Review article

**The clinical and cost-effectiveness of apremilast for treating active psoriatic arthritis: a critique of the evidence.**

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**Key points for decision makers**

* The economic model submitted by the company compared sequences of treatments with apremilast positioned as an additional line of treatment. The ERG considered that model represented a limited set of potentially relevant sequences; these were not necessarily a sufficient basis to inform the most efficient use and position of apremilast.
* The company’s base-case resulted in an ICER of £14,683 per QALY gained for the sequence including apremilast.
* The company failed to provide compelling evidence that the benefit, in terms of disease progression, for patients who remain on treatment with apremilast was maintained beyond the randomised placebo-controlled phases.
* The ERG’s exploratory analyses focused on alternative approaches to treatment sequencing in the model and on the impact of the assumption of no HAQ progression for patients on treatment with apremilast.
* The NICE Appraisal Committee concluded that the addition of apremilast resulted in cost savings but also a QALY loss, when taking into account the Committee’s preferred assumptions and the pricing in the initial company submission. These cost savings were not high enough to compensate for the clinical effectiveness that would be lost.

# Abstract

As part of the National Institute for Health and Clinical Excellence (NICE) single technology appraisal

(STA) process, the manufacturer of apremilast was invited to submit evidence for its clinical and cost effectiveness for the treatment of active psoriatic arthritis (PsA) for whom disease-modifying anti-rheumatic drugs (DMARDs) have been inadequately effective, not tolerated or contraindicated. The Centre for Reviews and Dissemination and Centre for Health Economics at the University of York were commissioned to act as the independent Evidence Review Group (ERG). This paper provides a description of the ERG review of the company’s submission, the ERG report and submission and summarizes the NICE Appraisal Committee’s subsequent guidance (December 2015).

In the company’s initial submission the base-case analysis resulted in an ICER of £14,683 per QALY gained for the sequence including apremilast (positioned before TNF-α inhibitors) versus a comparator sequence without apremilast. However, the ERG considered the base-case sequence proposed by the company represented a limited set of potentially relevant treatment sequences and positions for apremilast. The company’s base case results were therefore not a sufficient basis to inform the most efficient use and position of apremilast.

The exploratory ERG analyses indicated that apremilast is more effective (i.e. produces higher health gains) when positioned after TNF-α inhibitor therapies. Furthermore, assumptions made regarding a potential beneficial effect of apremilast on long-term HAQ progression, which cannot be substantiated, have a very significant impact on results. The NICE Appraisal Committee (AC), when taking into account their preferred assumptions for HAQ progression for patients on treatment with apremilast, placebo response and monitoring costs for apremilast, concluded that the addition of apremilast resulted in cost savings but also a QALY loss. These cost savings were not high enough to compensate for the clinical effectiveness that would be lost. The AC thus decided that apremilast alone or in combination with disease modifying antirheumatic drug (DMARD) therapy is not recommended for treating adults with active PsA that has not responded to prior DMARD therapy, or where such therapy is not tolerated.

# 1. Introduction

NICE is an independent body responsible for issuing guidance in a number of areas for the English NHS, including the use of new medicines. This guidance is provided through its technology appraisal programme, which draws on clinical and cost-effectiveness evidence in guiding recommendation decisions.

Single technology appraisals (STA), in contrast to multiple technology appraisals (MTAs), evaluate a single product, device or other technology, which is, typically, close to launch. The evidence required by NICE is provided by the company or sponsor of the new medicine for review by an independent ERG appointed by NICE.

A range of stakeholders, including the company, the ERG, expert clinical representatives and patient representatives present evidence for the appraisal. This is considered by the NICE Appraisal Committee (AC). The AC concludes on the clinical effectiveness of the new treatment and whether it represents a cost-effective use of NHS resources.

This article presents a summary of the ERG’s independent critique of the company’s submission to NICE and additional work conducted by the ERG is presented, as well as the key issues that arose during the review process and the subsequent committee decision making. Full details of the appraisal documents can be found on the NICE website. ([1](#_ENREF_1))

# 2. The Decision Problem

PsA is a chronic disease which most often appears between the ages of 30 and 50 years and usually around 10 to 15 years after the onset of psoriasis.([2-4](#_ENREF_2)) PsA is a heterogeneous condition. Clinical manifestations may include both articular (joint) and non-articular disease features. The joint pain experienced in PsA is typically a severe, sharp pain. PsA can be associated with clinically significant functional impairment. The progression of joint damage associated with PsA can be slow, but damage is irreversible.

Determining the numbers of patients with PsA in the UK is complicated by the fact that until recently there was a lack of validated classification criteria for PsA, and that PsA often remains undiagnosed. ([5](#_ENREF_5)) The recent NICE commissioning guide on biologic therapies in psoriasis suggested that PsA may affect 0.3% to 1% of the population. ([6](#_ENREF_6)) The mid-point of this estimate translates to approximately 291,200 people with PsA in England and Wales. ([7](#_ENREF_7))

While there is no NICE clinical guideline specifically for the management of patients with PsA, the NICE clinical guideline on psoriasis (NICE CG153 ([8](#_ENREF_8))) advises that patients with PsA should be referred to a rheumatologist and may require systemic biologic therapy, in accordance with NICE recommendations. NICE provides guidance on the use of the biologic therapies etanercept, infliximab and adalimumab (TA199), and golimumab (TA220) for patients with active and progressive PsA. ([9-11](#_ENREF_9)) The use of golimumab is recommended on the assumption that this therapy is provided through a patient access scheme. Ustekinumab, a monoclonal antibody that acts as a cytokine inhibitor by targeting interleukin (IL-12) and interleukin-23 (IL-23), is recommended (NICE TA340) ([12](#_ENREF_12)) for use in subgroups of active PsA patients who have had prior TNF-α inhibitor treatment or if they are contraindicated for TNF-α inhibitors.

Apremilast (Otezla®) is an oral, small molecule, targeted phosphodiesterase-4 enzyme (PDE4) inhibitor. A positive opinion from the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) was adopted in November 2014 for the use of apremilast 30 mg twice daily “alone or in combination with DMARDs, for the treatment of active PsA in adult patients who have had an inadequate response to or who have been intolerant to DMARD therapy”.

The NICE final scope for apremilast in PsA determined the appropriate comparators as: (i) DMARDs, (ii) TNF-α inhibitors (including etanercept, infliximab, adalimumab and golimumab), and ustekinumab [subject to NICE review outcome at the time of scope development] or (iii) Best Supportive Care (BSC). However, the comparators included in the company submission were restricted to TNF-α inhibitors and BSC. DMARDs and ustekinumab were not included in the economic model. A head-to-head comparison of apremilast versus a single comparator was also not presented. Instead, the decision problem was addressed by comparing treatment sequences with apremilast as an additional pre- TNF-α inhibitor therapy, rather than replacing an existing TNF-α inhibitor therapy or being placed anywhere else in the treatment sequence.

# 3. The Independent Evidence Review Group (ERG) Review

The role of the ERG through their critical review can be seen as threefold:

1. To assess whether the company submission conformed to the methodological guidelines issued by NICE;
2. To assess whether the company’s interpretation and analysis of the evidence was appropriate;
3. To indicate the presence of other sources of evidence or alternative interpretations of the evidence that could help inform NICE guidance.

## Clinical Evidence

The company conducted a systematic review evaluating the efficacy and safety of the use of apremilast for the treatment of PsA.

Four phase 3 RCTs and one phase 2 RCT were identified. The three phase 3 RCTs that met the inclusion criteria were: PSA-002 (also known as PALACE 1), ([2](#_ENREF_2)) PSA-003 (PALACE 2), ([3](#_ENREF_3)) and PSA-004 (PALACE 3). ([4](#_ENREF_4)) All three trials compared apremilast 20mg twice daily versus apremilast 30mg twice daily (bid) versus placebo. A pooled analysis from these three trials was also identified. The PALACE 4 (PSA-005) ([13](#_ENREF_13)) study was excluded as the population had received no prior DMARD therapy, and the Schett trial (PSA-001) ([14](#_ENREF_14)) was excluded as it did not investigate the licensed dose. Trials of apremilast in psoriasis (PSOR 008 ([15](#_ENREF_15))and PSOR 009 ([16](#_ENREF_16))) were included as supporting evidence of apremilast’s tolerability and safety.

All three included trials were international, parallel-group studies of similar design, with two active treatment groups (apremilast 20 mg bid and apremilast 30 mg bid) and a placebo group. Baseline characteristics were very similar across studies. Although the trials were randomised until week 24, randomised comparisons with placebo were only available up to week 16. At week 16, all patients in the placebo group with inadequate response were required to enter early escape to blinded active treatment (re-randomised 1:1 to apremilast 20 mg bid or apremilast 30 mg bid). At week 24, all remaining patients in the placebo group were re-randomised to apremilast 20 mg bid or apremilast 30 mg bid. After week 24, 4.5 year long-term safety phases were planned. In the manufacturer submission, PSA-002 ([2](#_ENREF_2)) reported follow up data up to 104 weeks and PSA-003 ([3](#_ENREF_3))and PSA-004 ([4](#_ENREF_4)) reported follow up data up to 52 weeks.

In all three trials, the primary efficacy outcome was ACR20 response at week 16 and the major secondary efficacy outcome was change from baseline to Week 16 in HAQ-DI score. Modified PsARC response was one of the many other secondary outcomes. PASI-75 response was included to account for skin manifestations of PsA. In response to a point for clarification from the ERG about radiographic disease progression outcomes, the company stated that no radiographic assessments were performed.

The company’s submission focused on efficacy results from trial PSA-002 ([2](#_ENREF_2)) (thus not utilising the pooled analysis of all three trials), and results from the pooled analysis for data on improvements in enthesitis, dactylitis, and psoriatic skin manifestations. The results of trial PSA-002 (Table 1) showed that apremilast 30mg was associated with statistically significant improvements compared with placebo for ACR20/50, PsARC, PASI-75, and change in HAQ-DI.

**Table 1 Summary of the efficacy results at Week 16 from the PSA-002 trial**

| **Outcome** | **Apremilast 30 mg bid,**  **n = 168** | **Placebo, n = 168** |
| --- | --- | --- |
| Number (%) of patients achieving an **ACR20** response | 64 (38.1)\*\* | 32 (19.0) |
| Number (%) of patients achieving an **ACR50** response | 27 (16.1)\* | 10 (6.0) |
| Number (%) of patients achieving an **ACR70** response | 7 (4.2) | 2 (1.2) |
| LS mean (SE) change from baseline in **HAQ-DI** score (0–3) | −0.24 (0.04)\* | −0.08 (0.04) |
| Number (%) of patients achieving a MCID of ≥0.13 on the **HAQ-DI** | 81 (48.2) | 64 (38.1) |
| Number (%) of patients achieving a MCID of ≥0.30 on the **HAQ-DI** | 64 (38.1) | 45 (26.8) |
| Number (%) of patients achieving a modified **PsARC** response | 78 (46.4)\* | 50 (29.8) |
| Number (%) of patients achieving a **PASI-75** | 18 (22.0)\* | 3 (4.4) |

ACR - American College of Rheumatology; HAQ-DI - Health Assessment Questionnaire-Disability Index; PsARC - Psoriatic Arthritis Response Criteria; PASI - Psoriasis Area and Severity Index

\*p ≤0.05; \*\*p ≤0.001; \*\*\*p ≤0.0001

Longer term data (up to week 52 for apremilast 30 mg from pooled PSA-002/003/004 and up to week 104 from PSA-002 ([2](#_ENREF_2))) demonstrated that responses beyond week 24 were maintained over those at week 16 for several outcomes including ACR20 ACR50, ACR70, PsARC and HAQ-DI. However, these longer-term data are subject to numerous methodological limitations, which the ERG discussed in its critique (see Section 3.1.1).

A network meta-analysis (NMA) was presented to compare the efficacy of apremilast with the licensed TNF-α inhibitors adalimumab, etanercept and infliximab. At the ERG’s request, trial data for ustekinumab and certolizumab were also included in the initial company submission. The highest probability of response for ACR 20/50/70 outcomes was seen with infliximab. For all three ACR thresholds apremilast showed a higher probability of response compared with placebo, but a lower probability of response than any of the TNF-α inhibitors. A similar pattern of results was seen for the PsARC and PASI response outcomes and HAQ-DI score changes.

## Critique of the Clinical Evidence

The ERG considered that the three included apremilast trials appeared to be well-conducted. However, the ERG commented that the size of the treatment benefit was modest compared to placebo. The proportion of apremilast patients achieving an ACR50 response - a much more clinically relevant response than ACR20 - was quite low (Table 1). There is also uncertainty about whether the improvement in function (HAQ-DI) provided by apremilast reaches clinically-relevant levels. The proportion of patients on apremilast achieving a minimum clinically important difference (MCID) for HAQ-DI of ≥0.30 was 36.4% compared with 26% on placebo.

Only limited evidence was presented to support the assumption of a HAQ-DI benefit for patients who remain on treatment with apremilast beyond the randomised placebo-controlled phases. The longer-term results that the company presented (up to 52 weeks for PSA-003 (3) and PSA-004 (4) and up to 104 weeks for PSA-002 (2)) are based on observed data from selected patients who remain on treatment and therefore represent an optimistic estimate of treatment benefit. Methodological limitations such as the lack of control groups, lack of adequate blinding, lack of treatment stopping criteria and lack of data on radiographic progression were not discussed by the company. Notably, when the ERG also requested additional details on radiographic disease progression of joint damage in the apremilast trials, they were informed by the company that such data was not collected. This absence of evidence is very important, given the availability of such evidence for TNF-α inhibitors and the importance of early management of PsA, as emphasised by the NICE clinical guidance. (8, 10) Without such evidence for apremilast, the validity of positioning apremilast before TNF-α inhibitors in a treatment sequence appears highly questionable.

The systematic searches and the methods used for the company’s NMA were found to be appropriate and the quality assessment of the trials included in the NMA suggested that these were of good quality. The ERG, however, questioned the appropriateness of including a trial not examining the licensed dose of apremilast (PSA-001 ([14](#_ENREF_14))) and data from the identified apremilast trials relating to unlicensed doses of apremilast (20mg). The company responded with updated NMAs in which inappropriate data were excluded.

Ustekinumab and certolizumab were incorporated as NMA comparators only after a request from the ERG. NMA results for relevant subgroups of the patient population (TNF-α inhibitor experienced patients, TNF-α inhibitor contraindicated patients) were also made available only after an ERG request. A NMA scenario comparing apremilast with conventional DMARDs was not presented. In addition, although the company suggested positioning apremilast before TNF-α inhibitors in the treatment pathway, the submission did not present any data on patient response to TNF-α inhibitor therapies after having received apremilast. In terms of safety, there is still uncertainty about the long-term safety of apremilast as the data is currently limited to two years.

## Cost-Effectiveness Evidence

The company submitted a de novo economic model. The cost-effectiveness model submitted was based on the Markov cohort structure presented in the original cost-effectiveness analysis of TNF-α inhibitors for PsA by the York Assessment Group (TA199 ([17](#_ENREF_17))). The York model structure was extended by the company to evaluate sequences of treatments. The target population for the base case analysis was patients with active PsA who have not responded to or are intolerant to at least two previous conventional DMARD therapies. A subgroup analysis examined the cost-effectiveness of apremilast in biologic-naïve patients. The model had a 40 year time horizon and a 28-day cycle length.

The base-case analysis compared two sequences, with the inclusion of apremilast as a pre- TNF-α inhibitor line of treatment. Patients not responding to or discontinuing from all treatment options were placed on best supportive care (BSC):

* **Apremilast sequence:** apremilast → adalimumab → etanercept → BSC
* **Comparator sequence:** adalimumab → etanercept → BSC

A schematic of the company’s economic model is presented in Figure 1.

**Figure 1 Company’s de novo Markov model structure**



Each treatment in the company’s model consisted of two distinct health states: trial period (i.e. response period) and continued use (maintenance). Response to treatment was evaluated at the end of a treatment-specific trial period according to PsARC criteria. Non-responders transitioned to the subsequent treatment option and responders were assumed to continue treatment until they withdrew due to lack of efficacy or adverse events. Adverse events were not explicitly modelled.

The decision rule for continuing treatment was the presence of a PsARC response, assessed at 16 weeks (for apremilast) or 12 weeks (for TNF-α inhibitors). Treatment impact in terms of skin disease was based on the probability of achieving PASI-75. PsARC response rates and conditional mean changes in the HAQ-DI and PASI scores were obtained from the company’s NMA. A reduction in terms of and short-term efficacy (i.e. PsARC response at the end of the trial period) and long-term efficacy (i.e. withdrawal rates) was applied for subsequent lines of TNF-α inhibitors following primary non-response to a previous TNF-α inhibitor treatment (i.e. not attaining PsARC response at the end of the trial period) based on a study from Hyrich et al. ([18](#_ENREF_18))

A constant annual withdrawal rate of 16.5% beyond the primary response period (16 weeks for apremilast and 12 weeks for TNF-α inhibitors) was applied to all treatments in the model, based on TA199. ([17](#_ENREF_17)) Patients who discontinued a treatment transitioned to the next treatment option or BSC when they had failed all treatments. Rebound to the baseline HAQ value (rebound to gain) was assumed for patients entering BSC.

EQ-5D utilities were mapped onto HAQ-DI and PASI scores to reflect the quality of life associated with levels of psoriasis and arthritis functional status. In the base case analysis, utilities were derived using the algorithm from TA199. ([17](#_ENREF_17)) A utility model based on apremilast trial data was only used in a scenario analysis. Costs relating to drug acquisition, drug administration, physician visits, monitoring, laboratory testing and disease-related costs were included in the economic model. The disease-related healthcare costs were estimated as a function of HAQ-DI score, following the approach in TA199. ([17](#_ENREF_17)) Psoriasis-related costs were estimated separately, similarly to TA199. ([17](#_ENREF_17))

Table 2 presents the base-case cost effectiveness results, after these were updated for discrepancies in the clinical efficacy inputs between the model and the company submission, identified by the ERG. The base case ICER for the comparison of the apremilast sequence versus the comparator sequence was £14,683 per QALY gained.

**Table 2 Revised Base Case Results (provided in company clarification responses)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
| Apremilast 🡪 Adalimumab 🡪 Etanercept 🡪BSC | 115,837 | 8.01 | 10,902 | 0.74 | 14,683 |
| Adalimumab 🡪 Etanercept 🡪BSC | 104,936 | 7.27 | N/A | N/A | N/A |

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

This indicates that apremilast is a cost-effective use of NHS resources as an additional line of therapy (pre TNF-α inhibitors), according to threshold range likely to be considered cost effective by NICE. The major driver in the economic model appeared to be the reduced time spent in BSC in the apremilast sequence, due to the addition of apremilast as an additional pre- TNF-α inhibitor step. This did not affect the total life years accrued between sequences, because none of the treatment options had an impact on mortality. However, the QALY difference between the two sequences was driven by the reduced time spent in BSC in the apremilast sequence. However, according to the ERG this could occur with the addition of any active treatment in the sequence. The robustness of the results was tested by the company using a range of alternative parameter assumptions. The model results were most sensitive to the rate of HAQ-DI natural disease progression, the time horizon, the positioning of apremilast, the utility model used and the cost model applied for disease-related costs.

## Critique of the Cost-Effectiveness Evidence

Despite meeting many of the typical requirements of the NICE reference case, the ERG had a number of concerns regarding the company’s submission and economic model. Key among them was that the model submitted by the company represented a limited set of relevant comparators. The model considered the use of apremilast only as an additional line of treatment prior to two TNF-α inhibitors (a sequence of adalimumab and etanercept in the base-case model). By failing to present fully incremental cost-effectiveness results, which would simultaneously consider all possible comparator sequences, the ERG was concerned that this does not provide a sufficient basis to inform the most efficient use and position of apremilast, in terms of clinical or cost effectiveness. Furthermore, there were concerns that uncertainties surrounding the cost-effectiveness of the comparator sequence and any implications for the cost-effectiveness of apremilast had not been robustly demonstrated by the company.

In addition, the ERG report highlighted concerns relating to the fact that not all comparators relevant to the decision problem were included in the company’s analysis. i.e. (i) DMARDs and (ii) ustekinumab (despite having been provisionally approved by NICE for subgroups of PsA patients, at the time of the appraisal).

Importantly, a key assumption underpinning the company’s analysis was that patients who remain on therapy with apremilast will maintain their response over time i.e. have no HAQ-DI progression while on treatment. The ERG was very doubtful of this assumption given that no reliable long-term evidence is available to support it, such as evidence on radiographic disease progression which is available for TNF-α inhibitor therapies.

The ERG also found that a number of critical assumptions made in the model had not been robustly justified by the company and the existing evidence. These included: (i) the reduced efficacy of subsequent lines of TNF-α inhibitor therapies following primary non-response, sourced from a non-PsA study including a limited selection of TNF-α inhibitor agents, (ii) the exclusion of placebo response in the economic model, (iii) the use of the utility model from TA199, ([17](#_ENREF_17)) despite EQ-5D utility values being available from apremilast trial data, (iv) the limited justification for incorporating disease-related costs similarly to TA199, ([17](#_ENREF_17)) (v) optimistic treatment monitoring assumptions towards apremilast (i.e. apremilast requiring less frequent monitoring compared to TNF-α inhibitors) and (vi) withdrawal rate for apremilast equal to that for TNF-α inhibitors, despite withdrawal data being available from apremilast trials.

To explore the above areas of criticism, the ERG performed a series of exploratory analyses focusing primarily on the approaches to sequencing in the company’s model and the assumption of zero HAQ progression for PsARC responders to apremilast. The ERG also tested the effect degradation for subsequent lines of TNF-α inhibitor therapies and uncertainties relating to other parameters of the model.

1. In terms of the sequencing approach, the ERG explored additional sequences and comparisons from the updated (for clinical efficacy discrepancies) company model. These analyses, although still a small subset of all possible treatment sequences, were considered vital in understanding the economic model submitted and the evaluation of apremilast within its licenced indication, as required by the NICE scope. The ERG evaluated scenarios where apremilast displaced a TNF-α inhibitor in a treatment sequence of one or two TNF-α inhibitors (resulting in comparing treatment sequences of equal length) and scenarios where apremilast extended a sequence of one or two TNF-α inhibitors, being positioned either before or after TNF-α inhibitor therapies. The fully incremental results of these analyses are shown in Table 3.

**Table 3 Fully incremental analysis of ERG displacement and sequence extension strategies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Sequence** | **Mean Costs** | **Mean QALYs** | **Incremental Costs** | **Incremental QALYs** | **ICER vs. next more costly strategy** | **Fully incremental ICER** |
| **apremilast** → BSC | £73,272 | 5.56 |  |  |  |  |
| adalimumab → BSC | £83,153 | 5.98 | £9,881 | 0.4207 | £23,487 | ED |
| etanercept → BSC | £89,184 | 6.40 | £6,031 | 0.4169 | £14,466 | ED |
| **apremilast** → adalimumab → BSC | £96,676 | 6.91 | £7,492 | 0.5091 | £14,716 | ED |
| adalimumab → apremilast →BSC | £97,267 | 6.94 | £591 | 0.0258 | £22,907 | ED |
| **apremilast** → etanercept → BSC | £102,023 | 7.27 | £4,756 | 0.3378 | £14,079 | £16,811 |
| etanercept → **apremilast** → BSC | £102,959 | 7.32 | £936 | 0.0479 | £19,541 | ED |
| adalimumab → etanercept → BSC | £104,936 | 7.27 | £1,977 | -0.0537 | Dominated | - |
| etanercept → adalimumab → BSC | £107,541 | 7.44 | £2,605 | 0.1719 | £15,154 | ED |
| **apremilast** → adalimumab → etanercept → BSC | £115,837 | 8.01 | £8,296 | 0.5705 | £14,542 | ED |
| adalimumab → etanercept → **apremilast** →BSC | £117,188 | 8.06 | £1,351 | 0.054 | £25,019 | ED |
| **apremilast** → etanercept → adalimumab → BSC | £118,145 | 8.16 | £957 | 0.0958 | £9,990 | £18,188 |
| etanercept → adalimumab → **apremilast** → BSC | £119,552 | 8.22 | £1,407 | 0.0582 | £24,175 | £24,175 |

ED = Extendedly dominated

These results demonstrate that:

* 1. adding lines of treatment (i.e. moving from sequences including only one treatment to sequences including two and then three lines of treatment) resulted in more effective (i.e. higher QALYs) and in many cases more cost-effective strategies
  2. in terms of the comparator strategies without apremilast, etanercept followed by adalimumab was more effective than adalimumab followed by etanercept,
  3. apremilast was generally more cost-effective when positioned after TNF-α inhibitor therapies and
  4. the most cost-effective sequence was apremilast positioned after two TNF-α inhibitors, i.e. etanercept followed by adalimumab, leading to an ICER of £24,175 per QALY compared to apremilast 🡪etanercept 🡪 adalimumab 🡪BSC. When excluding the degradation of TNF-α inhibitor effect, the conclusion that apremilast is more effective (i.e. produces higher QALYs) when positioned after the TNF-α inhibitors was strengthened.

1. Regarding HAQ progression for responders to apremilast, it was not possible for the ERG to test different alternative disease progression assumptions for apremilast within the broader set of comparisons. The model programming did not provide the flexibility to assign differential HAQ progression neither between apremilast and TNF-α inhibitor therapies nor between apremilast and BSC. Such analyses would be necessary to appropriately address the decision problem and not being able to implement these was a severe limitation. The only analysis that the ERG was able to implement, to approximate the impact of a scenario where apremilast is not associated with zero HAQ progression, was the comparison of apremilast versus BSC, when setting HAQ progression to zero for both apremilast and BSC. Such a comparison was argued by the ERG to still be very insightful in determining the magnitude of the effect of an alternative HAQ progression assumption within the broader set of comparators. This scenario had a very significant impact on results; the ICER of apremilast versus BSC in this scenario increased to £66,045 per QALY gained, versus £14,645 when assuming natural disease progression for BSC and zero progression for apremilast.
2. The individual parameter scenarios, which appeared to have a greater impact on the ICER, included placebo response inclusion, use of the apremilast utility model and use of the disease-related cost model from an alternative study Poole et al. ([19](#_ENREF_19)) However, only the use of the apremilast utility model led to an ICER that exceeded the threshold range likely to be considered cost effective by NICE.

Despite the additional exploratory work, the ERG still considered that several key areas of uncertainty remained unresolved. These included (i) the impact of the sequencing approach chosen by the company, failing to simultaneously consider all possible comparator sequences and possible positions of apremilast and (ii) the consideration of alternative HAQ progression assumptions for apremilast within the broader set of comparisons. We therefore did not consider that a preferred analysis is available.

## Conclusions of the ERG Review

Evidence from three good quality RCTs demonstrate that apremilast was associated with statistically significant improvements in PsA patients compared with placebo. However, the size of the treatment benefit was modest and there is uncertainty about whether the improvement in function provided by apremilast reaches clinically-relevant levels. The NMA demonstrated that apremilast was not as effective as any of the TNF-α inhibitor therapies. Meanwhile, methodological limitations of the longer-term data were not discussed by the company and the efficacy results of the long-term studies could not be considered as being reliable. Importantly, there was no evidence to support the impact, if any, of apremilast on radiographic progression of joint disease. There was also uncertainty regarding the long-term safety of apremilast.

As a consequence, the company’s cost-effectiveness results were also highly uncertain. The ERG considered that the company’s analysis represented a limited set of potentially relevant sequences and that the base-case results were not a sufficient basis to inform the most efficient use and position of apremilast. The ERG was also extremely constrained in testing the alternative HAQ progression assumptions for apremilast. The results of the ERG additional analyses suggested that apremilast is more effective when positioned after TNF-α inhibitor therapies and that the cost-effectiveness results would likely be significantly altered (i.e. become less favourable for the treatment sequences including apremilast) if alternative assumptions regarding disease progression for patients on treatment with apremilast were to be explored. In view of all the unresolved uncertainties ERG did not consider that they were in a position to present a preferred analysis.

# 4. Consideration of All Available Evidence

The NICE AC reviewed the evidence available on the clinical and cost-effectiveness of apremilast for the treatment of active PsA, alongside expert testimony from clinical specialists and patient representatives.

**4.1 NICE Preliminary Guidance**

After considering the available evidence from the company’s submission, the ERG report, expert testimony and other consultees, the NICE AC preliminary recommendation, issued in the ACD, was that apremilast is not recommended for treating adults with active PsA that has not responded to prior DMARD therapy or where DMARDs are contraindicated.

# 5. NICE Final Guidance

As reported in their Final Guidance, ([1](#_ENREF_1)) the AC concluded that “in order to prevent the model being confounded by any QALY gain occurring only because of one group in the model having an extra active treatment, it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence”.

The AC noted that all the ERG’s post-ACD additional analyses in which apremilast replaced a TNF-α inhibitor therapy (being considered either before or after TNF-α inhibitors) resulted in cost savings, but also a QALY loss. The AC noted that the most plausible ICERs for apremilast were: (i) £18,300 saved per QALY lost, when administered before TNF-α inhibitors and (ii) £14,800 saved per QALY lost, when administered after TNF-α inhibitors. These cost savings from apremilast were not high enough, in terms of additional capacity released into the healthcare system, to compensate for the clinical effectiveness that would be lost. The final guidance concluded that apremilast could not be recommended as a treatment either before or after TNF-α inhibitors, taking into account the pricing information included in the initial company submission.

# 6. Appeal against the Final Appraisal Determination

An appeal against NICE’s FAD was submitted by the company supporting that the Committee (i) unreasonably dismissed the scenario in which apremilast would be used in addition to existing treatment options and (ii) rejected robust clinical trial evidence supporting the assumption of zero deterioration in HAQ-DI whilst on apremilast therapy. An Appeal Panel was convened in November 2015 to consider the appeal and rejected both aforementioned points. ([1](#_ENREF_1)) The final guidance from NICE thus remained that apremilast is not recommended for adults with active PsA, taking into account the pricing information included in the initial company submission.

**6. ERG Conclusion**

While the described appraisal is a typical example of the NICE STA process, this case study has several implications and highlights the role of independent academic review groups in interpreting and amending the modelling approaches and evidence submitted by manufacturers.

A number of general issues were raised by the ERG throughout this appraisal. The first concerns the positioning of a new therapy in a sequence and the appropriate consideration of the often large number of potential combinations and treatment strategies. Secondly, the significant impact of the *lack* of any reliable evidence of a beneficial longer-term effect on disease progression.

The ERG were critical of the company for not presenting a full range of incremental analyses considering the wide range of possible combinations of treatments available for PsA patients, covering potential alternative treatments and the positioning of apremilast. While the sequences presented were expected to represent the most typically used current practice and placement of apremilast, there was neither any demonstration that the comparator sequence was itself cost-effective nor any consideration of any implications for the resultant cost-effectiveness of apremilast. Additionally the company made the initial assumption that apremilast would be used prior to existing TNF-α inhibitors, without any clinical or cost-effectiveness justification, although the use of apremilast prior to more effective treatments may not be clinically appealing. Failing to report or provide a model able to conduct fully incremental analyses comparing all the possible sequences simultaneously can be potentially misleading, as has previously been demonstrated by the NICE decision support unit (DSU). ([20](#_ENREF_20))

Equally important, the company failed to provide compelling supporting evidence that the HAQ-DI benefit for patients who remain on treatment with apremilast was maintained beyond the randomised placebo-controlled phases; in particular they did not present any radiographic data. Methodological limitations of the longer-term data that were submitted, such as the lack of control groups, lack of adequate blinding and lack of treatment stopping criteria were not discussed by the company. Without such evidence for apremilast, the validity of positioning this treatment before TNF-α inhibitors in a sequence of treatments appears highly questionable.

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**Author contributions**

Eleftherios Sideris, Mark Corbett, Stephen Palmer, Laura Bojke and Nerys Woolacott all formed part of the ERG that produced the ERG report that this paper describes. Laura Bojke and Nerys Woolacott took overall responsibility for the cost-effectiveness and clinical effectiveness parts of the project. Eleftherios Sideris wrote the draft of the manuscript. All authors commented on the manuscript and approved the final version.

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