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REVIEW ARTICLE

Apremilast for the Treatment of Moderate to Severe Plaque Psoriasis: A Critique of the Evidence

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Abstract As part of the National Institute for Health and Care Excellence's (NICE) single technology appraisal (STA) process, apremilast was assessed to determine the clinical and cost effectiveness of its use in the treatment of moderate to severe plaque psoriasis in two patient populations, differentiated by the severity of the patient's Psoriasis Area Severity Index (PASI) score. The Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE) Technology Appraisal Group at the University of York was commissioned to act as the evidence review group (ERG). This article provides a summary of the company's submission, the ERG report and NICE's subsequent guidance. In the company's initial submission, a sequence of treatments including apremilast was found to be both more effective and cheaper than a comparator sequence without it in both populations considered. However, this result was found to be highly sensitive to a series of assumptions made by the company, primarily reflecting the costs of best supportive care once no further treatments are available, and the source of utility estimates. A re-estimation of the cost effectiveness of apremilast by the ERG suggested that the apremilast sequence in the two populations was more effective, but due to high additional costs was not indicative of a cost-effective use of NHS resources. As such, in the final appraisal decision NICE concluded that apremilast was not cost effective in either population.

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Key Points

A sequence including apremilast was found to not be cost effective for the treatment of moderate to severe plaque psoriasis in two patient populations considered, with incremental cost-effectiveness ratios (ICERs) above £30,000 per quality-adjusted life-year in both cases.

The resource use of patients on best supportive care once no further treatments in the sequence are available was found to be highly uncertain and the primary driver of cost effectiveness.

The use of EQ-5D tariffs for the wrong international setting (US rather than UK in this case) can have a significant effect on the ICER, and as such should be interpreted carefully.

1 Introduction

This article presents a summary of the recent appraisal of the use of apremilast in the treatment of moderate to severe plaque psoriasis by the National Institute for Health and Care Excellence (NICE) from the perspective of an independent academic group, the evidence review group (ERG). 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 (TA) programme, which draws on clinical and cost-effectiveness evidence in guiding recommendation decisions.

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

A range of stakeholders, including the company, the ERG, expert clinical representatives and patient representatives are brought together by a NICE appraisal committee. The committee considers all of the evidence provided in order to determine the clinical effectiveness of the new treatment and whether it represents a cost-effective use of NHS resources.

In addition to the ERG's independent critique of the company's submission to NICE and additional work conducted by the ERG, this article presents a summary of the development of the NICE TA guidance. The key issues that arose during the review process and the subsequent committee decision making/meeting are summarised. Full details of the appraisal documents can be found on the NICE website [1]. This is one in a series of STA summaries published in *PharmacoEconomics* [2–6].

2 Decision Problem

Plaque psoriasis is a chronic, inflammatory skin disorder, resulting from a T cell autoimmune response to multiple genetic and environmental factors. In the UK, the prevalence of psoriasis is estimated to be between 1.3 and 2.6 %, with plaque psoriasis constituting 90 % of cases [7]. The largest prevalence is in the white population, with men and women equally affected. While disease onset can occur at any age, it is uncommon in children but typically occurs before the age of 35 years [8].

In the UK, standard treatment is determined by a number of factors, including severity, area affected and previous treatments used. A typical treatment pathway will involve the attempted use of topical treatments and phototherapy before progression to systemic treatments, including biological and non-biological therapies [9].

Apremilast [an oral, small-molecule, targeted phosphodiesterase-4 enzyme (PDE4) inhibitor] was given a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in November 2014 for use in "adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA)" [10]. This indicates that apremilast should be used in the later stages of the treatment pathway, after topical, phototherapy and non-biological systemic therapies.

At the time of appraisal, in the UK there were four biological therapies approved by NICE for the treatment of plaque psoriasis in people who have failed to respond to or are intolerant of systemic non-biological therapies: three tumour necrosis factor (TNF) antagonists (adalimumab, etanercept and infliximab) and one interleukin (IL)-12/23 antagonist (ustekinumab).[1] In addition to the required failure of, or intolerance to, previous therapies, the use of these biological therapies is defined by patients' Psoriasis Area Severity Index (PASI) and Dermatology Life Quality Index (DLQI) scores: NICE guidance recommends adalimumab, etanercept and ustekinumab only when a PASI ≥ 10 and a DLQI >10 are reported by the patient; infliximab is only recommended in the very severe case when the PASI is ≥ 20 and DLQI is >18.

The company presented two populations in their decision problem to NICE that differed in the severity of plaque psoriasis (i.e. DLQI score); both complied with the CHMP positive opinion. The main population was considered to be those with a PASI ≥ 10 and a DLQI >10 who were being considered for biologic therapies. In this population, apremilast was considered to be a potential additional line of treatment prior to biologics. The second population considered was those with a PASI ≥ 10 but a DLQI ≤ 10. This population was argued to be unserved by current therapies as, under NICE guidance [8], none of the existing biologics are recommended.

3 Evidence Review Group (ERG) Report

NICE requires the ERG to consider and report on the clinical and cost effectiveness of the new treatment, based on the company's submission. The role of the ERG through this critical review can be seen as threefold:

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

3.1 Clinical Evidence

The company conducted a systematic review evaluating the efficacy and safety of apremilast for the treatment of patients with moderate to severe plaque psoriasis.

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[1] Subsequently, secukinumab (Cosentyx®) has been approved by NICE [11].

Four randomised controlled trials (RCTs) were included in the review: two phase III trials (PSOR-008 [12] and PSOR-009 [13]), which both compared apremilast at the licensed dose with placebo; a phase II trial (PSOR-005 [14]), which compared three different dosages of apremilast with placebo; and a phase IIIb trial (PSOR-010 [15]), which compared the licensed dose of apremilast with placebo and etanercept (50 mg once per week) with placebo.

The company's submission focused on two of the four RCTs: PSOR-008 and PSOR-009 [12, 13]. To be eligible for inclusion in these trials, patients had to be adults with chronic moderate to severe plaque psoriasis for at least 12 months prior to screening. Patients had to be candidates for phototherapy and/or systemic therapy without a history of any other clinically significant disease, severe renal impairment, active or incompletely treated tuberculosis and significant infection or psoriasis flare or rebound within 4 weeks of screening. These two RCTs, individually and when their results were pooled, demonstrated that apremilast significantly reduced the severity of psoriasis and its impact on physical, psychological and social functioning compared with placebo: a statistically significant difference was found between apremilast and placebo for the majority of outcomes at 16 weeks; these are shown in Table 1.

These findings were supported by those of the other two RCTs (PSOR-005 and PSOR-010) [14, 15]. The PSOR-010 trial also demonstrated statistically significant improvements in psoriasis severity and impact with etanercept 50 mg once weekly over placebo [PASI-75 response 48.2 vs. 11.9 % (PASI-x being defined as x % reduction in the PASI from baseline)]; the ERG-calculated odds ratio for apremilast versus etanercept was 1.41 (95 % CI 0.76–2.61).

Longer-term data demonstrated that treatment response was maintained for those who remained on therapy but that withdrawal rates were quite high: in PSOR-008 only 36.8 % of patients remained on treatment at week 104. The primary reason for discontinuation was lack of efficacy.

In the pooled analysis of safety data from PSOR-008 and PSOR-009, more patients receiving apremilast experienced at least one adverse event than did with placebo (68.9 vs. 57.2 %). The most frequently reported adverse events in patients receiving apremilast were diarrhoea (17.8 %), nausea (16.6 %), upper respiratory tract infections (8.4 %), nasopharyngitis (7.3 %), tension headache (7.3 %) and headache (5.8 %). The proportion of patients reporting severe or serious adverse events was low and was similar between treatment groups. In terms of the short-term withdrawal rates due to adverse events, the pooled analysis of PSOR-008 and PSOR-009 showed that, compared with placebo, apremilast had a slightly higher withdrawal rate due to adverse events at 16 weeks (apremilast 5.4 % vs. placebo 3.8 %). Similar adverse events results were seen in the PSOR-005 and PSOR-010 trials.

A network meta-analysis (NMA) was presented to compare the efficacy of apremilast with the biological therapies—adalimumab, etanercept, infliximab and ustekinumab—based on the short-term efficacy data from individual trials. The results of the NMA demonstrated that, of the active treatments, apremilast achieved the lowest absolute probability of achieving a PASI response (PASI-50, -75 and -90). Infliximab achieved the highest probability of a PASI-75 response (85 %), followed by ustekinumab (90 mg dose 81 %, 45 mg dose 77 %), adalimumab (62 %), etanercept (43 %), apremilast (confidential data) and placebo (6 %).

Table 1 Outcome comparisons for apremilast and placebo at 16 weeks from pooled PSOR-008 and PSOR-009 trials

Outcomes	Apremilast ($n = 836$) (%)	Placebo ($n = 419$) (%)
sPGA score of 0 or 1	21.3	4.1
PASI-50 response	57.7	17.9
PASI-75 response (primary outcome)	31.7	5.5
PASI-90 response	8.7	0.7
Mean change in PASI score from baseline	−51.6	−16.5
Mean change in psoriasis-affected BSA	−48.0	−6.8
Mean change in DLQI score from baseline	−6.6	−2.3
DLQI decrease of ≥5 points	70.4	36.6
Mean change in baseline SF-36 MCS score	2.5	−0.7
Mean change in pruritis VAS score from baseline	−32.2	−8.9
Mean change in NAPSI score from baseline for patients with nail psoriasis	−24.6	2.1
ScPGA score 0 or 1 for patients with scalp psoriasis	44.7	17.4

BSA body surface area, *DLQI* Dermatology Life Quality Index, *MCS* Mental Component Summary, *NAPSI* Nail Psoriasis Severity Index, *PASI-x* x % reduction in the PASI, *ScPGA* Scalp Physician's Global Assessment, *sPGA* Static Physician's Global Assessment, *VAS* visual analogue scale

3.1.1 Critique and Interpretation

The company's systematic review did not appear to have missed any relevant RCTs. The four included RCTs were good quality and the results are likely to be reliable. Similarly, the Bayesian NMA appeared to be conducted appropriately for the comparison of the treatments available for moderate to severe psoriasis. However, there was a lack of trial evidence directly comparing apremilast with biological therapies. The PSOR-010 trial was the only trial to assess both apremilast and a biological therapy (etanercept) against placebo; however, the company stated that the trial was not adequately powered to directly compare apremilast with etanercept, reducing its weight within the NMA. As such, the NMA relies largely on the indirect-comparison RCTs, weakening the strength of any inference drawn.

The ERG was concerned about the representativeness of the patients in the four trials to the population being analysed in the STA. Specifically, patients included in the PSOR-008 and PSOR-009 trials may not be representative of the licensed population or of those who might be eligible for apremilast in NHS practice, as not all patients in the trials had failed conventional systemic therapy. To consider this potential bias the company provided data for a number of subgroups, including those patients who had failed two or more conventional systemic therapies or were contraindicated to systemic therapy and were biologic naïve, which reflects the population for their preferred positioning of apremilast in NHS practice. The results were similar to the main analysis; however the sample size for this subgroup analysis was only 110 patients.

The company did not present any evidence to demonstrate that apremilast is better tolerated than biological therapies. Safety data were not included in the NMA. The PSOR-010 trial suggests that adverse events may be more frequent with apremilast than etanercept. There is still uncertainty about the longer-term safety and tolerability of apremilast, as current safety data only extends to 2 years.

3.2 Cost-Effectiveness Evidence

No previous cost-effectiveness studies of apremilast for moderate to severe psoriasis were identified by the company. Therefore, a de novo analysis to estimate the cost effectiveness of a sequence including apremilast in the two separate populations was submitted, distinguished by a DLQI >10 or DLQI ≤10; both populations considered have a PASI ≥10. The cost-effectiveness models submitted were based on the structure presented in the original cost-effectiveness analysis of biologics by the York Assessment Group [16]. The York model structure was extended by the

company to evaluate sequences of biologics. The base-case analysis for the DLQI >10 population compared two sequences, with the presentation of apremilast as a pre-biologic additional line of treatment. Once the sequence of treatment has been completed, patients are placed on best supportive care (BSC):

– Apremilast sequence: apremilast → adalimumab → etanercept → BSC.
– Comparator sequence: adalimumab → etanercept → BSC.

The DLQI ≤10 population analysis considered only apremilast followed by BSC versus BSC alone due to the ineligibility of patients in this population to receive biologic therapies under current NICE guidance. In both models, a cycle length of 28 days and a time period of 10 years was applied. Health states are defined by the PASI improvement as a percentage change from baseline considered in five states: PASI0 (i.e. no change from baseline), PASI0–50, PASI50–75, PASI75–90 and PASI90–100.

All of the treatments in the sequence were made up of a 'trial period'—the initial 10- to 16-week period over which initial response to the treatment is assessed—and a period of continued use of the treatment. All patients were assumed to complete the full trial period for each biologic/apremilast, unless they died from other causes (no psoriasis or treatment-related mortality was considered). At the end of the trial period, patients stayed on that line of treatment if they have had a PASI improvement of 75 % or more: the 'continued use' phase. Response parameters were informed by the company's NMA. If an inadequate response occurred, patients moved to the next line of treatment or BSC if at the end of the sequence. During the continued use period of each biologic/apremilast, patients were assumed to stay in the same health state unless they died or withdrew from that treatment. Withdrawal was applied as a fixed rate per cycle and assumed to be the same for all active treatments. The position of a biologic in the sequence was assumed not to impact its effectiveness, nor the effectiveness of any subsequent treatments.

In the DLQI >10 population model health-related quality of life (HR-QOL) scores were applied to the five modelled health states, independent of treatment. HR-QOL values were taken from the original York model [16] and are applied to the four PASI improvement health states (i.e. not PASI0). In the DLQI ≤10 model, EQ-5D scores observed directly from the PSOR-008 and PSOR-009 trials are used to inform the four PASI improvement health states. After the completion of the first Appraisal Consultation Document (ACD) by NICE, the company identified they had inappropriately used utilities derived from the US value set applied to the EQ-5D, rather than the UK set

required by NICE, in all cases where EQ-5D values had been considered. This error had a significant impact on the quality-adjusted life-year (QALY) gains associated with both treatment arms in the relevant scenarios, substantially reducing the incremental cost-effectiveness ratio (ICER) from that initially presented to the Committee. This report incorporates the results associated with both the initial, erroneous, set of EQ-5D estimates presented at the first ACD and the corrected set, presented subsequently at the second ACD. Only the additional scenarios using the EQ-5D estimates in the DLQI >10 population model were affected by this error; it did not include the company's base-case, which drew values directly from published estimates as discussed earlier. The company did not provide a corrected analysis for the DLQI ≤10 population using the set of UK tariff-based EQ-5D estimates.

Treatment, administration, monitoring and laboratory costs are all incorporated into both population models in the same way and are largely based on costs presented in previous TAs and the NICE Guidance CG153 [8]. All non-responders to active treatment are assumed to require hospitalisation for 1.6 days per cycle during the 'trial period' of the next treatment.

A major driver of both of the population models is the approach taken to BSC. The company assumed no treatment effect of BSC. All patients were assumed to be in the PASI0 health state and were assigned the baseline HR-QOL. This assumption is based on clinical opinion. The estimated cost associated with BSC is very high, including an average of 26.6 days of hospitalisation per year for all patients and the provision of cyclosporine and methotrexate in 45 % of patients. The resultant cost for BSC was £11,543 per year, making it more expensive than apremilast, adalimumab, etanercept or ustekinumab. The cost of BSC is based on the highest cost presented in the NICE Guidance CG153 [8]. This source is also used to inform the resource use of non-response to any line of treatment, estimating a cost of £462.56 per cycle of non-response to treatment (based on 1.6 days of hospitalisation at the point of non-response).

Validation of the model was carried out by the company, with the model structure and assumptions validated by a clinical expert. A range of one-way scenarios and deterministic sensitivity analyses were presented by the company as well as a probabilistic sensitivity analysis (PSA).

The company reported apremilast arms being dominant in both the DLQI >10 and ≤10 population, models with cost savings of £3226 and £5911 and QALY gains of 0.14 and 0.05, respectively. The results of the PSA are reported for the DLQI >10 population, finding a 100 % probability of the apremilast arm being cost effective for all cost-effectiveness thresholds.

3.2.1 Critique and Interpretation

The model submitted by the company for the DLQI >10 and PASI ≥10 population represented a limited set of relevant comparators. The model considered the use of apremilast only as an additional line of treatment prior to one or more biologics (a sequence of adalimumab and etanercept in the base-case model). The ERG's concern was that the proposed use and position of apremilast within an existing comparator sequence (i.e. whether apremilast might replace an existing therapy or extend a sequence and its position within an extended sequence) should be formally demonstrated rather than simply stated. The ERG considered that the company's base-case cost-effectiveness results were not necessarily a sufficient basis to inform the most efficient use and position of apremilast, in terms of clinical or cost effectiveness. By failing to present the fully incremental cost-effectiveness results, which would simultaneously consider all possible comparator sequences, the ERG was also concerned 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.

The ERG demonstrated to the appraisal committee that the main driver of the result was the relatively high cost of BSC. Table 2 presents the cost per cycle of all of the treatments modelled in the sequences, based on the cost of continued use. The table shows that BSC is more expensive than any active treatment. By introducing an additional line of treatment (i.e. apremilast), the company's model reduces the time that patients receive BSC. As BSC has the highest cost without being effective, and additional lines of treatment are not assumed to affect efficacy, any sequence that extends the time on an active therapy will dominate, regardless of the additional treatment's efficacy relative to other active treatments. As such, a direct comparison of any treatment sequence longer than the comparator will result in dominance of the longer strategy. The ERG noted that this result was in contrast to the findings of previous TAs considered by NICE for etanercept, adalimumab and

Table 2 Cost per cycle (28 days) of the treatments modelled

Treatment	Modelled total cost per cycle, continuous use (£)
BSC	887.90
Apremilast	567.60
Adalimumab	736.17
Etanercept	746.93
Ustekinumab	747.56

BSC best supportive care

ustekinumab [17–19], none of which reported dominance over BSC (with most reporting ICERs above £30,000/QALY).

The company applied BSC costs from NICE Guidance CG153. These costs represent a population of high- or very high-need patients who would be hospitalised for on average 26.6 days each year. This high hospitalisation was the main driver of the high BSC cost. The ERG acknowledged that there may be a subpopulation of very high-need patients who fail to respond to multiple lines of biologics and incur very high BSC costs; however, the company did not undertake an analysis in this subpopulation and it is not clear how these patients could be identified prior to initiation of a biologic. Furthermore, it is not clear that apremilast would be appropriate as the first-line treatment for this very severe subpopulation.

The ERG were additionally concerned about the approach taken to applying utility estimates. Despite EQ-5D being available for apremilast and etanercept from the PSOR-008, -009 and -010 trials, the company chose, in the DLQI >10 population, to use an algorithm mapping DLQI scores from an etanercept trial. No consideration was given to alternative, better fitting algorithms or to the incorporation of treatment-specific DLQI data to the algorithm. This approach contrasts with the NICE methods guide [20]. The EQ-5D data collected were used to inform the DLQI ≤10 population, introducing a level of inconsistency between the models.

A number of other concerns were raised by the ERG, including the failure to associate a treatment effect with the BSC treatment state, despite the NMA used to inform the rest of the treatment efficacies reporting a placebo effect. This approach was inconsistent with the NICE Guidance model [8]. Additionally, the company assumed fewer physician visits for patients taking apremilast and no wastage of the drug.

To explore the impact of the areas of criticism raised, the ERG undertook a series of scenario analyses to inform the committee:

1. Replacement of the cost of BSC with that reported in a UK-based retrospective cohort study (£348.22 per cycle) [21]. This was felt to be more representative of the costs associated with BSC as, although the costs reported were for a population prior to initiation of biologics, psoriasis is considered a non-progressive disease, and therefore costs before and after initiation were considered to be similar. For consistency, the cost per cycle for a non-responder was also reduced to this estimate.
2. Changing of the utility estimates associated with PASI response categories to the EQ-5D scores observed from the combined three trials. This is the point at

which the erroneous US EQ-5D tariff values were introduced by the company that conducted the EQ-5D estimations from the trials.
3. Incorporation of the BSC efficacy data drawn from the base-case analysis presented in the NICE guidance [8]. This had been presented as a scenario by the company but not incorporated into the base-case analysis.
4. Standardisation of the number of physician visits made by patients on apremilast to the four visits a year (from one visit) for all other treatments.
5. Consideration of the impact of potential wastage of apremilast by factoring in the cost of 3 and 6 months of wastage. Only the 3 months of wastage analysis is presented here.

Due to the inclusion of EQ-5D data in the company's base-case model, the DLQI ≤10 population does not incorporate change 2 listed above. The combination of the first three scenarios represents the ERG's base case, with scenarios 4 and 5 representing additional considerations deemed relevant by the ERG.

The results of combining the above analyses are presented in Tables 3 and 4. As discussed earlier, due to the erroneous presentation of US EQ-5D tariffs in the DLQI >10 population at the first ACD, two sets of results are reported. In both populations modelled, the incorporation of the cost of BSC from Fonia et al. [21] (point 1 above) has a significant impact, changing the result from the apremilast sequence dominating to being more effective and more expensive (ICERs of £18,577 for the DLQI >10 population and £87,207 for the DLQI ≤10 population). The incorporation of all of the ERG's preferred analyses changes the results significantly, resulting in ICERs of £39,896 and £28,574 for the DLQI >10 population for the US and UK EQ-5D value sets, respectively, and £89,623 for the DLQI ≤10 population.

3.3 Conclusions of the ERG Report

Evidence from four good-quality RCTs demonstrates that apremilast reduces the severity of psoriasis and its impact on physical, psychological and social functioning compared with placebo. However, the NMA demonstrated that apremilast is not as effective as any of the biological therapies. Rates of withdrawal are quite high and driven by lack of efficacy. There is no evidence that apremilast is better tolerated than biologics in the short-term and, as with all new drugs, there is great uncertainty regarding the longer-term safety and tolerability of apremilast.

For apremilast to be cost effective it has to be assumed that the costs of BSC are very high and that BSC has no

Table 3 Results of the evidence review group base-case analysis scenarios Dermatology Life Quality Index (DLQI) >10 model: all incremental values of apremilast sequence compared with no apremilast sequence

Technologies	US EQ-5D value set (presented in first ACD)			UK EQ-5D value set (presented in second ACD)		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case						
Apremilast sequence incremental results	−2144	0.14	Dominant	−2144	0.14	Dominant
Addition of BSC cost from Fonia et al. [21] (1)						
Apremilast sequence incremental results	2611	0.14	18,577	2611	0.14	18,577
Addition of HR-QOL observed from trials (1 + 2)						
Apremilast sequence incremental results	2611	0.08	33,055	2611	0.11	23,620
Addition of BSC effectiveness data (1 + 2 + 3), ERG base case						
Apremilast sequence incremental results	2611	0.07	39,896	2611	0.09	28,574
Standardisation of physician visits to four visits for all treatments in ERG base case (1 + 2 + 3 + 4)						
Apremilast sequence incremental results	2943	0.07	44,965	2943	0.09	32,204
Addition of 3 months of apremilast wastage to ERG base-case (1 + 2 + 3 + 5)						
Apremilast sequence incremental results	4290	0.07	65,542	4290	0.09	46,941

ACD Appraisal Consultation Document, *BSC* best supportive care, *ERG* evidence review group, *HR-QOL* health-related quality of life, *ICER* incremental cost-effectiveness analysis, *QALY* quality-adjusted life-year

Table 4 Results of evidence review group base-case analysis scenarios Dermatology Life Quality Index (DLQI) ≤10 model

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company's base case			
Apremilast sequence incremental results	−6300	0.049	Dominant
Incorporating BSC cost from Fonia et al. [21] (1)			
Apremilast sequence incremental results	4301	0.049	87,207
Addition of BSC effectiveness data (1 + 3), ERG base case			
Apremilast sequence incremental results	4301	0.048	89,623
Standardisation of physician visits to four visits for all treatments in ERG base case (1 + 3 + 4)			
Apremilast sequence incremental results	4681	0.05	97,535
Addition of 3 months of apremilast wastage to ERG base case (1 + 3 + 5)			
Apremilast sequence incremental results	6014	0.05	125,307

BSC best supportive care, *ERG* evidence review group, *ICER* incremental cost-effectiveness analysis, *QALY* quality-adjusted life-year

beneficial effect. The ERG did not consider that the cost approach taken by the company represented an accurate representation of the BSC for the average patient. Using evidence from UK clinical practice, the ICER of apremilast increased above £20,000 per QALY in both patient populations of interest. Significant areas of uncertainty remain concerning the cost effectiveness of apremilast in both populations.

4 NICE Guidance

4.1 First Appraisal Consultation Document Findings and Preliminary Guidance

After considering the available evidence from the company's submission, the ERG report, expert testimony and other consultees, the NICE appraisal committee's

preliminary recommendation issued in the first ACD was that apremilast was not recommended for the treatment of psoriasis in either population evaluated.

The Committee concluded that the most plausible ICER was somewhere between £45,000 and £65,000 per QALY for the DLQI >10 population and between £97,500 and £125,300 per QALY for the DLQI ≤10 population. These findings were drawn directly from the results reported in Table 3 (using the erroneous US EQ-5D tariff) and Table 4, as the committee believed that the most plausible estimate lay between the final two scenarios presented in Table 3 (with ICERs of £32,204 and £46,941) and Table 4 (£97,535 and £125,307). Specifically, the Committee concluded that the most plausible set of assumptions would include an equalised number of physician visits for all treatments (scenario 4) and some level of apremilast wastage (scenario 5), but less than the 3–6 months proposed by the ERG.

The Committee recognised that the cost associated with BSC was the main driver of uncertainty around the cost-effectiveness result, specifically the rate of hospitalisation implied from the competing sources (the NICE guideline [8] and Fonia et al. [21]). The Committee noted that both sources were likely to overestimate resource use associated with BSC due to them reflecting a more severe population than the NICE decision problem and a recent fall in the rate of hospitalisation for patients being treated with BSC (raised by the clinical experts).

The Committee also heard that, while market authorisation allowed positioning of apremilast at any point relative to biologics, the clinical experts believed it would be generally used after biological therapy due to its reduced efficacy, but that placement would largely be driven by patient choice and intolerance to biologics. The Committee noted that the ERG demonstrated that all sequences with apremilast as a pre-biologic dominated those with it as a post-biologic, and as such positioning as a post-biologic must also not be cost effective. The Committee additionally concluded that apremilast replacing a biologic was not cost effective, as well as being deemed clinically unlikely by expert clinicians.

As such, the Committee concluded that apremilast was not a cost-effective use of NHS resources in either population.

4.2 Response to Preliminary Guidance

As noted earlier in this report, in response to the ACD the company submitted a correction to the EQ-5D data relevant to scenarios in the DLQI >10 population analysis. The company also submitted additional scenarios concerning the costs associated with non-responders and the wastage of apremilast. All additional scenarios were focused on the DLQI >10 population.

In response the ERG's base-case analysis the company:

1. Corrected their error around the EQ-5D estimates;
2. Equalised physician visits between apremilast and biological therapies (at 4 per annum);
3. Reduced the resource use associated with non-responders to an active treatment;
4. Incorporated an assumption of 14 days of apremilast wastage.

The correction of the EQ-5D estimates (from US to UK tariffs) increased the utility increment associated with each of the PASI response categories, further increasing the QALY benefit of being on an effective treatment. This has the effect of increasing the QALYs associated with the apremilast sequence and thus reducing the ICERs, as shown in Table 3.

As noted by the Committee in the first ACD, it was deemed unrealistic to assume apremilast required fewer physician visits than other treatments; as such, the company equalised the number of visits in their revised base case, at 4 per annum, as presented in the ERG additional scenario 4. This assumption increased the relative cost of the apremilast sequence.

The company argued that the ERG approach of assuming the same cost to non-responders as to BSC double-counted outpatient attendance, presenting four new non-responder cost estimates between £0 (i.e. no cost of non-response) to £108.62 (using a different interpretation of results from Fonia et al. [21]), compared with the ERG base-case estimate of £348.22.

Finally, in response to the Committee's comments on wastage, the company presented an additional scenario incorporating 14 days of apremilast wastage at the point of non-response (at a cost of £275).

The company considered the combination of the first three scenarios in addition to the ERG base case as their revised base case (using a non-responder cost of £45.04), giving an ICER of £20,593 per QALY. The addition of the wastage scenario increased the reported ICER to £23,419 per QALY.

The ERG considered the company's additional scenarios 1, 2 and 4 to be reasonable, incorporating them into the ERG revised base case. The ERG additionally acknowledged the potential for double counting of outpatient visits in their estimate of non-responder costs. However, the use of Fonia et al. [21] for such a purpose was deemed to be too uncertain to identify a 'true' cost of non-response, highlighting that different interpretations put the cost of non-response between £45.04 and £348.22 per cycle, with the ERG submitting a revised estimate from Fonia et al. of £225. The ERG concluded that this uncertainty around non-responder costs made the estimation of a single revised base case challenging, suggesting a revised base-case ICER

of £30,311 per QALY with a plausible range between £23,419 and £35,029 per QALY.

4.3 Final Guidance

The Committee considered the additional evidence provided by the company for the DLQI >10 population, accepting that the UK tariffs were the most appropriate for the estimation of EQ-5D utility increments. The Committee concluded that the ERG's revised base-case assumptions, as detailed in Sect. 4.2, represented the most robust estimate. The Committee thus concluded that the most plausible ICER available for decision making was about £30,300 per QALY, noting that this was above the threshold range normally considered to be cost effective. It was noted that there was substantial uncertainty around this estimate which could drive the ICER in both directions. However, as the cost of BSC (the major driver of the model result) was expected to be lower than that presented, it was deemed most likely that this ICER represented an underestimate.

In the DLQI ≤10 population, no additional analyses or evidence were submitted by the company, despite the use of the erroneous US tariff-based EQ-5D values. As such, the Committee estimated a rough estimate of the ICER of apremilast in this population to be twice that of the DLQI >10 population, giving a figure of £60,000 per QALY. As such, the use of apremilast in this population was deemed not to be within a range considered to be a cost-effective use of NHS resources.

5 ERG Conclusion

A number of general issues were raised 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. The second concerns the significant impact of the resource use of patients on BSC on the cost effectiveness of a therapy. Finally, the importance of appropriately applied country-specific tariffs was noted.

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 the DLQI >10 population, 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 no 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 biologics, without any clinical or cost-effective justification, with the Committee noting that the use of apremilast prior to more effective treatments may not be clinically appealing. Failing to report or provide a model able to conduct incremental analyses comparing all of the possible sequences simultaneously can be potentially misleading, as has previously been demonstrated by the NICE decision support unit (DSU) [22].

Due to the presentation of apremilast as an additional line of therapy, with no detrimental effects on the other treatment in the sequence, the evaluation presented by the company can essentially be reduced to a comparison of apremilast versus BSC, as the additional therapeutic line displaces time on BSC. While this does not invalidate the assumption, it results in the cost effectiveness of apremilast being driven by the cost and disutility of being on BSC. In the case of the appraisal, the company was criticised for making unsubstantiated assumptions regarding BSC, primarily around resource use, with the Committee concluding that no evidence existed as to the appropriate cost of BSC. As presented in Table 3, the relaxation of the associated cost changed the ICER from one of dominance over the no apremilast arm to an ICER of £18,577 per QALY. This shows the importance of a prior understanding of the key drivers of cost effectiveness by the company so that research can be conducted into the relevant drivers prior to NICE appraisal.

Finally, as shown in Table 3, the application of UK rather than US EQ-5D tariffs reduced the ICER by over £10,000 per QALY in the ERG's initial base case, and over £20,000 per QALY in some scenarios. While the ERG agrees that the use of the UK tariff is wholly appropriate, in this context the significant impact warrants further research by NICE as to whether the consideration of international tariffs as scenario analyses represents an important means of conceptualising the full uncertainty around their values, as has been suggested by recent research [23].

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