate	Agree	Consensus in first round
	Active cancer	8	1.65	Appropriate	Agree	Consensus in first round
	Other immunosuppressive states	8	1.24	Appropriate	Agree	Consensus in first round

Table 5 (Continued)

	Item	Median	MAD-M	Appropriateness	Agreement	Result
39	Apremilast has advantages over biologic therapies in patients with psoriasis with Cardiovascular disease	5	1.59	Not true	Neutral	No consensus
	Congestive heart failure	8	1.76	Appropriate	Agree	Consensus in first round
	Dyslipidemia	5	1.41	Not true	Neutral	No consensus
	Type 2 diabetes mellitus	5	1.24	Not true	Neutral	No consensus
	Obesity	7	1.12	Appropriate	Neutral	No consensus
	Metabolic syndrome	7	1.29	Appropriate	Neutral	No consensus
	Liver disease	7	1.35	Appropriate	Neutral	No consensus
	Chronic kidney failure	3	1.29	Inappropriate	Neutral	No consensus
	Demyelinating disorders	8	1.24	Appropriate	Agree	Consensus in second round
	Inflammatory bowel disease	5	1.29	Not true	Neutral	No consensus
	Mood disorders	2	1.12	Inappropriate	Agree	Consensus in second round
	Multiple comorbidities	7	1.29	Appropriate	Neutral	No consensus
	Recurrent or chronic infections including HIV, HVB, and HVC infections and tuberculosis	8	0.76	Appropriate	Agree	Consensus in first round
	Active infections including HIV, HVB, and HVC infections and tuberculosis	8	0.88	Appropriate	Agree	Consensus in first round
	A recent history of cancer (< 5 y)	9	0.47	Appropriate	Agree	Consensus in first round
	Active cancer	9	1.00	Appropriate	Agree	Consensus in first round
Other immunosuppressive states	8	1.12	Appropriate	Agree	Consensus in first round	
23	Screening before treatment initiation is not as necessary with apremilast as with other conventional systemic therapies.	8	2.06	Appropriate	Agree	Consensus in first round

Table 5 (Continued)

	Item	Median	MAD-M	Appropriateness	Agreement	Result
24	Screening before treatment initiation is not as necessary with apremilast as with biologic therapies.	9	1.35	Appropriate	Agree	Consensus in first round
25	Screening is not necessary before treatment initiation with apremilast.	6	1.94	Not true	Disagree	No consensus
26	Screening before treatment initiation with apremilast is necessary in the following situations:					
	Conventional blood tests are advisable before treatment initiation with apremilast.	9	1.06	Appropriate	Agree	Consensus in first round
	A complete blood test, including serology for viral infections (HIV, HVB, and HVC), is necessary before treatment initiation with apremilast.	2	1.94	Inappropriate	Neutral	No consensus
	A chest radiograph is necessary before treatment initiation with apremilast.	2	1.29	Inappropriate	Agree	Consensus in first round
	Latent tuberculosis testing is necessary before treatment initiation with apremilast.	2	1.29	Inappropriate	Agree	Consensus in first round
	A pregnancy test is advisable before treatment initiation with apremilast in women of childbearing age.	9	1.65	Appropriate	Agree	Consensus in first round
	It is not necessary to change a patient's vaccine schedule after initiation of treatment with apremilast.	9	1.18	Appropriate	Agree	Consensus in first round

Abbreviations: HIV, human immunodeficiency virus; HVB, hepatitis virus B; HVC, hepatitis virus C; MAD-M, mean absolute deviation from the median.

**Table 6** Safety Issues Associated With the Use of Apremilast.

	Item	Median	MAD-M	Appropriateness	Agreement	Result
34	One of the most important characteristics of apremilast compared with other treatments is its good safety profile.	8	1.06	Appropriate	Agree	Consensus in first round
35	Apremilast can be considered to be safer than other conventional systemic treatments.	8	0.71	Appropriate	Agree	Consensus in first round
36	Apremilast can be considered to be safer than biologic therapies.	7	0.76	Appropriate	Agree	Consensus in first round
31	Apremilast is a particularly appropriate option for polymedicated patients as it has very few interactions with other drugs.	8	0.82	Appropriate	Agree	Consensus in first round
33	Apremilast is a particularly appropriate option for patients with injection phobia.	9	0.59	Appropriate	Agree	Consensus in first round
40	Weight loss during treatment with apremilast is a factor that should be monitored during routine follow-up	8	1.53	Appropriate	Neutral	No consensus
	only relevant in underweight patients	8	1.71	Appropriate	Neutral	No consensus
	a potentially beneficial effect in patients who are overweight/obese (possible risk factors for metabolic syndrome)	9	1.59	Appropriate	Neutral	No consensus

Table 6 (Continued)

	Item	Median	MAD-M	Appropriateness	Agreement	Result
27	Patients require less monitoring during clinical follow-up with apremilast than with other conventional systemic therapies.	9	0.53	Appropriate	Agree	Consensus in first round
28	Patients require less monitoring during clinical follow-up with apremilast than with biologic therapies.	8	0.65	Appropriate	Agree	Consensus in second round
29	Monitoring during clinical follow-up is not necessary in patients being treated with apremilast.	5	1.82	Not true	Neutral	No consensus
30	Monitoring during clinical follow-up is necessary in patients being treated with apremilast.					
	A complete blood test once or twice a year is advisable during treatment with apremilast.	8	1.35	Appropriate	Agree	Consensus in first round
	Annual latent tuberculosis testing is advisable during treatment with apremilast.	1	1.06	Inappropriate	Agree	Consensus in first round
	Additional tests and procedures should only be performed on a case-by-case basis according to the patient's underlying disease.	8	1.29	Appropriate	Agree	Consensus in first round
41	Periodic monitoring of weight changes is advisable during treatment with apremilast.	7	1.24	Appropriate	Neutral	No consensus

Table 6 (Continued)

	Item	Median	MAD-M	Appropriateness	Agreement	Result
42	Periodic monitoring of weight changes is only advisable in underweight patients during treatment with apremilast.	8	1.12	Inappropriate	Agree	Consensus in first round
43	The possibility of mood disorders should be taken into account before deciding to start a patient on apremilast and during routine follow-up.	8	1.18	Appropriate	Agree	Consensus in first round
44	During treatment with apremilast, it is advisable to:					
	periodically check for mood disorders in all patients	7	1.00	Appropriate	Agree	Consensus in first round
	periodically check for mood disorders only in patients with depression and patients being treated with antidepressants	8	1.41	Appropriate	Agree	Consensus in first round
32	Apremilast is an appropriate option for women of childbearing age who wish to become pregnant because of its pharmacokinetic profile.	8	1.12	Appropriate	Neutral	No consensus
45	The possibility of adverse gastrointestinal effects should be taken into account during routine follow-up.	9	0.71	Appropriate	Agree	Consensus in first round

Table 6 (Continued)

	Item	Median	MAD-M	Appropriateness	Agreement	Result
46	The most appropriate management strategy in patients with adverse gastrointestinal effects is to: reduce fluid intake during meals	7	1.18	Appropriate	Neutral	
	administer apremilast during meals	8	0.76	Appropriate	Agree	Consensus in first round
	recommend avoidance of caffeine-containing drinks	8	0.65	Appropriate	Agree	Consensus in first round
	administer antidiarrheals, antiemetics, and/or analgesics in patients with clinically relevant adverse effects that could affect continuation of treatment with apremilast.	9	0.88	Appropriate	Agree	Consensus in first round
	use a longer induction phase.	8	0.53	Appropriate	Agree	Consensus in first round
	temporarily withdraw the morning dose in patients with clinically relevant adverse effects that could affect continuation of treatment of apremilast and reintroduce the dose once the effects have cleared.	8	1.12	Appropriate	Agree	Consensus in first round
	temporarily withdraw treatment in patients with clinically relevant adverse effects that could affect continuation of treatment of apremilast and restart once the effects have cleared.	7	1.41	Appropriate	Agree	Consensus in first round
	administer prophylactic antidiarrheals, antiemetics, and/or analgesics on starting treatment in all patients.	1	1.00	Inappropriate	Agree	Consensus in first round
	administer antidiarrheals, antiemetics, and/or analgesics only in patients with clinically relevant adverse effects.	9	0.82	Appropriate	Agree	Consensus in first round

Table 6 (Continued)

	Item	Median	MAD-M	Appropriateness	Agreement	Result
47	Headache is a possibility that should be taken into account during routine follow-up of patients on apremilast.	7	1.12	Appropriate	Neutral	No consensus
48	The most appropriate management strategy in patients who experience headache is to:					
	use a longer induction phase	7	0.65	Appropriate	Agree	Consensus in second round
	temporarily withdraw the morning dose in patients with clinically relevant adverse effects that could affect continuation of treatment of apremilast and reintroduce the dose once the effects have cleared.	7	0.71	Appropriate	Agree	Consensus in second round
	temporarily withdraw treatment in patients with clinically relevant adverse effects that could affect continuation of treatment of apremilast and restart once the effects have cleared.	8	1.29	Appropriate	Agree	Consensus in first round
	administer prophylactic analgesics on starting treatment in all patients.	1	1.18	Inappropriate	Agree	Consensus in first round
administer anti-diarrheals, antiemetics, and/or analgesics only in patients with clinically relevant adverse effects.	9	0.65	Appropriate	Agree	Consensus in first round	

Abbreviation: MAD-M, mean absolute deviation from the median.



## Discussion

The efficacy of apremilast in the treatment of moderate to severe plaque psoriasis has been evaluated in several phase II and III randomized clinical trials.

In the phase III ESTEEM 1 and 2 trials,<sup>2,3</sup> one-third of patients in the apremilast arm achieved PASI-75 by week 16 compared with 6% in the placebo arm. Half of the patients maintained this response at week 50, and over 75% maintained a reduction in PASI of 70% or greater.

Outcomes from clinical trials, however, even when significant, do not necessarily reflect the use of conventional new-generation drugs such as apremilast in real-world clinical practice.

The expert panel agreed that apremilast was most likely to be successful in patients with stable, moderate psoriasis. There are, however, no clear or agreed-on definitions of *moderate psoriasis*. The 2011 American Academy of Dermatology guidelines of care for the management of psoriasis and psoriatic arthritis defined 3 categories of psoriasis according to percentage of body surface area (BSA) affected and considered that patients with a BSA involvement of between 5% and 10% had moderate psoriasis.<sup>8</sup>

In a survey of US dermatologists, Knuckles et al.<sup>9</sup> found that most dermatologists considered a median BSA of 5% to 10% to indicate moderate psoriasis, although cutoff scores mentioned varied considerably. Llamas-Velasco et al.<sup>10</sup> proposed that moderate psoriasis should be defined by either a PASI score of less than 7 and a DLQI score of at least 5 or a PASI score of between 7 and 15 regardless of DLQI; these latter scores overlap with scores indicating candidacy for biologic therapy. The prospective LAPIS-PSO study of 500 patients treated with apremilast in routine care found that patients were more likely to achieve PASI-75 or a physician global assessment score of 0 or 1 (PGA 0/1) when their baseline PASI was lower than that in the ESTEEM 1 and 2 trials.<sup>11,12</sup> Papadavid et al.,<sup>13</sup> in a series of 51 patients with a mean PASI score of 10.8 treated in everyday practice, reported a PASI-75 rate of 59.3% at week 16. Aragón-Miguel et al.<sup>14</sup> and Lukoviek et al.<sup>15</sup> also reported lower PASI scores (9.37 and 9.01, respectively) in real-life settings. Finally, in the real-world APRIL study,<sup>16</sup> patients still on apremilast 6 months after initiating treatment had a lower mean baseline PASI score than those who discontinued treatment due to a lack of response (9.4 vs. 11.8).

Most of the members of the expert panel considered that apremilast is an appropriate option for patients in whom conventional treatment fails or is contraindicated, and that it should ideally precede biologic therapy. This treatment profile differs to that of the pivotal trials, where most patients had severe, extensive psoriasis that was often refractory to biologic therapy. The outcomes could therefore vary. In the ESTEEM-2 study, for example, PASI-75 rates were significantly lower in patients who had been previously treated with biologics (22.8%) than in patients who had never been treated with systemic therapy, whether biologic (31.9%) or conventional (33.3%).<sup>3</sup>

In addition, patients still on apremilast after 6 months had on average been treated with fewer systemic treatments (mean, 1.47) and biologic therapies (0.20) than those no longer taking apremilast (1.96 and 0.70, respectively).

Twenty-seven percent of patients in this group had received biologic therapy. Apremilast was clearly positioned by the panel as a conventional therapy in psoriasis, which seems reasonable considering both its chemical nature and effectiveness and safety profile. However, because of its price, similar to that of drugs in the biologics segment, access to this drug has been strongly shaped by reimbursement policies.<sup>17</sup> Despite the above considerations, it should be recalled that there are no clinical trial data for the specific use of apremilast in moderate psoriasis.

The expert panel considered that treatment effectiveness should be measured not just by objective indicators of complete or near-complete response (absolute PASI scores), but by a combination of indicators and other factors, in particular overall patient-reported satisfaction, tolerability, and safety. They also considered that a leeway of 24 weeks could be left before deciding whether or not to continue with treatment. This recommendation is in contrast to the treatment goals established in the clinical trials of apremilast, highlighting the challenges that lie ahead in terms of determining treatment goals and follow-up intervals for patients with psoriasis and also highlighting the role of patient empowerment in terms of the consideration of patient-reported outcome measures.<sup>18</sup> Nonetheless, this recommendation also complicates the objective comparison of the drug's effectiveness—and efficiency—relative to other treatments on the market.

Despite the limited evidence available, the expert panel considered that apremilast is a useful option for treating refractory disease in difficult-to-treat areas (palms/soles, nails, and scalp). This recommendation is supported by observations (limited by patient numbers) from phase II and III clinical trials.<sup>19–21</sup> In the observational LAPIS-PSO study, 62% of patients treated with apremilast in routine care achieved nail PASI-50 after 4 months; in the same period, approximately 60% achieved scalp PGA 0/1 and almost 70% achieved palmoplantar PGA 0/1<sup>11,22</sup> (Appendix B Table S2. See supplementary material).

In the only randomized trial to specifically evaluate the efficacy of apremilast in palmoplantar psoriasis, Bissonnette et al.<sup>19</sup> found no significant differences in PGA 0/1 between patients treated with apremilast and placebo after 16 weeks (4%,  $P = .1595$ ). Nonetheless, 24% of patients treated with apremilast achieved this goal by week 32. In addition, patients in the apremilast arm performed better in terms of PASI-75 (22% vs. 8% for placebo,  $P = .0499$ ) and DLQI ( $-4.3$  [5.1] vs.  $-0.8$  [4.5],  $P = .0004$ ) scores. In the STYLE study, the first phase III multicenter, placebo-controlled, randomized clinical trial to evaluate the efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp, 43.4% of patients in the treatment arm versus 13.8% in the placebo arm achieved the primary endpoint, which was scalp PGA 0/1 with an improvement of 2 points or more from baseline to week 16.<sup>23</sup>

The panel considered that the concomitant presence of psoriatic arthritis constituted an additional reason to use apremilast, particularly in patients with moderate psoriasis, joint involvement, or dactylitis. The phase III PALACE-1-3 clinical trial assessed the efficacy of apremilast in the treatment of psoriatic arthritis.<sup>24–26</sup> After 16 weeks of treatment, 40% of patients in the apremilast arm (30 mg twice daily) versus 20% of those in the placebo arm achieved a 20% or

greater improvement in American College of Rheumatology response criteria.

Over 70% of patients treated with apremilast maintained this response in the long term (260 weeks).

Approximately 55% and 80% of patients who achieved complete resolution of enthesitis and dactylitis, respectively, remained stable on 30 mg of apremilast administered twice a day.<sup>26</sup>

Overall, the panel members considered safety to be one the most attractive attributes of apremilast. The most common adverse effects (affecting  $\geq 5\%$  of patients) are summarized in Appendix B Table S3 of the supplementary material.<sup>27,28</sup> In the pooled safety analysis of the ESTEEM 1 and 2 trials, the incidence of adverse effects at 156 weeks was not significantly higher than that observed after 1 year for cardiovascular events (exposure-adjusted incidence rate of 0.5/100 patient-years), malignancies (1.2/100 patient-years), depression (1.8/100 patient-years), and suicide attempts (0.1/100 patient-years).<sup>28</sup> Data from the observational LAPIS-PSO study, which analyzed 500 patients, suggested that the overall incidence of adverse events might be lower in routine care than in clinical trial settings.

The members of the expert panel considered that patients treated with apremilast need less rigorous prescreening and follow-up than patients treated with conventional systemic treatments or biologic therapy. A priori, this could be viewed as offering certain advantages over the standard protocol required for systemic therapies and could lead to greater prescribing of apremilast in centers where it takes time or considerable effort to gain access to conventional systemic treatments and biologic therapy. The summary of product characteristics (SPC) does not mention the need for special tests before or during treatment with apremilast.<sup>27</sup>

In addition to the contraindications described for apremilast in the SPC, the European S3-Guideline mentions acute, severe infections as an absolute contraindication for apremilast.<sup>29</sup> It also includes acute and chronic infections, cancer, lymphoproliferative disorders, and depression as relative contraindications. There is no evidence on the use of apremilast in patients with cancer, as, with the exception of cervical intraepithelial neoplasia and squamous cell carcinoma, malignancy was an exclusion criterion in the clinical trials. Depression, aside from being a common comorbidity in patients with psoriasis,<sup>30,31</sup> is listed as a potential adverse effect in the SPC for apremilast. Just over 1% of patients treated with apremilast in the phase III clinical trials and 0.5% of those treated with placebo experienced depression.<sup>27</sup>

Regarding follow-up recommendations, the panel considered that an annual blood test was sufficient and that other tests or procedures should be performed on an as-needed basis. This consideration is consistent with the recommendations of the European Academy of Dermatology and Venerology.<sup>29</sup>

The most relevant adverse events associated with apremilast according to the expert panel are gastrointestinal problems, mood changes, and weight loss. Supporting observations in the literature,<sup>32</sup> it was agreed that awareness and prompt management of adverse effects can help minimize their impact and enable patients to continue with

treatment. Nonetheless, treatment discontinuation due to tolerability problems is likely to be more common in real-world settings than in clinical trials, probably as patients treated in routine practice have access to other treatments. In a series of 77 patients treated with apremilast in a real-world setting, Lee et al.<sup>33</sup> reported a treatment discontinuation rate of 23% over a mean period of 123 days, contrasting with the rate of 5.3% reported in the clinical trials. Treatment was stopped in most cases because of adverse effects.

In brief, the clinicians who participated in this study view apremilast as an attractive option for the individualized treatment of psoriasis and consider that objective indicators of effectiveness should be contemplated together with safety, convenience, and patient satisfaction. In particular, they appreciated the versatility of the drug as an option for patients who are not candidates for other treatments as well as its favorable safety profile and positive impact on symptoms, quality of life, and lesions in difficult-to-treat areas. Disadvantages that should be considered include its lower effectiveness compared with other new-generation drugs and certain tolerability aspects that could influence efficiency in this highly competitive setting.

This study highlights the importance of defining moderate psoriasis to enable comparative studies of apremilast and other drugs as well as the need for greater evidence from clinical trials and real-world settings to verify the recommendations of the experts.

## Conflicts of Interest

Jose Manuel Carrascosa has served as a consultant and speaker, participated in clinical trials, and attended meetings and conferences with financial support from AbbVie, Celgene, Janssen-Cilag, Leo-Pharma, Lilly, Novartis, Pfizer, Biogen, Sandoz, Milan, Sanofi-Aventis, and Almirall.

Mariano Ara has given talks and attended consultancy meetings sponsored by AbbVie, Pfizer, MSD, Janssen, Celgene, Almirall, Amgen, Novartis, Lilly, and Leo.

Pedro Herranz has worked as a consultant/speaker/researcher for AbbVie, Celgene, Lilly, Janssen-Cilag, MSD, Novartis, Pfizer, Regeneron, and Sanofi-Aventis

Isabel Belinchon has participated in clinical trials and received consultancy and speakers' fees from AbbVie, Janssen, MSD, Pfizer-Wyeth, Leo, Celgene, Novartis, and Lilly.

Marta García-Bustinduy has served as a consultant and speaker, participated in clinical trials, and attended meetings and conferences with financial support from AbbVie, Celgene, Janssen-Cilag, Leo, Lilly, Novartis, MSD, Pfizer-Wyeth, and Sanofi-Aventis.

Celgene provided bibliographic support and collaborated with the organization of working meetings and the design and development of the Delphi study carried out by the independent scientific group. Nobody involved with Celgene participated in the generation of proposals or other content produced by this working group or in the writing of this manuscript.

## Acknowledgement

Celgene provided bibliographic support and collaborated with the organization of working meetings and the design and development of the Delphi study carried out by the independent scientific group.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ad.2019.07.005>.

## References

- Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: A randomised controlled trial. *Lancet*. 2012;380:738–46, [http://dx.doi.org/10.1016/s0140-6736\(12\)60642-4](http://dx.doi.org/10.1016/s0140-6736(12)60642-4).
- Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (pde4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM 1]). *J Am Acad Dermatol*. 2015;73:37–49, <http://dx.doi.org/10.1016/j.jaad.2015.03.049>.
- Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br J Dermatol*. 2015;173:1387–99, <http://dx.doi.org/10.1111/bjd.14164>.
- Puig L, Ribera M, Hernanz JM, Belinchon I, Santos-Juanes J, Linares M, et al. Tratamiento de la psoriasis del cuero cabelludo. Revisión de la evidencia y Consenso Delphi del Grupo de Psoriasis de la Academia Española de Dermatología y Venereología. *Actas Dermosifiliogr*. 2010;101:827–46.
- Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lázaro P, et al. Library of Congress Cataloging-in-Publication Data; 2001.
- Hsu CC, Sandford BA. The Delphi technique: making sense of consensus. *Practical assessment. Res Evaluation*. 2007;12:1–8.
- Scott G. Strategic planning for high-tech product development. *Technol Anal Strateg Manage*. 2001;13:343–64.
- Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: Case-based presentations and evidence-based conclusions. *J Am Acad Dermatol*. 2011;65:137–74, <http://dx.doi.org/10.1016/j.jaad.2010.11.055>.
- Knuckles MLF, Levi E, Soung J. Defining and treating moderate plaque psoriasis: a dermatologist survey. *J Dermatolog Treat*. 2018;29:658–63, <http://dx.doi.org/10.1080/09546634.2018.1443200>.
- Llamas-Velasco M, de la Cueva P, Notario J, Martínez-Pilar L, Martorell A, Moreno-Ramírez D. Moderate psoriasis: A proposed definition. *Actas Dermosifiliogr*. 2017;108:911–7, <http://dx.doi.org/10.1016/j.ad.2017.07.002>.
- Reich K, Bomas S, Korge B, Schwichtenberg U, Mentz H, Groegel K, et al. Physician- and patient-reported outcomes with apremilast for patients with plaque psoriasis during routine clinical care in Germany: A second interim analysis. In: *Proceedings of the AAD Annual Meeting*. 2018.
- Iversen L, Paul C, Cirulli J, Chen R, Andersson C, Yamauchi P. Efficacy of apremilast versus placebo in patients with lower plaque psoriasis disease activity: Results of a pooled post hoc analysis of the ESTEEM 1 and 2 trials. In: *Proceedings of the 26th Congress of the EADV*. 2017.
- Papadavid E, Rompoti N, Theodoropoulos K, Kokkalis G, Rigopoulos D. Real-world data on the efficacy and safety of apremilast in patients with moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol*. 2018;32:1173–9, <http://dx.doi.org/10.1111/jdv.14832>.
- Aragón-Miguel R, Calleja-Algarra A, Pinilla-Martín B, Andrés-Lencina JJ, Vico-Alonso C, Sánchez-Velázquez A, et al. Apremilast in plaque psoriasis: A retrospective, real-life study up to 12-month observation. In: *Proceedings of the 2019 AAD Annual Meeting*. 2019.
- Lukoviek V, Arteaga-Henríquez M, Ramírez-Conchas J, Markthaler M, Pestana-Eliche M, García-Bustinduy M, et al. Real-world experience with apremilast for the treatment of psoriasis: Retrospective single-centre study in the Canary Islands. In: *Proceedings of the 2019 AAD Annual Meeting*. 2019.
- de Jong E, van den Reek J, van Vugt L, de Groot M, Koopmans K, Verkouteren B, et al. Characteristics of psoriasis patients who continue apremilast treatment in real life in the Netherlands—results from the prospective, multicenter, real-world APRIL study. In: *Proceedings of the 2019 AAD Annual Meeting*. 2019.
- CatSalut SCdSGdCdS, Servei Català de la Salut, Apremilast (Psoriasis) [Cited 3 September 2018]. Available from: <http://catsalut.gencat.cat/web/.content/minisite/catsalut/proveïdors-professionals/medicaments-farmacia/harmonitzacio/informes/apremilast/Informe-tecnic-CAMHDA-apremilast.pdf>, 2016.
- Carrascosa JM, Rebollo F, Gomez S, De-la-Cueva P. Effects of etanercept on the patient-perceived results (PROs) in patients with moderate-to-severe plaque psoriasis: systematic review of the literature and meta-analysis. *J Dermatolog Treat*. 2018;1–6, <http://dx.doi.org/10.1080/09546634.2018.1467536>.
- Bissonnette R, Haydey R, Rosoph LA, Lynde CW, Bukhalo M, Fowler JF, et al. Apremilast for the treatment of moderate-to-severe palmoplantar psoriasis: Results from a double-blind, placebo-controlled, randomized study. *J Eur Acad Dermatol Venereol*. 2018;32:403–10, <http://dx.doi.org/10.1111/jdv.14647>.
- Bissonnette R, Pariser DM, Wasel NR, Goncalves J, Day RM, Chen R, et al. Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from Phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) clinical trials in patients with moderate to severe psoriasis. *J Am Acad Dermatol*. 2016;75:99–105, <http://dx.doi.org/10.1016/j.jaad.2016.02.1164>.
- Rich P, Gooderham M, Bachelez H, Goncalves J, Day RM, Chen R, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). *J Am Acad Dermatol*. 2016;74:134–42, <http://dx.doi.org/10.1016/j.jaad.2015.09.001>.
- Reich K, Bomas S, Korge B, Manasterski M, Schwichtenberg U, Altmann M, et al. First “real-world” insights on apremilast therapy for patients with plaque psoriasis from the LAPIS-PSO study: An interim analysis. In: *Proceedings of the 75th Annual Meeting of the American Academy of Dermatology*. 2015.
- Van Voorhees A, Stein Gold L, Lebwohl M, Strober B, Lynde C, Tyring S, et al. Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp: Results of a phase 3, multicenter, randomized, placebo-controlled, double-blind study. In: *Proceedings of the Winter Clinical Dermatology Conference - Hawaii*. 2019.

24. Cutolo M, Myerson GE, Fleischmann RM, Liote F, Diaz-Gonzalez F, Van den Bosch F, et al. A phase III, randomized, controlled trial of apremilast in patients with psoriatic arthritis: results of the PALACE 2 trial. *J Rheumatol*. 2016;43:1724–34, <http://dx.doi.org/10.3899/jrheum.151376>.
25. Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: A phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis*. 2016;75:1065–73, <http://dx.doi.org/10.1136/annrheumdis-2015-207963>.
26. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis*. 2014;73:1020–6, <http://dx.doi.org/10.1136/annrheumdis-2013-205056>.
27. CHMP. Anexo i - ficha técnica o resumen de las características del producto. [Consultado 11 ene 2019]. Available in: [https://www.ema.europa.eu/documents/product-information/otezlaepar-product-information\\_es.pdf](https://www.ema.europa.eu/documents/product-information/otezlaepar-product-information_es.pdf).
28. Crowley J, Thaci D, Joly P, Peris K, Papp KA, Goncalves J, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for  $\geq 156$  weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol*. 2017;77:310–7 e1, <http://dx.doi.org/10.1016/j.jaad.2017.01.052>.
29. Nast A, Spuls PI, van der Kraaij G, Gisondi P, Paul C, Ormerod AD, 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;31:1951–63, <http://dx.doi.org/10.1111/jdv.14454>.
30. Dommasch ED, Li T, Okereke OI, Li Y, Qureshi AA, Cho E. Risk of depression in women with psoriasis: A cohort study. *Br J Dermatol*. 2015;173:975–80, <http://dx.doi.org/10.1111/bjd.14032>.
31. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: A population-based cohort study. *Arch Dermatol*. 2010;146:891–5, <http://dx.doi.org/10.1001/archdermatol.2010.186>.
32. Langley A, Beecker J. Management of common side effects of apremilast. *J Cutan Med Surg*. 2018;22:415–21, <http://dx.doi.org/10.1177/1203475417748886>.
33. Lee EB, Amin M, Egeberg A, Wu JJ. Adverse events associated with apremilast use and withdrawal for psoriasis in a real-world setting. *J Eur Acad Dermatol Venereol*. 2018;32:e393–4, <http://dx.doi.org/10.1111/jdv.15061>.