NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Apremilast moderate to severe - psoriasis (rapid review of TA368) [ID987]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

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Contents:

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NICE National Institute for Health and Care Excellence

NICE guidance

Apremilast for treating moderate to severe plaque psoriasis

Technology appraisal guidance
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Contents

1 Guidance

1.1 Apremilast is not recommended within its marketing authorisation for treating psoriasis, that is, for treating adults with moderate to severe chronic plaque psoriasis that has not responded to systemic therapy, or systemic therapy is contraindicated or not tolerated.

1.2 People whose treatment with apremilast was funded by the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Apremilast (Otezla, Celgene) is a small-molecule inhibitor of phosphodiesterase 4 (PDE4). Apremilast down-regulates the inflammatory response by modulating the expression of cytokines and mediators associated with psoriasis (including tumour necrosis factor [TNF]-alpha and interleukin [IL]-23). Apremilast has a marketing authorisation in the UK 'for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including [ciclosporin], methotrexate or psoralen and ultraviolet-A light (PUVA)'.

2.2 The summary of product characteristics includes the following adverse reactions for apremilast: gastrointestinal disorders (most commonly diarrhoea and nausea), upper respiratory tract infections, headache and tension headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Apremilast is administered orally. The recommended dosage is 30 mg twice daily after an initial titration schedule. A single 10-mg dose is given on the first day of treatment; this is titrated to 30 mg twice daily over 5 days (see the summary of product characteristics for the dose titration schedule). The price of apremilast is £265.18 for a 14-day treatment initiation pack (4×10 mg, 4×20 mg, 19×30 mg) and £550.00 for a 28-day pack (56×30 mg tablets) (excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] online, accessed March 2015). According to the company submission, the cost of 18 months of treatment with apremilast is estimated at £10,644. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 6) considered evidence submitted by Celgene and a review of this submission by the Evidence Review Group (ERG; section 7).

Clinical effectiveness

3.1 The clinical evidence for apremilast came from 4 multicentre, placebo-controlled, double-blind randomised controlled trials (RCTs) in people with moderate to severe chronic plaque psoriasis:

- PSOR-005 (n=352): a phase IIb trial across 35 sites in the USA and Canada.
- PSOR-008 (also called ESTEEM 1, n=844): a phase III trial across 72 sites in 8 countries (including the UK).
- PSOR-009 (also called ESTEEM 2, n=411): a phase III trial across 45 sites in 9 countries (not including the UK).
- PSOR-010 (n=250): a phase IIIb trial across 65 sites in 11 countries (including the UK).

The primary endpoint in all 4 trials was a 75% reduction in the Psoriasis Area Severity Index (PASI) score at week 16 (known as a PASI 75 response).

3.2 PSOR-005 was a 24-week trial of apremilast compared with placebo. People with moderate to severe psoriasis were randomised 1:1:1:1 to placebo or apremilast at 1 of 3 different doses (10 mg, 20 mg or 30 mg twice daily). At week 16, people receiving placebo were re-randomised to apremilast 20 mg or 30 mg for a further 8 weeks; people receiving apremilast continued with their allocated treatment.

3.3 In PSOR-008 and PSOR-009, people were randomised (2:1) to apremilast 30 mg (twice daily) or placebo. The PSOR-010 trial was powered to compare apremilast with placebo, and etanercept with placebo. People were randomised 1:1:1 to placebo (tablet and injection), apremilast (30 mg twice daily) plus placebo injections, or etanercept (50 mg injection once weekly) plus placebo tablets. In all 3 trials, moderate to severe plaque psoriasis was defined by a PASI score of at least 12, 10% or more of body surface area affected, and a static Physician Global Assessment score (sPGA) of at least 3. There was no requirement for people to have a particular Dermatology Life Quality Index

(DLQI) score at baseline. The studies excluded people with tuberculosis, HIV and hepatitis. PSOR-010 also excluded patients with prior use of biological therapies (for treating psoriatic arthritis or psoriasis).

3.4 PSOR-008 and PSOR-009 each had 4 treatment phases with a planned overall duration of 5 years:

- Placebo-controlled phase (weeks 0–16): patients were randomised to have apremilast or placebo in a 2:1 ratio.
- Maintenance phase (weeks 16–32): patients randomised to placebo were switched to apremilast.
- Treatment withdrawal phase (weeks 32–52) to assess whether the effect of treatment continues (or decreases) after stopping apremilast:
  - Patients originally randomised to apremilast whose disease responded to treatment were randomised again (1:1) to apremilast or placebo; patients randomised to placebo at 32 weeks were switched back to apremilast if the response was lost.
  - Patients originally randomised to apremilast whose disease did not respond remained on apremilast and could additionally have topical therapies and/or phototherapy.
  - All patients originally randomised to placebo (and switched to apremilast at week 16) remained on apremilast, and those whose psoriasis had not responded by week 32 could additionally have topical therapies and/or phototherapy.
- Long-term extension (weeks 52–260; data available up to week 104 for PSOR-008 and week 52 for PSOR-009).

  All efficacy and safety outcomes assessed during the placebo-controlled phase (weeks 0–16) were also measured during the maintenance phase and treatment withdrawal phase. The long-term extension phase is continuing to collect the same data. Blinding was maintained until all patients completed week 52. The main difference in design between the PSOR 008 and PSOR 009 was the definition of response to treatment to determine whether patients continued treatment after 32 weeks: PASI 75 in PSOR 008 and PASI 50 in PSOR 009.

3.5 PSOR-010 had 2 treatment phases with a planned overall duration of 104 weeks. At week 16, all patients who had previously not received apremilast were switched to apremilast for the 88-week extension phase of the trial. The ongoing long-term extension phase is continuing to collect the same efficacy and safety outcomes as the placebo-controlled phase.

3.6 The company considered the baseline characteristics of patients to be similar between PSOR-008 and PSOR-009, and similar between the treatment groups within the trials. In PSOR-010, a higher proportion of people had previously had conventional systemic therapy than in the other trials, and the proportion of patients with a 'severe' score on the PGA was lower (15.7–27.4% across the treatment groups) than in the other trials (27.4–35.8%). Mean PASI score ranged from 18.7 to 20.3 across the 3 phase III trials (PSOR-008, PSOR-009, PSOR-010), and mean DLQI score ranged from 12.1 to 12.8.

3.7 The results for key outcomes in the 2 pivotal phase III trials (PSOR-008 and PSOR-009) are presented in table 1. The company provided results from PSOR-010 as 'academic in confidence'. After 16 weeks of treatment in PSOR-010, a statistically significantly greater proportion of people treated with apremilast achieved a PASI 75, PASI 50 or PASI 90 response, or an sPGA score of clear or almost clear with a 2 or more unit change from baseline, compared with placebo.

Table 1 Key outcomes in the PSOR-008 and PSOR-009 clinical trials

Outcome	PSOR-008			PSOR-009		
	16 weeks		32 weeks	16 weeks		32 weeks
	APR (n=562)	Placebo (n=282)	APR (n=562)	APR (n=274)	Placebo (n=137)	APR (n=274)
PASI 75, %	33.1*	5.3	28.3	28.8*	5.8	24.8
sPGA score 0 or 1, %	21.7*	3.9	24.0	20.4*	4.4	17.9
PASI 50, %	58.7*	17.0	53.6	55.5*	19.7	46.0
PASI 90, %	9.8*	0.4	12.1	8.8†	1.5	9.5

*p<0.0001 (statistically significant difference, week 16 comparison with placebo).
†p<0.05 (nominally significant difference using hierarchical testing, week 16 comparison with placebo).
Abbreviations: APR, apremilast; CI, confidence interval; PASI, Psoriasis Area Severity Index; sPGA, static Physician Global Assessment (0=clear, 1=almost clear).

3.8 During the treatment withdrawal phase of PSOR-008 (weeks 32–52), several patients in the apremilast arm lost PASI 75 response (data marked as 'academic in confidence' by the company). After 104 weeks, 63.2% of the 844 patients who had had apremilast during the trial had stopped apremilast. The primary reasons for stopping apremilast were lack of efficacy (27.5%), withdrawal of consent by the patient (12.8%) and adverse events (9.5%).

3.9 Health-related quality of life in PSOR-008 and PSOR-009 was measured at baseline and again at 16 and 32 weeks after starting treatment. Health-related quality of life improved statistically significantly after 16 weeks of treatment with apremilast, and the improvement was sustained at 32 weeks (according to the 4 questionnaires used: DLQI, 36-item Short-Form Health Survey [SF-36], EQ-5D, 100 mm Pruritus Visual Analogue Scale [VAS]). People receiving apremilast in PSOR-010 also had statistically significantly improvements in mean change in DLQI score and mean change in pruritus VAS score after 16 weeks of treatment.

3.10 In an exploratory analysis of PSOR-008, a clinical benefit was seen with apremilast regardless of baseline DLQI score. Similar proportions of patients with a baseline DLQI of 10 or less or a DLQI of more than 10 achieved PASI 75 at week 16 with apremilast (33.5% and 32.9% respectively).

3.11 Pooled data from PSOR-008 and PSOR-009 showed that more patients receiving apremilast had at least 1 adverse event (68.9%) than people receiving placebo (57.2%) in the first 16 weeks of treatment. Adverse events occurring in 5% or more of either the apremilast or placebo treatment populations were diarrhoea (17.8% with apremilast and 6.7% with placebo), nausea (16.6% and 6.7%), upper respiratory tract infection (8.4% and 6.5%), tension headache (7.3% and 3.3%), nasopharyngitis (7.3% and 6.9%) and headache (5.8% and 3.3%). Few patients reported severe or serious adverse events during the placebo-controlled phase of the trials, and the incidence of severe or serious adverse events was similar for placebo and apremilast. Few patients stopped

therapy due to adverse events in the first 16 weeks of treatment (5.4% with apremilast, 3.8% with placebo). In the first 16 weeks of treatment in the PSOR-010 trial, more patients receiving apremilast had at least 1 adverse event (69.9%) compared with placebo (59.5%) or etanercept (53.0%) and the proportion of patients reporting a serious adverse event was higher in the apremilast group (3.6%) than the placebo (0%) or etanercept (1.2%) groups, although numbers were low.

3.12 Because PSOR-010 was not powered to compare apremilast with etanercept, and there were no other head-to-head trials comparing apremilast with any of the biological therapies currently recommended by NICE for psoriasis (adalimumab, etanercept, infliximab, secukinumab and ustekinumab), the company did a systematic review and network meta-analysis, which included 22 studies. This was subsequently updated to include outcomes from 2 additional studies (including PSOR-010, which was unavailable at the time of the company's original submission). All except 1 study included placebo as the control group (the other study investigated 2 different doses of ustekinumab). The company did a sensitivity analysis including the 17 trials that reported separate results for people who had not had biological therapy. The company reported that the probability of moderate to severe psoriasis responding was greatest for infliximab, followed by ustekinumab and adalimumab; etanercept had the lowest probability of a response among the biological therapies. Response rates with apremilast (marked as 'academic in confidence' by the company) were lower than for the biological therapies; this difference was statistically significant for comparisons with all biological therapies except with etanercept. The results of the company's sensitivity analysis in patients who had not had biological therapies were consistent with the base-case results for the overall population.

ERG comments

3.13 The ERG concluded that the trials were of good quality and that treatment groups were generally similar at baseline. The ERG noted that, although the follow-up period for PSOR-005 was relatively short (24 weeks), it was adequate for assessing the primary outcome of PASI 75 response at week 16.

3.14 The ERG suggested that the populations in the 4 trials of apremilast may not be representative of patients seen in clinical practice. All 4 trials excluded people

with a history of other clinically significant diseases (including cardiac, neurological, psychiatric, hepatic, renal, haematological and immunological disease), and PSOR-008, PSOR-009 and PSOR-010 excluded people with significant infection or a psoriasis flare or rebound within 4 weeks of screening. Not everyone in the PSOR-008 and PSOR-009 trials had systemic therapy or had disease that had not responded to systemic treatments, whereas the marketing authorisation for apremilast is in people whose disease has responded inadequately to, or who have a contraindication to or cannot tolerate, systemic therapies, including non-biological treatments and phototherapy. Less than half of people in PSOR-008 and PSOR-009 had conventional systemic therapy and only about 65% had any form of systemic therapy. Based on this, the ERG suggested that the PSOR-008 and PSOR-009 trials might have overestimated the clinical effectiveness of apremilast because people may have had less severe disease than those for whom apremilast would be considered in NHS practice. The ERG considered that the proportion of patients who had conventional systemic therapy in PSOR-010 better reflected patients seen in UK clinical practice.

3.15 The ERG noted that withdrawal rates were quite high and that treatment benefit was not fully maintained in a substantial proportion of patients (marked as 'academic in confidence' by the company).

3.16 Based on data from PSOR-008, a consistent beneficial treatment effect across all subgroups was seen with apremilast compared with placebo. However, the ERG suggested that only 13% of the PSOR-008 trial population would be eligible for apremilast based on the company's preferred positioning for apremilast in the treatment pathway (2 or more conventional systemic therapies failed or contraindicated and no previous biological therapy). For people whose psoriasis had not responded to at least 1 biological therapy, the ERG judged the sample size to be too small to inform the treatment effect of apremilast in this subgroup. In addition, the ERG suggested that this small subgroup of people who had used biological agents does not accurately reflect UK clinical practice because many of the people in the apremilast trials had biological therapies for psoriasis without first trying conventional systemic therapies.

3.17 For PSOR-010, the company did not submit results that directly compare apremilast with etanercept. The ERG calculated odds ratios (ORs), which

indicated that etanercept improved PASI response slightly more than apremilast (PASI 75: OR for etanercept 1.41, 95% confidence interval [CI] 0.76 to 2.61). The ERG noted that the trial was not powered to compare etanercept and apremilast, and therefore these results should be interpreted with caution.

3.18 The ERG stated that the company's network meta-analysis appeared to have included all trials relevant to the decision problem and that most of the 24 trials were rated good or excellent in quality. The ERG stated that the results from the company's network meta-analysis were likely to be reasonably reliable. However, the ERG said that, for people who never had biological therapies, the results of the company's sensitivity analysis should be interpreted with caution because:

- trials did not consistently report whether patients had biological therapy
- some data were based on people who did not have tumour necrosis factor-inhibitor therapy (adalimumab, etanercept or infliximab) but may have had other types of biological therapies, for example, those that target interleukins, such as ustekinumab
- some trials in the sensitivity analysis included a small number of patients (less than 20% of the trial population) who previously had biological therapies, whereas the sensitivity analysis was meant to include people who never had biological treatments.

3.19 The ERG noted that the company did not present any data on the response of psoriasis to biological therapies after treatment with apremilast. Therefore the ERG was unclear whether apremilast affects the effectiveness of subsequent biological therapies.

Cost effectiveness

3.20 The company provided a Markov state-transition cohort model over a 10-year time horizon, using a 28-day cycle length. All costs and outcomes were discounted by 3.5% and the company stated that costs were from the NHS and personal social services perspective.

3.21 The health states in the company's Markov model comprised a short-term 'trial period' to determine initial response rate, and a long-term 'continued response' period. Apremilast was modelled as an additional treatment in a sequence. In the apremilast treatment sequence, patients could move through a maximum of

3 lines of treatment in addition to apremilast. In the comparator sequence, patients moved through the same lines of therapy, but without apremilast. In the company's base-case analysis, 2 different populations were modelled according to differences in DLQI score (both populations had the same PASI score). For people with a PASI score of at least 10 and a DLQI score of more than 10, the company compared a treatment sequence including apremilast (apremilast followed by 2 biological therapies and best supportive care) with a treatment sequence without apremilast (2 biological therapies and best supportive care). For people with a PASI score of at least 10 and a DLQI score of equal to or less than 10, the company compared a treatment sequence of apremilast followed by best supportive care with best supportive care alone. Patients who moved to best supportive care remained in this health state for the rest of the analysis (up to 10 years) or until they died. The company did not define best supportive care in its submission. The NICE psoriasis guideline defined it as a combination of systemic non-biological therapies, phototherapy and complex topical agents delivered in day-care settings and during inpatient stays.

3.22 The duration of the trial period in the model ranged from 10 to 16 weeks for biological therapies depending on the treatment (16 weeks for adalimumab or ustekinumab, 12 weeks for etanercept and 10 weeks for infliximab), based on current recommendations in the NICE guideline on psoriasis for assessing response with each treatment. The company used a 16-week trial period for apremilast because response to treatment was evaluated 16 weeks after starting apremilast in the phase 3 clinical trials (PSOR-008 and PSOR-009). In the base-case analysis, the company defined response to treatment at the end of the trial period as a 75% reduction in PASI score (PASI 75). Patients who had a PASI 75 response at the end of the trial period transitioned to the 'continued use' health state. The estimates of response to treatment in the model of people with a DLQI score of more than 10 were based on probabilities generated in the company's original base-case network meta-analysis (which did not include results from the PSOR-010 trial). For the analysis in people with a DLQI score of 10 or less, response to treatment was based on subpopulation results from the PSOR-008 and PSOR-009 trials. The probability of response for each treatment was assumed to be the same regardless of its point in the sequence. The company assumed that best supportive care provided no benefit.

3.23 To extrapolate data beyond the clinical trials, the company assumed that response rates (PASI 50, 75 and 90 rates) remain constant over time,

irrespective of patients' ages and response to previous treatments. Patients in the model could die in any health state. In the company's model, psoriasis did not affect the death rate.

3.24 The company assumed the same all-cause withdrawal probability for all biological therapies in the model (20%) and also for apremilast in the base case, in the absence of long-term withdrawal data.

3.25 Although the company collected EQ-5D scores at baseline and at 16 weeks in the clinical trials of apremilast, these data were not used in the base-case analysis for people with a DLQI score of more than 10 because EQ-5D scores were not available for all of the biological therapies included in the model. The company assigned utility values to each health state in the model based on the change in utility from baseline associated with the different PASI response categories reported in published literature (Woolacott et al. 2006), and the proportion of patients whose disease responded in each health state (see table 2). The utility values in Woolacott et al. had been estimated through mapping the DLQI associated with PASI responses from etanercept trials to changes in EQ-5D utility. However, for the analysis in people with a DLQI score of 10 or less, the company used EQ-5D data collected from PSOR-008 and PSOR-009. The company used the same baseline utility value (0.7; based on published data) in both analyses (DLQI more than 10 and DLQI 10 or less). The company assumed that best supportive care is not associated with any improvement in health-related quality of life.

Table 2 Health-related quality of life in the company model for DLQI more than 10 (data not reported for DLQI 10 or less model): changes in utility from baseline based on PASI response

PASI response	Change in utility from baseline	Confidence interval
More than PASI 90	0.21	0.11 to 0.31
PASI 90	0.19	0.11 to 0.27
PASI 75	0.17	0.09 to 0.25
Less than PASI 50	0.05	0.03 to 0.07
Abbreviation: PASI, Psoriasis Area Severity Index.		

3.26 The company's model did not include administration costs associated with apremilast or other oral therapies (including ciclosporin and methotrexate) or subcutaneous injections (adalimumab, etanercept and ustekinumab) because these were all assumed to be self-administered. An administration cost was included for each infusion of infliximab, to cover inpatient hospitalisation. The company assumed that all people whose disease had not responded to treatment were hospitalised for an average of 26.6 inpatient days per year based on the resource-use estimates used in NICE's psoriasis guideline. The company estimate of 26.6 days was based on 1 hospital admission in people with a high need (that is, those eligible for a first biological therapy) and 2.55 admissions in people with a very high need (that is, those eligible for a second biological therapy). The guideline was also used to source costs associated with best supportive care, which were estimated at approximately £888 per cycle in both populations modelled (DLQI more than 10 and DLQI 10 or less), based on an average of 26.6 inpatient days per year. The cost of apremilast was approximately £558 per cycle.

3.27 The company's model did not incorporate the cost of adverse events, or their impact on health-related quality of life (that is, reduced utility associated with each adverse event).

3.28 In the company's analysis of people with a DLQI score of more than 10, the sequence with apremilast dominated the sequence without apremilast. That is, the apremilast sequence was more effective (providing an additional 0.14 quality-adjusted life years [QALYs]) and less expensive (providing a cost saving of £3226). Adding data from the updated network meta-analysis (which, after consultation, included results from the PSOR-010 study) did not affect the cost-effectiveness results. In the company's analysis of people with a DLQI score of 10 or less, the apremilast sequence (apremilast followed by best supportive care) dominated best supportive care alone (providing an additional 0.05 QALYs with a cost saving of £6300). In the company's probabilistic sensitivity analysis, the apremilast sequence dominated the comparator sequence.

3.29 The company did scenario analyses to assess the uncertainty around structural assumptions. In addition, the company compared a sequence in which patients used apremilast after biological agents (adalimumab, then etanercept, then apremilast, then best supportive care) with the original sequence in which

apremilast came before biological therapies (apremilast, adalimumab, etanercept, best supportive care). In all scenario analyses, the apremilast sequence either dominated the comparator sequence without apremilast, or provided cost savings but with lower QALY gains. The sequence in which apremilast was positioned after the biological therapies was dominated by the original base-case sequence (apremilast before biological therapies).

3.30 The company also modelled apremilast as a replacement treatment for 1 of the biological therapies in the sequence. The apremilast sequences cost less, but were also less effective than the comparator sequences, with savings of £21,098–£39,121 per QALY lost.

ERG comments

3.31 For people with a DLQI score of 10 or less, the ERG considered best supportive care to be an appropriate comparator, but noted that the company did not present separate patient characteristics according to DLQI score.

3.32 The ERG noted that the company's assumption that treatments had the same efficacy in all positions in the treatment sequence differed from NICE's psoriasis guideline. The guideline found that efficacy of some biological therapies dropped when they were used second line (based on a meta-analysis of infliximab and ustekinumab).

3.33 The results of the company's network meta-analysis showed a placebo response for best supportive care (the mean absolute probabilities of a PASI 50, PASI 75 and PASI 90 response were 17%, 6% and 1% respectively). However, the company's model assumed best supportive care provided no benefit. The ERG noted that this was not consistent with the trial results or the approach used in NICE's psoriasis guideline. In the guideline model, about 4% of people receiving best supportive care had a PASI 50 response.

3.34 The ERG considered that it is uncertain if all treatments have the same withdrawal rates (20%) because of the different forms of administration, mechanisms of action and efficacy of all the treatments.

3.35 The ERG had several concerns with the company's utility values for people with a DLQI score of more than 10:

- the company did not use the EQ-5D data collected in clinical trials of apremilast
- the company did not appropriately justify the mapping algorithm used; there are other published algorithms with better predictive statistics and the company's analysis may overestimate the benefit of apremilast
- the company used a mapping algorithm that was based on etanercept data, thereby assuming that apremilast and etanercept have the same effect on health-related quality of life for any given change in PASI score.

3.36 The ERG considered that it was appropriate to use PSOR-008 and PSOR-009 trial data for the analysis in people with a DLQI score of 10 or less, but suggested that data from PSOR-010 also should have been included. The ERG considered that assuming the same baseline utility value (0.7) regardless of DLQI score was not clinically plausible, and contradicted the assumptions of the EQ-5D mapping algorithm.

3.37 The ERG considered the cost associated with best supportive care to be the most important model input because the estimates of the incremental cost-effectiveness ratios (ICERs) were driven by the difference in costs and outcomes with apremilast compared with best supportive care. The ERG stated that, because of the company assumption that best supportive care costs more than apremilast (based on NICE's psoriasis guideline), a sequence in which active therapy within a 10-year fixed timeframe is extended with apremilast (and consequently best supportive care is shortened) will always dominate the same sequence without apremilast.

3.38 The ERG had 3 concerns with using cost estimates for best supportive care from the psoriasis guideline:

- The definition and cost of best supportive care in the guideline was developed in the context of people with moderate to very severe plaque psoriasis who were being considered for a second biological therapy, and therefore may not be generalisable to the company's proposed positioning of apremilast in people with a DLQI score of more than 10 because these people are being considered for a first biological therapy.
- The definition of best supportive care in the guideline may be not generalisable to the company's model of people with a DLQI score of 10 or less because this group of patients is not eligible for biological therapies.

- The Guideline Development Group for the guideline recognised that there were substantial uncertainties in its estimated resource use costs for best supportive care, and performed and considered extensive sensitivity analyses when making the guideline recommendations.

3.39 For other costs in the model, the ERG considered the company's application of costs for treatment acquisition and administration appropriate, but the ERG had concerns about the costs associated with monitoring, drug wastage and adverse events. The company assumed that people receiving apremilast needed 3 fewer physician visits per year than people receiving biological therapies. The ERG's clinical adviser considered that the frequency of monitoring visits in clinical practice was likely to be similar regardless of treatment. The ERG noted that the frequency of monitoring had implications for treatment wastage; fewer physician visits could mean that more medication is prescribed at one time, which could result in more wasted medication when the person withdraws from treatment. The ERG considered that excluding costs of adverse events may favour apremilast, given that the company positioned apremilast as an additional line of treatment rather than replacing an existing one.

ERG exploratory analyses

3.40 The ERG conducted several exploratory analyses. The ERG's preferred scenario included the combination of the following analyses:

- Addition of the company's updated network meta-analysis (including data from PSOR–010) to the analysis in people with a DLQI score of more than 10.
- The ERG explored 4 scenarios that varied the costs associated with best supportive care. It stated that its preferred estimate was based on a publication by Fonia et al. (2010; adjusted for inflation to reflect 2012–13 prices), which assumed 0.312 hospital admissions of 20.8 days regardless of need. The ERG's preferred estimate lowered the cost per cycle of best supportive care to about £348 per cycle.
- In the company's base-case analysis, the company assumed that best supportive care provided no benefit. The ERG developed 4 alternative scenarios and stated that its preferred estimate was based on the base case in NICE's psoriasis guideline (4% of people had a PASI 50 response with best supportive care).

- For people with a DLQI score of more than 10, using EQ-5D data directly obtained from 3 apremilast trials (PSOR-008, PSOR-009 and PSOR-010) instead of a mapping algorithm.

3.41 The ERG's other exploratory analyses used the company's treatment sequences (that is, a sequence extended by apremilast compared with a sequence without apremilast) but varied the:

- probability of response to treatment (by including the company's updated network meta-analysis with PSOR-010 data)
- cost associated with best supportive care
- effectiveness of best supportive care
- approach to calculating health-related quality of life (by using trial-based EQ-5D data instead of a mapping algorithm)
- withdrawal rates associated with all treatments
- assumptions about treatment waste.

Following consultation, the company noted that it had made an error in its original submission when it used EQ 5D data based on US rather than UK tariffs. The company presented updated, corrected EQ 5D trial data for people with a DLQI score of more than 10. The ERG agreed that using UK tariffs was appropriate. For people with a DLQI score of more than 10, the apremilast before biological therapy sequence was associated with an incremental cost of £2611, incremental QALYs of 0.09 and an ICER of £28,574 per QALY gained, compared with a sequence without apremilast. The preferred analysis for people with a DLQI score of 10 or less did not include EQ 5D data from trials and was based on the US tariff. The ICER for the apremilast sequence was £89,374 per QALY gained, compared with a sequence without apremilast.

3.42 The ERG further varied rates of withdrawal associated with all treatments, and assumptions about how much is wasted when patients stop or change treatments. In its base case, the company applied a 20% annual withdrawal rate to all treatments. The ERG applied a higher annual withdrawal rate, based on results from the PSOR-008 trial of apremilast (marked as 'academic in confidence' by the company). The ERG did additional scenario analyses that showed that its cost-effectiveness results were sensitive to different costs associated with monitoring and waste. In the first scenario, the ERG assumed

that everyone would have the same number of physician visits (n=4) regardless of treatment. In an alternative scenario, the ERG assumed that patients who withdrew from apremilast would have 3 months of wasted medication (at a cost of £1787). The ERG also explored a scenario assuming 6 months of wasted medication at a cost of £3575. All 3 assumptions increased the ICER in both populations. The ERG suggested that 6 months of wasted medication might represent the average waste if people were prescribed medication only once a year.

3.43 Full details of all the evidence are available.

Additional analyses submitted by the company

3.44 During the consultation period, the company submitted a revised cost-effectiveness analysis for people with severe psoriasis (PASI score 10 or more, DLQI more than 10), comparing apremilast in a sequence before biological therapies with a sequence without apremilast. The company incorporated the following amendments suggested by the ERG and preferred by the Committee:

- using network meta-analysis results including the PSOR-010 trial
- and using trial-based EQ-5D data (using UK tariffs)
- and assuming that people receiving best supportive care would derive some clinical benefit
- and assuming that patients on different treatments have the same number of visits to the doctor (n=4).

3.45 The company also incorporated the ERG's preferred approach of basing estimates of resource use associated with best supportive care from Fonia et al. (2010), while at the same time maintaining that this study underestimated the rate of hospitalisation, and that defining best supportive care as in the NICE guideline on psoriasis was more appropriate. The company also presented hospital episode statistical data, which estimated that the average length of hospital stay for patients with a primary diagnosis of psoriasis was 3.5 days. Additionally, the company stated that the ERG's assumption was implausible that patients whose psoriasis does not respond to an active therapy will, when starting and trialling a new active treatment, incur the same resources as those

having best supportive care. The company stated therefore that it considered a cost of £345 per cycle for disease that does not respond to be too high. The company explored using costs from Fonia et al. (2010), reflecting the costs incurred after biological therapy as a proxy for the period in which patients trial new active treatments. However, in its preferred analysis, the company reduced the costs associated with being admitted to a day ward for infliximab infusion, and also reduced the costs associated with outpatient visits to avoid 'double counting'. This resulted in the company estimating costs for people whose disease has not responded and who are trialling new treatments of £45.04 per 28-day cycle. The company did not alter its pre-existing assumption of the model that 20% of patients withdraw from biological therapies each year. The company's revised base-case ICER comparing apremilast in a sequence before biological therapies with a sequence without apremilast was £20,593 per QALY gained (difference in QALYs 0.09, difference in costs £1882).

3.46 The company presented a scenario analysis that assumed that people whose condition does not respond to drugs that have already been dispensed waste an average of 14 days' worth of the drug at a cost of £275. This increased the company's base-case ICER to £23,419 per QALY gained for apremilast in a sequence before biological therapies compared with a sequence without apremilast. Additionally, the company explored using different resource-use costs for people whose condition does not respond, referred to as 'non-responders' (see table 3).

Table 3 Company exploratory analyses on non-responder costs (DLQI 10 or more): cost-effectiveness results for an apremilast sequence compared with a sequence without apremilast

Scenario	Non-responder cost estimate*	Inc. cost (£)	Inc. QALYs	ICER (£/QALY)
Company base case assuming resource use for non-responders in trial period for biological therapy, based on costs derived from the 12-month period after starting a biological therapy, from Fonia et al. (2010), less day-ward costs relating to infliximab infusion and less outpatient visits	£45.04	£1882	0.09	£20,539

Assuming resource use for non-responders in trial period for biological therapy, based on costs derived from the 12-month period after starting a biological therapy – from Fonia et al.	£108.00	£2015	0.09	£23,035
Assuming no resource use for non-responders in the trial period for biological therapy	£0.00	£1724	0.09	£18,868
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; QALY, quality-adjusted life year.				

3.47 The ERG agreed that an assumption of 2 weeks' waste for apremilast, and assuming equal number of physician visits between treatments (n=4), was appropriate. This increased the ERG's preferred ICER from £28,574 to £35,029 per QALY gained for apremilast in a sequence before biological therapies, compared with a sequence without apremilast. The ERG looked at the company's preferred approach to estimating costs associated with best supportive care needed when starting another active treatment in people whose psoriasis does not respond to a therapy; it acknowledged the importance of eliminating double counting and supported excluding outpatient and drug costs. However, the ERG disagreed with the company that costs derived from the 12-month period after starting a biological therapy were more appropriate because this would include both people whose disease did or did not respond to biological therapy and therefore would underestimate the costs involved. Instead, the ERG considered that costs based on the12-months before a patient starts a biological therapy were more appropriate. This would result in costs of £225 per cycle for people whose disease did not respond, associated with an ICER of £30,311 per QALY gained for apremilast in a sequence before biological therapies, compared with a sequence without apremilast.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of apremilast, having considered evidence on the nature of psoriasis and the value placed on the benefits of apremilast by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical management

4.1 The Committee heard about the experience of people with psoriasis. It heard that the disease results in itchy, dry, scaly and thickened skin, which can be physically and psychologically debilitating, particularly if located on the hands, feet, face and genitals. Severe psoriasis is also associated with a shortened life expectancy. The Committee heard that, because psoriasis is visible to others, it can make people feel isolated and lonely, which could lead to them losing self-confidence and avoiding social situations, and could also affect career opportunities and influence intimate relationships. It heard from clinical experts that people with severe psoriasis are about 6 times more likely to have suicidal thoughts or commit suicide than the general population. The Committee agreed that severe psoriasis has a significant psychosocial impact and substantially decreases quality of life.

4.2 The Committee discussed how clinicians assess the severity of disease in people with psoriasis. It understood that several indices are used, and heard that clinicians routinely use both the Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI) to monitor the disease. The Committee was aware that the UK marketing authorisation for apremilast includes people with moderate and severe disease. It understood that, while the marketing authorisation did not specify the criteria for moderate or severe disease, the regulatory decision was based on trials that included people with a baseline PASI score of 12 or more (mean score 19), 10% or greater of body surface area affected, and a static Physician Global Assessment score of at least 3. The Committee noted that the trials did not stipulate that patients have a particular DLQI score at baseline. The Committee was aware that previous NICE technology appraisals defined severe psoriasis as a PASI score of 10 or more and a DLQI of more than 10. It understood that there is no universally accepted definition of moderate psoriasis. However, the Committee heard from clinical experts that, in practice, moderate disease would be characterised by a lower

PASI score (between 5 and 9). It noted that the company, in its submission, presented analyses in people with a PASI score of 10 or more and a DLQI score of 10 or less to represent people with disease not severe enough to be treated with biologicals in the UK. Clinical experts explained that the disadvantages of the DLQI are that it is not specific to psoriasis and does not capture all of the impacts of the disease (such as anxiety and depression). Clinical and patient experts suggested that some people with chronic psoriasis can develop coping mechanisms and so adjust to the impact of the disease, resulting in lower DLQI scores. The Committee heard that clinicians use the DLQI for treatment decisions with biologicals, but do not generally use it to define different levels of severity. The Committee acknowledged that PASI and DLQI, which reflect the outcomes used in the trials, are relevant measures used in clinical practice in the NHS. The Committee concluded that the evidence base for apremilast did not include people with moderate disease as defined in UK clinical practice.

4.3 The Committee considered the treatment pathway for people with psoriasis. It was aware that people have topical treatments as first-line treatment, followed by conventional (non-biological) systemic therapies (such as methotrexate or ciclosporin), and phototherapy. If these treatments do not adequately control the psoriasis, people may have biological treatments, which they continue to have as long as the drugs work. The Committee understood that if the disease no longer responds to a biological treatment, people will be offered another biological treatment. This pattern is likely to be repeated over their lifetime; clinical experts noted that people with psoriasis will often try many alternative biological agents in a short timeframe. The Committee heard that, for people whose disease does not respond to multiple biological agents, the only remaining treatment option is best supportive care, which usually consists of topical agents and bandaging. The Committee questioned whether best supportive care was effective in treating psoriasis (that is, whether it improved PASI score or other measures of disease). It heard from clinical experts that best supportive care can be effective in the short term. The Committee was aware that best supportive care can be accompanied by disutility because of the intensive time-consuming, inconvenient and unpleasant treatments, and that the psoriasis may worsen sooner than with biological therapies. The Committee concluded that best supportive care is associated with limited, short-term efficacy and recognised the value of having a range of treatments with different mechanisms of action available.

4.4 The Committee considered the potential positioning of apremilast in the treatment pathway in clinical practice. It noted that the marketing authorisation for apremilast allows it to be positioned before, instead of, and after biological therapies. The Committee heard from a clinical expert that apremilast would generally be prescribed in people who had already tried biological therapies because apremilast is less effective than biological therapies. The clinicians also considered that patients unable to take biological therapies might be offered apremilast but that, in general, apremilast would not displace a biological therapy in the treatment pathway. The clinicians agreed that the positioning of apremilast (either before or after biological therapy) would be driven largely by patient choice and intolerance or contraindications to biological therapy such as serious infections. The Committee heard from the patient expert that because apremilast is less effective than biological therapies, offering apremilast as a first-line treatment could delay more effective treatments, and apremilast may therefore not be preferred. The Committee heard from clinical experts that some people with psoriasis do not adhere to treatment, so it is important to consider the patient's choice of treatment to encourage adherence. It heard from the patient expert that apremilast is taken orally; some patients may prefer this but it could become a burden to some, given its twice-daily dosing and the life-long duration of psoriasis. By comparison, some biological therapies are administered only once every 3 months, by subcutaneous injection. One clinical expert noted that some people would avoid additional treatments if their psoriasis had already responded to therapy, even if the psoriasis had not been completely cleared. An advantage of apremilast over biological agents, noted by the clinical experts, is that apremilast is not contraindicated in people with tuberculosis. The Committee concluded that clinicians would like to prescribe apremilast, either before or after biological therapies, and that the decision would be driven partly by patient choice, and patients may well choose not to have apremilast before biological therapies because it is considered to be less effective.

Clinical effectiveness

4.5 The Committee considered the baseline characteristics of the patients in the apremilast trials and discussed whether the trials reflected the UK population with psoriasis who would be eligible to have apremilast. It noted the Evidence Review Group's (ERG's) comment that only 13% of the PSOR-008 trial population would be eligible for apremilast. The Committee heard from the

company that, in its view, the ERG had misinterpreted the intended positioning of apremilast. The company clarified that, according to the UK marketing authorisation, apremilast could be used after only 1 conventional systemic treatment, which could be phototherapy. The company stated that about 65% of the PSOR-008 and PSOR-009 trial populations had any prior systemic therapy (including conventional therapies but also biological agents). The Committee noted the ERG's comments that the PSOR-008 and PSOR-009 trials may have overestimated the benefit of apremilast; some patients in the trial had no previous systemic treatment, so their disease would have been more likely to respond to apremilast because it was less severe than in people who had more treatments. The Committee heard from clinical experts that there is no robust evidence to suggest that previous treatment with conventional therapy affects response to subsequent treatment, but the Committee did not consider that this fully addressed the ERG's concerns. The Committee heard from the company that other criteria for inclusion and exclusion used in apremilast trials were similar to trials of biological therapies. The Committee concluded that the apremilast trials broadly provided an appropriate basis for its decision making.

4.6 The Committee discussed the results of the apremilast clinical trials, and considered the company's network meta-analysis, which compared apremilast with other biological agents specified in the scope. It noted that clinical trial evidence showed that apremilast was more effective than placebo for key outcomes at 16 weeks, and that this benefit was consistent across subgroups studied (see section 3.16). The Committee heard from clinical experts that biological therapies are more effective than apremilast for treating psoriasis, and was aware that the company's network meta-analysis showed that the probability of response to treatment is highest with biological therapies and lowest with apremilast (see section 3.12). The Committee heard from the ERG that the company's network meta-analysis was technically robust, but any bias from trials would carry through to the results from this analysis. The Committee heard that the ERG compared the meta-analysis results for the apremilast: etanercept comparison with odds ratios calculated using results of the PSOR-010 trial, confirming that psoriasis is more likely to respond to etanercept than apremilast. The Committee was aware of the drawbacks of the PSOR-010 study in that it was powered to compare apremilast with placebo and etanercept with placebo (but not apremilast with etanercept), but still concluded that apremilast is more effective than placebo, but not as effective as biological therapies.

4.7 The Committee discussed the long-term effectiveness of apremilast, noting that a substantial proportion of people who had a PASI 75 response after 16 weeks of apremilast treatment subsequently lost their PASI 75 response during the treatment withdrawal phase (marked as 'academic in confidence' by the company). The Committee heard from the company that some of the people in the apremilast trials who lost response, later regained it. The company stated that everyone who had a PASI 75 response at week 16 had at least a PASI 50 response by week 52. The clinical experts stated that fluctuating PASI scores characterise the natural history of psoriasis and any decline in efficacy with apremilast is expected to be similar to a decline with biological therapies. The experts also stated that the same level of response would not be seen if patients were to stop and restart treatment with apremilast. The Committee concluded that some response to treatment with apremilast is maintained up to 1 year, but noted uncertainty about longer-term effectiveness beyond the clinical trial data.

4.8 When considering the tolerability of apremilast, the Committee heard from clinical experts that apremilast is associated with a number of adverse events early in treatment. The Committee heard that the most common adverse events with apremilast are related to the gastrointestinal tract (including diarrhoea and nausea), and that people are willing to tolerate gastrointestinal adverse effects if they are benefiting from the drug. The Committee concluded that apremilast is associated with gastrointestinal adverse events, but these would not preclude the use of apremilast.

4.9 The Committee discussed the probability of people stopping apremilast treatment, and heard from clinical experts that the rate of withdrawal from apremilast is similar to (or potentially lower than) the rate of withdrawal from biological therapies. It heard from the company that the ERG's reference to a higher withdrawal rate with apremilast based on PSOR-008 data was factually inaccurate (the company marked this withdrawal rate as 'academic in confidence'). The company stated that 2-year data from PSOR-008 indicate a withdrawal rate of 19.5% per year for apremilast, which is similar to the company's assumption of a 20% withdrawal rate for biological therapies, which it chose based on the rate used for biological therapies in previous NICE appraisals (adalimumab, etanercept, infliximab, secukinumab and ustekinumab). The Committee concluded that the probability of people stopping treatment with apremilast is likely to be similar to the probability of people stopping treatment with biological therapies.

Cost effectiveness

4.10 The Committee considered whether the company's health economic model included relevant treatment sequences and positions. The Committee noted that the treatment sequences modelled by the company reflected the likely positioning of apremilast according to the clinical experts (see section 4.4), although this differed from NICE's original scope for this appraisal. The Committee heard from clinical experts that etanercept is the least effective of the existing biological therapies for treating severe psoriasis. When queried, the company stated that it had selected etanercept for the model because it is the most used biological therapy for psoriasis in Europe. The ERG stated that this would not be a key driver of the results because the model includes biological therapies in both arms in the model and would not be displaced in the sequence including apremilast. Based on the likely positioning of apremilast in the treatment pathway (see section 4.4), the Committee concluded that,although the company did not compare the sequence in which apremilast came after biological therapies with a sequence without apremilast, the positions and comparisons modelled by the company were generally sufficient for decision making.

4.11 The Committee discussed the sources used by the company to estimate resource use and costs associated with best supportive care. It noted that the incremental cost-effectiveness ratios (ICERs) were highly sensitive to these inputs, and specifically whether the model included hospitalisation rates and costs from Fonia et al. (2010; the ERG's preferred assumption of best supportive care costs of £348 per cycle based on 6.49 days of hospitalisation per year) or NICE's psoriasis guideline (the company's base case assuming best supportive care costs £888 per cycle based on 26.6 days of hospitalisation per year). The Committee heard from the clinical experts that both sources were likely to overestimate the actual number of hospital days and resource use associated with best supportive care. This is in part because the populations described in Fonia et al. and NICE's guideline differed from the population covered in this appraisal; NICE's psoriasis guideline was for a specific, high-need subpopulation with very severe psoriasis, and Fonia et al. described care in a tertiary care centre known for treating the most severely affected people. The Committee heard from the company that the Fonia et al. study reflected a site that offered day care and therefore admitted fewer people to hospital than would normally be admitted in clinical practice. The clinical expert stated that the Fonia et al.

study describes a day unit that offered on-site hotel accommodation to people. The Committee noted that this option is much less costly than a hospital stay because it would not incur nursing and other hospital costs and, increasingly, is the model of care for people with psoriasis in the NHS. The Committee also heard from the clinical experts that, in recent years, the number of people hospitalised for severe psoriasis has fallen, and that clinicians give best supportive care to people during their outpatient visits; therefore, hospitalisation costs associated with psoriasis have fallen, and are continuing to fall. The Committee noted that after consultation, the company provided NHS hospital episode statistics data that showed that the average length of hospital stay associated with best supportive care was 3.5 days. It heard from the company that, in its view, these values underestimate actual length of NHS hospitalisation because they include people with different disease severities as well as people receiving concomitant medication and that, in patients who had received inpatient care, the average length of stay is 10.74 days. The clinical experts agreed that the hospital episode statistics data underestimated length of hospitalisation. The Committee agreed with this, but considered that the most plausible estimate would be lower than the ERG and company assumptions of 6.49 and 26.6 days per year. With respect to the proportion of people admitted to hospital, the clinical experts noted that the actual proportion is much lower than the 30% annual probability assumed by Fonia et al. (the lower of the 2 estimates). The Committee recognised the significant uncertainty in this model input, and agreed that the best supportive care costs are likely to be lower than in Fonia, and also noted that assuming a lower cost would increase the ICER. Additionally, the Committee noted that costs associated with hospitalisation were consistently applied to all days in hospital. The Committee, however, considered that it was reasonable to expect that the first few days in hospital would generate more expenses than later days; therefore the company may have overestimated the overall costs of best supportive care associated with hospitalisation in the model and accounting for this was likely to increase the ICERs presented. The Committee recognised the considerable uncertainty and concluded that shortcomings exist among all sources of data for resource use, but that resource use for best supportive care is closer to Fonia et al. than to the estimates from NICE's guideline psoriasis.

4.12 The Committee went on to discuss the cost estimates for people whose disease does not respond to 1 systemic treatment and who then go on to get another, during which time they need elements of best supportive care. The Committee

recognised this as a significant driver of cost-effectiveness results. The Committee heard that the company had originally assumed that this resource would be lower than best supportive care costs and included an estimate of £460 per cycle, based on its preferred best supportive care costs from the NICE guideline on psoriasis (see section 4.11). The ERG instead based its preferred estimate on the study by Fonia et al. (2010) and also assumed that this additional resource is the same as for best supportive care, therefore including an estimate of £348 per cycle. After consultation, the company explored the effect on the cost-effectiveness results of using the costs from Fonia et al. for the 12-month period after patients start biological therapies. However the company noted that because it had already included costs for outpatients and systemic treatments in its model (also from Fonia et al.), it deducted these costs to avoid double counting, resulting in a cost for people whose condition does not respond of £45 per cycle. The Committee agreed that avoiding double counting was appropriate, but also agreed with the ERG that using costs from the period after starting biological therapies includes costs for people whose condition responds, as well as costs for people whose condition does not respond, to biological therapies, therefore underestimating the true costs. Instead, the Committee preferred the ERG's inclusion of costs from Fonia et al. that reflect the 12-month period before a person starts a biological therapy while at the same time reducing the costs of outpatient and systemic treatments (£225 per cycle). The company agreed during the second Committee meeting that this estimate was plausible, but highlighted that the ERG applied this cost to all people starting a new biological therapy for the 16-week 'trial' period, whereas a proportion of people on new treatments benefit immediately or at least quickly. The company acknowledged that there was uncertainty around the proportion of patients to which this 'non-responder' cost should apply. The clinical experts agreed that response varies among people who try new active treatments, and that it is unlikely that all people will incur the same 'non-responder' costs. The Committee heard from the ERG that the costs from Fonia et al. include patients at different levels of response and therefore the model already accounted for variable 'non-responder' costs during the period in which modelled patients try new drugs. The Committee concluded that there was considerable uncertainty about the actual costs associated with starting a new therapy if a person's disease has previously not responded to another therapy in the model, but concluded that the ERG's estimate of £225 per cycle was the most plausible of those presented.

4.13 The Committee considered the quality-of-life and utility values used in the company's original model. It was aware that the company did not use the baseline EQ-5D data collected in the apremilast clinical trials. The Committee heard that the company sourced the baseline utility value in the model (0.7) from previous technology appraisals (adalimumab, etanercept, infliximab, secukinumab and ustekinumab), and noted that people in the apremilast clinical trials had a baseline utility value of 0.8. The company stated that the baseline EQ-5D value in the apremilast trials differed from the baseline value in trials of biological therapies (although other key baseline characteristics such as PASI score were consistent across the trials). The ERG confirmed that changing the baseline utility value used in the model would not significantly affect the cost-effectiveness results because the model is driven by the incremental changes in utility score from baseline. The Committee then discussed the company's approach to incorporating utility increments associated with a response to treatment in the model. The Committee was concerned that the company had included trial-based EQ-5D data in its model reflecting a DLQI score of 10 or less but that, in the model reflecting a DLQI score of more than 10, the company had used a mapping algorithm instead of clinical trial data. The Committee was also concerned that the company used etanercept data in the mapping algorithm instead of apremilast data. The company justified this on the basis that EQ-5D data in the apremilast trials were subject to a ceiling effect. However, following the first Committee meeting the company clarified that it had, in error, derived EQ-5D data from US instead of UK tariffs. The company agreed that the updated trial-based EQ-5D data were appropriate and presented revised results for the change in utility from baseline associated with the different PASI response categories in the model. The Committee noted that the company's models did not take into account the disutility values associated with adverse events, but the ERG was unable to comment on how including these values would have affected the ICER. The Committee concluded that the utility gains estimated from the company's revised model (for people with a DLQI score of more than 10) were plausible.

4.14 The Committee discussed the assumption in the company model that apremilast is associated with fewer visits to a physician than biological therapies (1 annual visit for apremilast, compared with 4 visits per year with biological therapies). The Committee heard from the clinical experts that because apremilast is a new drug dermatologists would be cautious in allowing fewer visits to a physician, and therefore the number of physician visits (including GP visits in 'shared care'

arrangements) for apremilast and biological therapies would be the same initially but, in the long term, the clinicians expected that the number of monitoring visits would be lower for apremilast. The Committee did not consider it realistic that people receiving apremilast would visit their physician only once each year, and concluded that 4 visits per year (including visits to GPs) is more appropriate (based on the company's assumption of 4 visits for biological therapies). The clinical experts agreed with this, but noted that monitoring costs for apremilast were likely to be lower than for biological therapies. The clinical experts also confirmed that for treatment with apremilast GPs could monitor patients under shared-care arrangements. However, the Committee noted that the cost of monitoring people on apremilast in primary care should reflect the assumption of additional payments to GPs, similar to arrangements for monitoring methotrexate. The Committee noted that if lower monitoring costs for apremilast were incorporated in the model, this would lower the ICERs presented, but acknowledged the lack of robust estimates available. Therefore, the Committee concluded that the assumption of equal monitoring visits was appropriate. The Committee discussed the potential for waste with apremilast. The clinical experts acknowledged that when people did not adhere to or withdrew from treatment, some tablets would be wasted. The Committee considered that it would be reasonable to account for some treatment waste with apremilast. It noted the company's revised model, which included an assumption of 14 days' wasted treatment; it heard from the ERG and experts that this was plausible. The company additionally stated that a waste assumption should be applied equally to biological therapies and apremilast. The ERG, however, considered that the waste for biological therapies in each arm of the model would cancel each other out but the company stated that would be true only if a lifetime horizon was assumed. The clinical experts also stated that while there will be waste with biological therapies, this is low because people get rigorous training before being prescribed biological therapies, in order to boost adherence. The Committee concluded that the assumption of 14 days' apremilast waste in the revised model was appropriate.

4.15 The Committee discussed the company's assumption that the probability of response for each treatment was the same regardless of its position in the sequence. It heard from the company that clinical trials show that the efficacy of apremilast appears consistent across the positions in the treatment sequence. The company noted that the response was slightly lower if apremilast were

positioned after biologicals, and that its model accounted for this reduced efficacy. The Committee was satisfied that the company had included the efficacy of apremilast appropriately in its model.

4.16 The Committee considered the other assumptions in the company model in light of its clinical discussion. It concluded that the model should include the possibility that psoriasis can improve with best supportive care (in contrast to the company's assumption of no effectiveness, see section 4.3). The Committee agreed with the company's assumptions that withdrawal rates are similar for apremilast and biologicals (see section 4.9), and that response rates remain relatively constant over time (see section 4.7).

4.17 The Committee discussed the ICERs for apremilast positioned before biological therapies in a population with a PASI score of 10 or more and a DLQI score of more than 10. The Committee considered the company's revised base-case results and the ERG's exploratory analyses. The Committee concluded that the most plausible ICER available for decision-making was about £30,300 per QALY gained and noted that this was above the range normally considered cost effective. However it noted that there was considerable uncertainty about key factors driving this ICER, such as monitoring costs (see section 4.13), amount of drug waste (see section 4.14), the likely costs associated with best supportive care (see section 4.11) and the costs associated with 'non-responders' (see section 4.12). The Committee considered that these uncertainties could drive the ICERs in different directions and the magnitude of impact was uncertain. However, the Committee recalled its consideration in section 4.11 that the costs associated with best supportive care are likely to be even lower than those estimated by the ERG from Fonia et al. (2010) and accounting for this would increase the ICER. Moreover, being mindful that apremilast was not as effective as biological therapies, the Committee noted comments from the consultation and from the patient expert that apremilast in a sequence before biological therapies could delay access to more effective treatment, and may therefore not be preferred. The Committee heard from the patient expert that achieving clear skin in the shortest possible time is important to people and that a PASI 75 response shown with apremilast means that people are still affected by psoriasis. Together with the uncertainties in the economic modelling, the Committee concluded that apremilast could not be recommended for severe psoriasis after the failure of conventional systemic therapy but before biological therapy.

4.18 The Committee discussed the ICERs for apremilast positioned before biological therapies in a population with a PASI score of 10 or more and a DLQI score of 10 or less (moderate disease), and where best supportive care was the only comparator because patients with moderate disease are not offered biological therapies. At its first meeting, the Committee concluded that the most plausible ICER for the apremilast sequence lay somewhere between £97,500 and £125,300 per QALY gained, taking into account its preferred assumptions. The Committee noted that the company had not updated this analysis with the UK tariff-based utility values, and estimated, based on the original modelling, that the ICER in the less severely affected population could be twice that seen for the population with a PASI and DLQI of 10 or more, that is, about £60,000 per QALY gained. The Committee noted that the evidence base for apremilast did not include people with moderate disease as defined in UK clinical practice (a PASI score of 5 to 9). Given that the company's model indicated that apremilast had a higher ICER in a less affected population (that is, people with a DLQI score of 10 or less), the Committee concluded that the ICER for apremilast for treating moderate psoriasis would not be within the range considered to be a cost-effective use of NHS resources.

4.19 The Committee considered the company's cost-effectiveness results for apremilast positioned after biological therapies and before best supportive care. It noted that the sequence in which apremilast was positioned after biological therapy was dominated (provided fewer QALYs at a higher cost) by the sequence in which apremilast came before biological agents. Having already concluded that apremilast, as a treatment in a sequence before biological therapy, is not a cost-effective use of NHS resources (section 4.17), the Committee concluded that a treatment sequence that provides fewer QALYs but costs more could not be considered a cost-effective use of NHS resources.

4.20 The Committee considered the company's cost-effectiveness results for apremilast as a replacement treatment for 1 of the biological therapies in the sequence, even though the clinical experts stated that apremilast was unlikely to displace a biological agent in the treatment pathway. It noted that the sequences containing apremilast were cost saving – but less effective – than the comparator sequences, resulting in ICERs that reflected 'savings per QALY lost' (ranging from £21,100 to £39,100 per QALY). The Committee considered that the ICERs were based on uncertain assumptions and noted that that ICERs based on its preferred assumptions were not available. The Committee noted

that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. The Committee concluded that the ICERs for apremilast as a replacement for biological therapies for severe psoriasis were not within the range considered to be a cost-effective use of NHS resources.

4.21 The Committee heard differing views about whether apremilast was innovative in its potential to make a significant and substantial impact on health-related benefits. It agreed that apremilast appeared to be innovative in its novel use of an existing mechanism of action, and agreed that it demonstrated innovation by providing an additional novel oral therapy. However, the Committee recalled that some people with psoriasis prefer less-frequent injectable treatments to more-frequent oral ones (see section 4.4) and therefore the Committee concluded that, in this respect, there were no additional gains in health-related quality of life over those already included in the QALY calculations.

4.22 The Appraisal Committee considered when appraising apremilast whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. The Appraisal Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as not an applicable consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view on the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was irrelevant for the consideration of cost effectiveness of apremilast.

4.23 The Committee discussed whether the recommendations could be considered unfair because a small group of people are unable to take any biological therapies because of contraindications that could be associated with protected characteristics according to the Equality Act. The Committee concluded that these patients would otherwise have best supportive care, and although the company did not present a revised ICER comparing apremilast with best supportive care for this group, the Committee expected the ICER to be around £60,000 per QALY gained. Considering that this was much higher than what is

normally accepted as good use of NHS resources, the Committee concluded that to recommend apremilast for this group would not achieve the legitimate aim of providing advice on cost-effective treatments.

Summary of Appraisal Committee's key conclusions

TA368	Appraisal title: Apremilast for treating moderate to severe plaque psoriasis	Section
Key conclusion		
Apremilast is not recommended within its marketing authorisation for treating psoriasis, that is, for treating adults with moderate to severe chronic plaque psoriasis that has not responded to systemic therapy, or systemic therapy is contraindicated or not tolerated.		1.1
The Committee concluded that the incremental cost-effectiveness ratios (ICERs) for apremilast for moderate and severe psoriasis were not within the range considered to be a cost-effective use of NHS resources.		4.17, 4.18, 4.19, 4.20
Current practice		
Clinical need of patients, including the availability of alternative treatments	Severe psoriasis has a significant psychosocial impact and substantially decreases quality of life. People with psoriasis have topical treatments as first-line treatment, followed by conventional (non-biological) systemic therapies and phototherapy. If these treatments do not adequately control the psoriasis, people may have biological treatments. People with psoriasis will often try many alternative biological agents in a short timeframe and, for people whose disease has failed to respond to multiple biological agents, the only remaining treatment option is best supportive care. Although best supportive care can provide limited, short-term benefits, it is associated with disutility because of the intensive time-consuming, inconvenient and unpleasant treatments.	4.1, 4.3
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Apremilast provides a novel use of an existing mechanism of action, and an oral alternative to injectable biological therapies. However, some people with psoriasis prefer less frequent injectable treatments to more frequent oral ones. Another advantage of apremilast over biological agents is that apremilast is not contraindicated in people with tuberculosis.	4.4, 4.20
What is the position of the treatment in the pathway of care for the condition?	The marketing authorisation for apremilast allows it to be positioned before, instead of, and after biological therapies. However, clinical experts did not consider that apremilast would displace a biological therapy in the treatment pathway, and agreed that the positioning of apremilast (either before or after biological therapy) would be largely driven by patient choice and intolerance or contraindications to biological therapy.	4.4
Adverse reactions	The most common adverse events with apremilast are related to the gastrointestinal tract (including diarrhoea and nausea), but these would not preclude the use of apremilast because people are willing to tolerate gastrointestinal adverse effects if they are benefiting from the drug.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The clinical evidence for apremilast came from 4 multicentre, placebo-controlled, double-blind randomised controlled trials in people with moderate to severe chronic plaque psoriasis. The trials were good quality and the treatment groups were generally similar at baseline. Because PSOR-010 was not powered to compare apremilast with etanercept, and there were no other head-to-head trials comparing apremilast with any of the biological therapies currently recommended by NICE for psoriasis, the company did a network meta-analysis that included 24 studies. The Evidence Review Group (ERG) stated that the results from the company's network meta-analysis were likely to be reasonably reliable, but that the results of the company's sensitivity analysis should be interpreted with caution.	3.1, 3.12, 3.18, 4.6

Relevance to general clinical practice in the NHS	Not everyone in the PSOR-008 and PSOR-009 trials had systemic therapies before starting the trial (a criterion of the UK marketing authorisation for apremilast). The ERG suggested that the PSOR-008 and PSOR-009 trials might have overestimated the benefit of apremilast because some patients in the trial had no previous systemic treatment, so their disease would have been more likely to respond to apremilast because it was less severe than in people who had more treatments.	4.5
Uncertainties generated by the evidence	The evidence base for apremilast did not include people with moderate disease as defined in UK clinical practice (Psoriasis Area Severity Index [PASI] score between 5 and 9).	4.2
	The Committee were uncertain about the longer-term effectiveness of apremilast, beyond the clinical trial data (beyond 1 year).	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that apremilast is more effective than placebo but not as effective as biological therapies.	4.6
Evidence for cost effectiveness		

Availability and nature of evidence	The company's base-case model included a treatment sequence positioning apremilast before biological therapies (adalimumab and etanercept) and best supportive care compared with a treatment sequence without apremilast. The company provided scenario analyses assessing the cost effectiveness of apremilast positioned after biological agents (compared with a sequence with apremilast positioned before biological therapies) and apremilast as a replacement treatment for 1 of the biological therapies in the sequence. Given that clinical experts suggested that apremilast would extend the treatment sequence (either before or after biologicals), the Committee concluded that, although the positions and comparisons modelled by the company differed from NICE's original scope for this appraisal, they were generally sufficient for decision-making.	4.4, 4.10
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee considered that the company's base-case results were based on uncertain assumptions about key factors driving this ICER, such as monitoring costs, amount of drug waste, the likely costs associated with best supportive care and the costs associated with 'non-responders'. The ERG addressed these uncertainties in its exploratory analyses.	4.11, 4.13, 4.14, 4.16, 4.17
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	Following the first Committee meeting the company clarified that it had, in error, derived EQ-5D data from US instead of UK tariffs. The company agreed that the updated trial-based EQ-5D data were appropriate and presented revised results for the change in utility from baseline associated with the different PASI response categories in the model. The Committee noted that the company's models did not take into account the disutility values associated with adverse events, but the ERG was unable to comment on whether including these values would have affected the model results. The Committee concluded that the utility gains estimated from the company's revised model (for people with a Dermatology Life Quality Index (DLQI) score of more than 10) were plausible. There were no additional gains in health-related quality of life over those already included in the quality-adjusted life year (QALY) calculations.	4.13, 4.20

Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	
What are the key drivers of cost effectiveness?	The ICERs were highly sensitive to the costs associated with best supportive care, and specifically whether the model included hospitalisation rates and costs from Fonia et al. (2010) or NICE's psoriasis guideline. The Committee concluded that resource use for best supportive care is closer to Fonia et al. than to estimates from NICE's guideline.	4.11
Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered that the most plausible ICER available for the apremilast sequence (in which apremilast was positioned before biological therapies) was about £30,300 per QALY gained. However it noted that there was considerable uncertainty about key factors driving this ICER, such as monitoring costs, amount of drug waste, the likely costs associated with best supportive care and the costs associated with 'non-responders'.	4.17, 4.18
	The Committee estimated that the ICER in the less severely affected population could be twice that seen for the population with a PASI and DLQI of 10 or more, that is, about £60,000 per QALY gained for apremilast positioned before biological therapies in a population with a PASI score of 10 or more and a DLQI score of 10 or less (moderate disease), and where best supportive care was the only comparator. The Committee concluded that a sequence in which apremilast is positioned after biological therapies would not be a cost-effective use of NHS resources because it is dominated by a sequence that was not considered cost effective (apremilast positioned before biological agents).	4.19

	The Committee noted that the sequences in which apremilast replaced 1 of the biological therapies were cost saving but less effective than the comparator sequences, resulting in ICERs that reflected 'savings per QALY lost' (ranging from £21,100 to £39,100 per QALY).	4.20
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	Not applicable.	

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
November 2015

6 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)
Professor of Public Health, University of Exeter Medical School

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns
Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Mr Matthew Campbell-Hill
Lay member

Mr Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Professor Daniel Hochhauser
Consultant in Medical Oncology, UCL Cancer Institute

Mrs Anne Joshua
NHS 111 Pharmacy Lead, Patients and Information, NHS England

Dr Sanjay Kinra
Reader in Clinical Epidemiology and Honorary Consultant in Paediatrics, London School of Hygiene and Tropical Medicine and University College London NHS Hospitals Trust

Dr Miriam McCarthy
Consultant, Public Health, Public Health Agency, Northern Ireland

Professor Ruairidh Milne
Professorial Fellow in Public Health, Wessex Institute, University of Southampton

Dr Sanjeev Patel
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy
Lay Member

Ms Marta Soares
Research Fellow, Centre for Health Economics, University of York

Dr Nicky Welton
Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

Dr Nerys Woolacott
Senior Research Fellow, Centre for Health Economics, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sophie Laurenson and Helen Tucker
Technical Leads

Raisa Sidhu
Technical Adviser

Jeremy Powell
Project Manager

7 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by CRD and CHE Technology Assessment Group (Centre for Reviews and Dissemination and Centre for Health Economics), University of York:

- Wade R, Hinde S, Yang H, et al. Apremilast for treating moderate to severe plaque psoriasis: A Single Technology Appraisal, March 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Celgene

II. Professional/expert and patient/carer groups:

- British Association of Dermatologists
- British Dermatological Nursing Group
- Psoriasis Association
- Psoriasis and Psoriatic Arthritis Alliance
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- AbbVie
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Janssen
- Merck Sharp & Dohme
- MRC Clinical Trials Unit
- Novartis
- Pfizer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on apremilast by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

- Professor Anthony Bewley, nominated by Celgene – clinical expert
- Professor Catherine Smith, nominated by British Association of Dermatologists – clinical expert
- David Chandler, nominated by Psoriasis and Psoriatic Arthritis Alliance – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Celgene

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE single technology appraisal process.

We have produced information for the public explaining this guidance. Information about the evidence it is based on is also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

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This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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Accreditation

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission for Apremilast (Otezla®) for the treatment of adults with moderate to severe chronic plaque psoriasis

April 28th 2016

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

This patient access scheme (PAS) is for all preparations of apremilast (Otezla®) and concerns its use on the NHS in England and Wales, within its marketing authorisation, as a treatment for adults with moderate to severe chronic plaque psoriasis who have 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).

3.2 Please outline the rationale for developing the patient access scheme.

A Single Technology Appraisal (STA) for apremilast for the treatment of adult patients with moderate to severe chronic plaque psoriasis was submitted to NICE in January 2015. NICE Technology Appraisal guidance (TA368) concluded that apremilast is not recommended within its marketing authorisation for treating psoriasis, that is, for treating adults with moderate to severe chronic plaque psoriasis that have not responded to systemic therapy, or in whom systemic therapy is contraindicated or not tolerated. This negative recommendation was based on the Appraisal Committee's conclusion that the most plausible incremental cost-effectiveness ratio (ICER) for apremilast, after the failure of conventional systemic therapy but before biologic therapy, is approximately £30,300 per quality-adjusted life year (QALY) gained in patients with severe disease as reflected by a Psoriasis Area and Severity Index (PASI) score of ≥10 and a Dermatology Life Quality Index (DLQI) score of >10 (see TA368 section 4.17).

The PAS has been developed to improve the cost-effectiveness of apremilast and enable therapy with apremilast to be considered a cost-effective use of NHS resources within the licensed indication. Adopting the Appraisal Committee's preferred assumptions detailed within TA368 and including the fixed price for apremilast provided by the PAS, the revised base case indicates that apremilast is associated with an ICER of approximately £[redacted] QALY when used as a pre-biologic therapy in a treatment sequence consisting of adalimumab and etanercept compared with a treatment sequence without apremilast.

Cost-effectiveness acceptability curve (CEAC) plots indicated that at willingness to pay thresholds of £20,000 and £30,000, apremilast has a probability of being cost-effective of [redacted]% and [redacted]% respectively, at the PAS fixed price.

Extensive sensitivity and scenario analyses, which address the Appraisal Committee's identified key uncertainties within the model, show that apremilast remains cost-effective at a threshold range of £20,000/QALY to £30,000/QALY, with the vast majority of values being below a [redacted]/QALY threshold. Thus at the fixed price provided by the PAS, apremilast represents a clinically-effective and cost-effective treatment option when used after the failure of conventional systemic therapy but before biologic therapy for severe plaque psoriasis for the NHS in England in Wales.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The PAS is a simple, financially-based scheme providing apremilast to the NHS at a confidential fixed price of [redacted] per 56-tablet pack containing 56 x 30 mg film-coated tablets or [redacted] per 14-day treatment initiation pack consisting of 27 film-coated tablets (4 x 10 mg, 4 x 20 mg, 19 x 30 mg), (currently a [redacted] from the NHS list price). The fixed PAS price is applied at the point of invoicing to the NHS. The Department of Health (DH) have approved that the fixed price within the PAS is to remain as confidential in nature, as is covered by the standard NHS terms and conditions.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been use to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The PAS is applied to all patients with severe psoriasis receiving apremilast treatment on the NHS in England and Wales within the European marketing authorisation in accordance with expected NICE Guidance. Severe psoriasis is defined as patients with a PASI≥10 and DLQI>10.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?

- How are the criteria measured and why have the measures been chosen.

The PAS will apply to all patients from initiation of treatment.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patients prescribed apremilast on the NHS, within its licensed indication, for management of severe psoriasis will meet the criteria for the scheme.

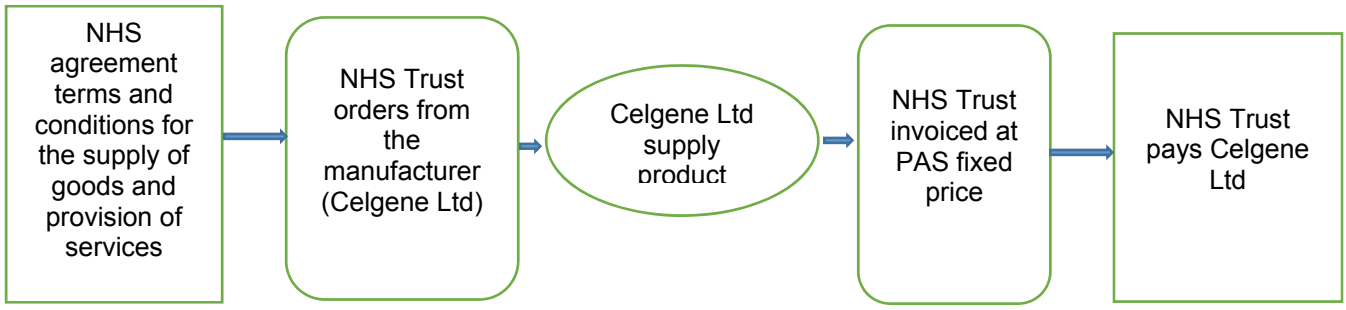
3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The PAS is a simple scheme, whereby a fixed price is applied at the point of invoice to the NHS. The fixed price will remain commercial in confidence as agreed with the DH. No rebates are applicable as part of the scheme and there is no administration burden above the usual supply of the product on the NHS.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

No additional information over and above that required to purchase the product without a PAS will be required.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.



3.10 Please provide details of the duration of the scheme.

The PAS will remain in place from the point of publication of a positive recommendation from NICE for the use of apremilast for the treatment of moderate to severe psoriasis [Rapid Review of TA368] until the recommendation is next reviewed by NICE and subject to the agreement of the DoH.

3.11 **Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?**

No.

3.12 **If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.**

Not applicable.

3.13 **In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.**

Not applicable

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

At the point of publication of a positive recommendation from NICE, the PAS will apply to all patients who receive apremilast for treatment severe psoriasis on the NHS within the licensed indication.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

The economic model has been updated to reflect the assumptions that the Appraisal Committee considered to be the most plausible for decision-making in TA368. No other changes have been made to the model.

The Appraisal Committee noted that there is uncertainty regarding several factors that drive the ICER and that these may affect the ICER in different directions, namely:

- monitoring costs;
- the amount of drug wasted through patients discontinuing therapy;
- the costs associated with BSC; and
- the cost of non-responders during the trial period of therapy with a new agent.

The impact of these uncertainties on the ICER has been investigated in extensive sensitivity and scenario analyses for apremilast with and without the PAS, as presented in sections 4.9 to 4.11.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The PAS has been incorporated into the economic model by changing the unit cost for apremilast from £9.82 to [redacted] (see worksheet appendix, cell J19 on the sheet labelled "Treatment Costs")

Appraisal Committee preferred scenario in TA368

Details of the changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible are summarized in Table 1.

Table 1 Summary of changes to the model to reflect the assumptions that the Appraisal Committee considered most plausible and the resulting ICER

Parameter	Company submission	Company consultation model	AC most plausible
Efficacy	NMA	NMA including PSOR-010 study	NMA including PSOR-010 study
Utility source	Woolacott et al.	Apremilast trial data	Apremilast trial data
BSC efficacy	None	NCGC model	NCGC model
BSC – days of hospitalization	26.6 days/year	6.49 days/year	6.49 days/year
BSC – cost per 28 day cycle	£888.00	£348.22	£348.22
Resource use cost of non-responders during trial period of subsequent therapy-cost per 28 day cycle	£462.56	£45.04	£225.00
Apremilast wastage	No wastage assumed	No wastage assumed	14 days wastage at non-response
ICER	Dominant	£20,593/QALY	£30,310/QALY

AC, Appraisal Committee; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PSOR-010, Psoriasis study 010

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data resulting from the evidence synthesis used in the rapid review model is identical to that used in the Appraisal Committee preferred model and is not affected by the inclusion of the PAS.

Clinical effectiveness data are based on the results of an NMA (probability of PASI-50, PASI-75 and PASI-90, Table 2).

Table 2 Absolute probability for each treatment for PASI-50, PASI-75 and PASI-90 (includes PSOR-010 data, random effects model)

	Mean	SD	Median	95% CrI
Probability of PASI-50				
Placebo	0.17	0.03	0.17	(0.12, 0.22)
Adalimumab 40 mg	0.83	0.04	0.84	(0.75, 0.9)
Apremilast 30 mg	0.54	0.05	0.54	(0.43, 0.63)
Etanercept 25 mg	0.68	0.05	0.69	(0.59, 0.77)
Infliximab 5 mg/kg	0.95	0.01	0.96	(0.92, 0.98)
Ustekinumab 45 mg	0.91	0.02	0.92	(0.87, 0.95)
Ustekinumab 90 mg	0.94	0.02	0.94	(0.9, 0.96)
Probability of PASI-75				
Placebo	0.06	0.01	0.05	(0.04, 0.08)
Adalimumab 40 mg	0.62	0.05	0.62	(0.51, 0.72)
Apremilast 30 mg	0.29	0.04	0.29	(0.21, 0.38)
Etanercept 25 mg	0.43	0.05	0.43	(0.33, 0.54)
Infliximab 5 mg/kg	0.85	0.04	0.85	(0.78, 0.91)
Ustekinumab 45 mg	0.77	0.04	0.77	(0.68, 0.84)
Ustekinumab 90 mg	0.81	0.04	0.81	(0.73, 0.87)
Probability of PASI-90				
Placebo	0.01	0.00	0.01	(0.01, 0.02)
Adalimumab 40 mg	0.35	0.05	0.35	(0.25, 0.46)
Apremilast 30 mg	0.10	0.02	0.10	(0.06, 0.15)

	Mean	SD	Median	95% CrI
Etanercept 25 mg	0.19	0.04	0.19	(0.13, 0.27)
Infliximab 5 mg/kg	0.64	0.06	0.64	(0.52, 0.74)
Ustekinumab 45 mg	0.51	0.05	0.51	(0.41, 0.61)
Ustekinumab 90 mg	0.57	0.05	0.57	(0.46, 0.67)

Celgene 2014[1]

bid, twice daily; biw, biweekly; CrI, credible interval; EOW, every other week; PASI-50/75/90, 50%/75%/90% or greater improvement in Psoriasis Area and Severity Index score; q12w, once every 12 weeks, QW, once weekly; SD, standard deviation.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

There are no costs associated with the implementation and operation of the PAS over and above those associated with the purchase of apremilast without the PAS.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

The PAS is a simple scheme applied at the point of invoice to the NHS. There are no additional treatment-related costs associated with implementation of the PAS.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

The base case corresponds to the Appraisal Committee's preferred assumptions and compares the following two treatment sequences in patients with severe disease defined as patients with a PASI≥10 and DLQI >10:

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

Table 3 summarises the results for the base-case analysis for apremilast at the list price. In agreement with the Appraisal Committee's estimate, the ICER for a treatment sequence including apremilast as a pre-biologic therapy compared with the corresponding treatment sequence excluding apremilast is £30,310/QALY.

Table 3 Base-case cost-effectiveness results: apremilast at the list price

	Apremilast sequence	**Comparator sequence**
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	£30,310	NA

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4 summarises the results for the base-case analysis for apremilast using the PAS fixed price [redacted] In this analysis, the ICER for the treatment sequence including apremilast as a pre-biologic therapy compared with the corresponding sequence excluding apremilast is [redacted]/QALY. This reflects a reduction in the total incremental costs of [redacted] compared to apremilast at the list price. The PAS does not affect the incremental QALYs. Thus at the PAS fixed price, apremilast, following the

failure of conventional systemic therapy but before biologic therapy, can be considered to be a cost-effective use of NHS resources for the treatment of patients with severe psoriasis being [redacted] the range considered to be cost-effective (i.e. £20,000/QALY–£30,000/QALY).

Table 4 Base-case cost-effectiveness results: apremilast with PAS

	Apremilast sequence	Comparator sequence
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.8 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Deterministic sensitivity analyses (DSA) have been performed on the Appraisal Committee's preferred model including apremilast with and without the PAS using the parameters varied in the original evidence submission (see the manufacturer's submission section 7.6.2). Key parameters such as the treatment efficacy (i.e. PASI response rates and long-term withdrawal probabilities), utility change by PASI response category, treatment dosages, hospitalisation, BSC costs and discounting rates are included in the analyses (Table 5).

The range for the DSA at list price was [redacted] to [redacted] and at the PAS fixed price was [redacted] to [redacted].

Results for the DSA show that, for the analysis including apremilast at the PAS fixed price, the ICER was less than [redacted] /QALY for all conditions considered except for the lowest monthly cost for BSC (highly conservative), where the ICER remained below [redacted] QALY (Table 6). Other drivers of the cost-effectiveness include the inpatient days associated with BSC, the efficacy of apremilast as reflected in the PASI-75 response rate, the long-term

withdrawal probability for apremilast and the utility associated with the ≤ PASI-50 health state (see Figure 1 and Figure 2).

Table 5 Values used in the deterministic sensitivity analyses

Input parameters	*Base-case*	*Lower*	*Upper*	*Source*
Efficacy				
PASI-50 - Apremilast	54.00%	43.00%	63.00%	Celgene NMA[1] (95% CrI)
PASI-50 - Adalimumab	83.00%	75.00%	90.00%	Celgene NMA[1] (95% CrI)
PASI-50 - Etanercept	68.00%	59.00%	77.00%	Celgene NMA[1] (95% CrI)
PASI-75 - Apremilast	29.00%	21.00%	38.00%	Celgene NMA[1] (95% CrI)
PASI-75 - Adalimumab	62.00%	51.00%	72.00%	Celgene NMA[1] (95% CrI)
PASI-75 - Etanercept	43.00%	33.00%	54.00%	Celgene NMA[1] (95% CrI)
PASI-90 - Apremilast	10.00%	6.00%	15.00%	Celgene NMA[1] (95% CrI)
PASI-90 - Adalimumab	35.00%	25.00%	46.00%	Celgene NMA[1] (95% CrI)
PASI-90 - Etanercept	19.00%	13.00%	27.00%	Celgene NMA[1] (95% CrI)
Withdrawal probabilities				
Long-term drop-out probability - Apremilast	20.00%	15.00%	25.00%	+/-25%
Long-term drop-out probability - Adalimumab	20.00%	15.00%	25.00%	+/-25%
Long-term drop-out probability - Etanercept	20.00%	15.00%	25.00%	+/-25%
Utilities				
Utility – PASI-90 - All treatments	[redacted]	[redacted]	[redacted]	Apremilast trials
Utility – PASI-75 90 - All treatments	[redacted]	[redacted]	[redacted]	Apremilast trials

Input parameters	*Base-case*	*Lower*	*Upper*	*Source*
Utility – PASI-50 75 - All treatments	[redacted]	[redacted]	[redacted]	Apremilast trials
Utility – PASI-50 - All treatments	[redacted]	[redacted]	[redacted]	Apremilast trials
Discount rates				
Discount rate - Costs	3.5%	0.0%	6.0%	Guide to the methods of technology appraisal; NICE 2013[2]
Discount rate - Outcomes	3.5%	0.0%	6.0%	Guide to the methods of technology appraisal; NICE 2013[2]
Hospitalisation for non-responders				
Non-responder Length of stay	1.00	0.75	1.25	Assumption (+/- 25%)
Non-responder cost	£225.00	£168.75	£281.25	Assumption (+/- 25%)
BSC				
Monthly cost of BSC	£348.22	£261.17	£435.28	Assumption (+/- 25%)
Inpatient days associated with BSC, days	6.49	4.87	8.11	Assumption +/- 25%
PASI-50 BSC response rate	3.80%	3.30%	4.40%	NCGC Appendix O. Table 3[3] (95% CI)
PASI-75 BSC response rate	0.80%	0.60%	1.10%	NCGC Appendix O. Table 3[3] (95% CI)
PASI-90 BSC response rate	0.10%	0.10%	0.20%	NCGC Appendix O. Table 3[3] (95% CI)

BSC, best supportive care; NCGC, National Clinical Guidelines Centre; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index

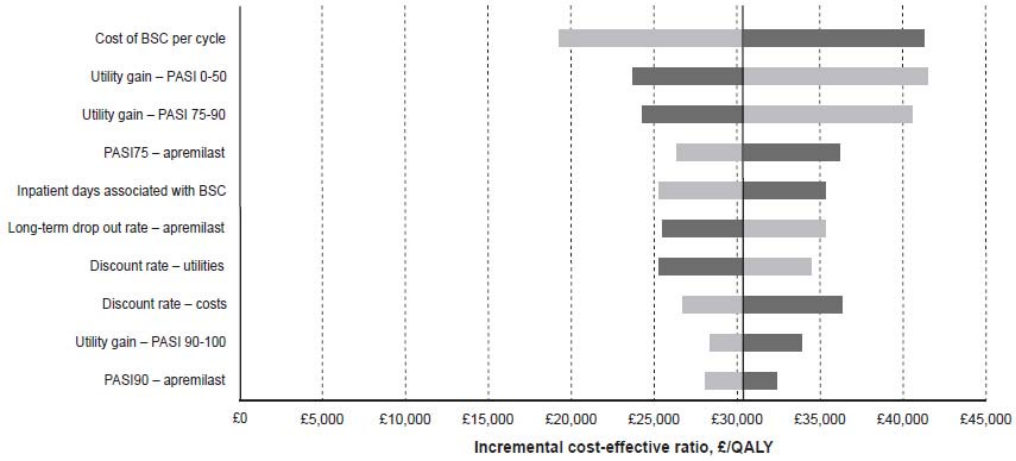
Table 6 **Univariate DSA results (£/QALY): apremilast at list price and with PAS**

	Apremilast at list price		Apremilast with PAS	
Input parameters	**Low value**	**High value**	**Low value**	**High value**
Efficacy				
PASI-50 - Apremilast	£30,959	£29,800	[redacted]	[redacted]
PASI-50 - Adalimumab	£30,287	£30,330	[redacted]	[redacted]
PASI-50 - Etanercept	£30,310	£30,310	[redacted]	[redacted]
PASI-75 - Apremilast	£36,140	£26,389	[redacted]	[redacted]
PASI-75 - Adalimumab	£30,838	£29,768	[redacted]	[redacted]
PASI-75 - Etanercept	£30,761	£29,748	[redacted]	[redacted]
PASI-90 - Apremilast	£32,415	£28,035	[redacted]	[redacted]
PASI-90 - Adalimumab	£29,748	£30,954	[redacted]	[redacted]
PASI-90 - Etanercept	£29,981	£30,761	[redacted]	[redacted]
Withdrawal probabilities				
Long-term drop-out probability - Apremilast	£25,669	£35,228	[redacted]	[redacted]
Long-term drop-out probability - Adalimumab	£30,226	£30,404	[redacted]	[redacted]
Long-term drop-out probability - Etanercept	£30,042	£30,489	[redacted]	[redacted]
Utilities				
Utility – PASI-90 - All treatments	£34,229	£27,197	[redacted]	[redacted]
Utility – PASI-75 90 - All treatments	£40,618	£24,175	[redacted]	[redacted]

	Apremilast at list price		Apremilast with PAS	
Input parameters	**Low value**	**High value**	**Low value**	**High value**
Utility – PASI-50 75 - All treatments	£31,102	£29,558	[redacted]	[redacted]
Utility – PASI-50 - All treatments	£23,770	£41,815	[redacted]	[redacted]
Discount rates				
Discount rate - Costs	£36,155	£26,936	[redacted]	[redacted]
Discount rate - Outcomes	£25,061	£34,517	[redacted]	[redacted]
Hospitalisation for non-responders				
Non-responder Length of stay	£28,156	£32,465	[redacted]	[redacted]
Non-responder cost	£28,156	£32,465	[redacted]	[redacted]
BSC				
Monthly cost of BSC	£41,175	£19,445	[redacted]	[redacted]
Inpatient days associated with BSC	£35,327	£25,295	[redacted]	[redacted]
PASI-50 BSC response rate	£30,228	£30,410	[redacted]	[redacted]
PASI-75 BSC response rate	£30,263	£30,382	[redacted]	[redacted]
PASI-90 BSC response rate	£30,310	£30,322	[redacted]	[redacted]

BSC, best supportive care; PASI, Psoriasis Area and Severity Index

Figure 1 Tornado plot for apremilast at list price



BSC, best supportive care; PASI, Psoriasis Area and Severity Index; QALY, Quality-adjusted life years

Figure 2 Tornado plot for apremilast with PAS

BSC, best supportive care; PASI, Psoriasis Area and Severity Index; QALY, Quality-adjusted life years

4.9 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analyses (PSA) were performed using the model corresponding to the Appraisal Committee's preferred assumptions and using the same parameter inputs as for the original submission (see manufacturer's submission section 7.6.3). A total of 5000 simulations were run.

For the analysis for apremilast at the list price, the totality of the simulations is located in the north-east quadrant indicating a positive differential in costs and in outcomes (see Figure 3a). This implies that, based on the uncertainty associated with the model parameters modelled in the PSA, the inclusion of apremilast as a treatment extension strategy before biologic therapy, produces incremental health benefits and an increase in cost in all simulations considered. For the corresponding analysis for apremilast with PAS, the cluster of simulation results moves downwards indicating that the fixed price of apremilast included in the PAS reduces the incremental cost, with no impact on incremental health benefits (Figure 3b).

The probabilistic and deterministic ICERs without PAS are £28,556 and £30,310 respectively. Similarly, with PAS, the probabilistic and deterministic ICERs are [redacted] and [redacted], indicating no issues with non-linearity within the model.

Cost-effectiveness acceptability curve (CEAC) plots indicate that at a willingness to pay threshold of £20,000, apremilast has a probability of being cost-effective of [redacted]% at the list price and this increases to [redacted]% at the PAS fixed price (Figure 4). When considering a willingness to pay threshold of £30,000, apremilast has a probability of being cost-effective of [redacted]% at the list price and [redacted]% at the PAS fixed price (Figure 5).

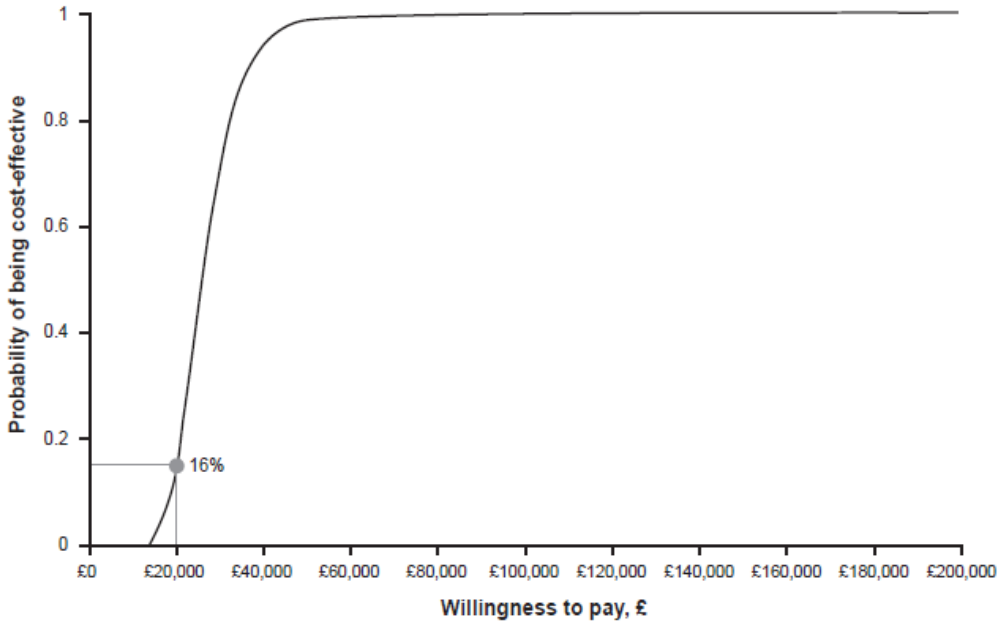
Figure 3 a) Cost-effectiveness plane for analysis of apremilast at a) the list price and b) with PAS

a)

b)

Figure 4 Cost-effectiveness acceptability curve for apremilast a) at list price and b) with PAS for a willingness to pay threshold of £20,000

a)

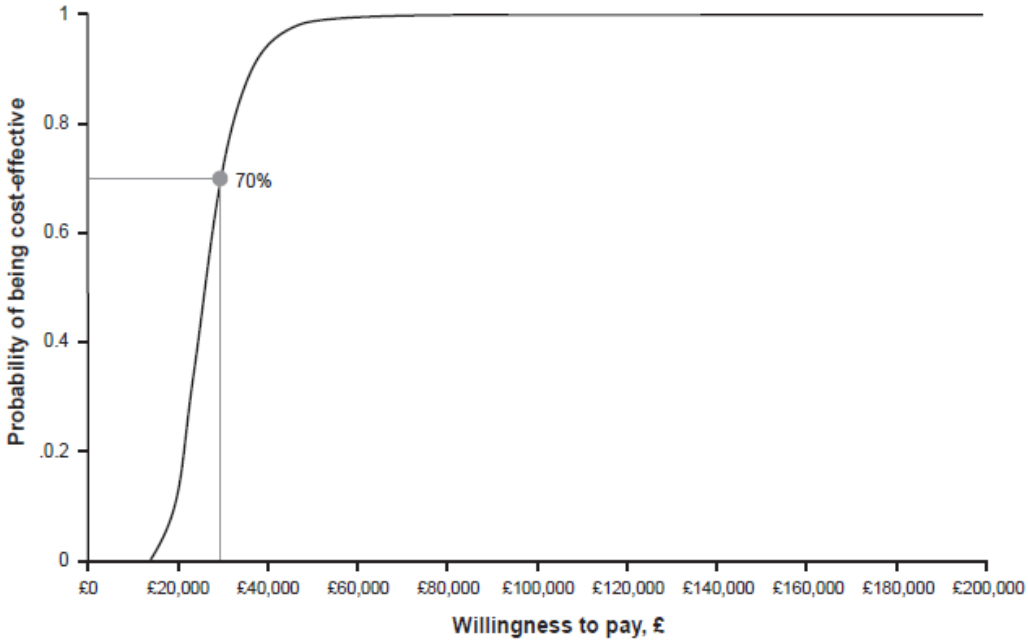


b)

[redacted]

Figure 5 Cost-effectiveness acceptability curve for apremilast a) at list price and b) with PAS for a willingness to pay threshold of £30,000

a)



b)

4.10 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Scenario analyses were performed to consider the effect of uncertainty around structural assumptions including the key uncertainties of the model highlighted in the by the Appraisal Committee.

Table 7 presents the results of scenario analyses corresponding to those presented in the original submission (see manufacturer's submission section 7.7.9) and relating to treatment of patients with severe disease. These relate to:

- alternative treatment sequence and length of sequence;
- time horizon;
- apremilast positioning within the sequence;
- decline in efficacy of biologic therapy after failure on first biologic therapy or on apremilast;
- alternative utility estimates for BSC;
- employing a 24-week trial period length for apremilast; and
- using alternative assumptions for the apremilast long-term withdrawal probability.

For the majority of scenarios, the apremilast sequence using the PAS fixed price for apremilast either had an ICER of [redacted] or dominated the comparator sequence.

Table 7 Results of scenario analyses at the list price and with the PAS fixed price corresponding to those performed for the initial submission

Technologies	Total costs (£)		Total QALYs	Incremental costs (£)		Incremental QALYs	ICER (£) incremental (QALYs)	
	List price	With PAS		List price	With PAS		List price	With PAS
Base case								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Alternative biologic treatment sequence								
Apremilast sequence (Apremilast → adalimumab → ustekinumab→ BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence: (Adalimumab → ustekinumab→ BSC)	[redacted]	[redacted]	[redacted]					
Alternative biologic treatment sequence length								

Technologies	Total costs (£)		Total QALYs	Incremental costs (£)		Incremental QALYs	ICER (£) incremental (QALYs)	
	List price	With PAS		List price	With PAS		List price	With PAS
1 biologic in treatment sequence								
Apremilast sequence (Apremilast → adalimumab → BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence: (Adalimumab → BSC)	[redacted]	[redacted]	[redacted]					
3 biologics in treatment sequence								
Apremilast sequence (Apremilast → adalimumab→ etanercept→ ustekinumab→ BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence (Adalimumab →	[redacted]	[redacted]	[redacted]					

Technologies	Total costs (£)		Total QALYs	Incremental costs (£)		Incremental QALYs	ICER (£) incremental (QALYs)	
	List price	With PAS		List price	With PAS		List price	With PAS
etanercept→ ustekinumab→ BSC)								
Apremilast positioning (pre biologic versus post biologic)								
Apremilast pre biologic in sequence: Apremilast → adalimumab → etanercept → BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast post biologic in sequence: Adalimumab → etanercept → apremilast → BSC	[redacted]	[redacted]	[redacted]					
One-year time horizon								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	**Total costs (£)**		**Total QALYs**	**Incremental costs (£)**		**Incremental QALYs**	**ICER (£) incremental (QALYs)**	
	List price	With PAS		List price	With PAS		List price	With PAS
								[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
5-year time horizon								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
40-year time horizon								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Decline in efficacy of biologic therapy after failure on first biologic therapy								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					

Technologies	Total costs (£)		Total QALYs	Incremental costs (£)		Incremental QALYs	ICER (£) incremental (QALYs)	
	List price	With PAS		List price	With PAS		List price	With PAS
Decline in efficacy of biologic therapy after failure on apremilast								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
No placebo response in BSC								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Alternative utility estimates (Woolacott et al[4] utilities)								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Trial period for apremilast increased to 24 weeks consistent with SPC								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)		Total QALYs	Incremental costs (£)		Incremental QALYs	ICER (£) incremental (QALYs)	
	List price	With PAS		List price	With PAS		List price	With PAS
Comparator sequence	[redacted]	[redacted]	[redacted]					
Apremilast annual withdrawal probability from clinical trial data (19.5%)								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Apremilast annual withdrawal probability set at arbitrary 10%								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					

Treatment sequences as follows unless stated otherwise: Apremilast sequence: apremilast → adalimumab → etanercept → BSC; Comparator sequence: adalimumab → etanercept → BSC

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NA, not available; QALY, quality-adjusted life-year

Scenario analyses addressing Appraisal Committee concerns in TA368

In TA368, the Appraisal Committee noted that there is uncertainty regarding several factors that drive the most-plausible ICER and that these may affect the ICER in different directions, namely monitoring costs, the amount of drug wasted through patients discontinuing therapy, the costs associated with BSC, and the cost of non-responders during the trial period of an active therapy.

Exploration of scenarios corresponding to the key uncertainties of the model as identified by the Appraisal Committee found that for the majority of scenarios considered (in patients with severe disease), the ICER for apremilast at the PAS fixed price was less than [redacted]/QALY, with all scenarios producing an ICER of well below [redacted] /QALY (Table 8 and Figure 6). The results suggest that, even for scenarios which are likely to be highly conservative towards apremilast, apremilast when positioned before biologic therapy, can be considered to be a cost-effective use of NHS resources for management of severe psoriasis in England and Wales at the PAS fixed price.

Table 8 Results of scenario analyses at the list price and with PAS for key uncertainties of the model as identified by the Appraisal Committee

Technologies	Total costs (£)		Total QALYs	Incremental costs (£)		Incremental QALYs	ICER (£) incremental (QALYs)	
	List price	With PAS		List price	With PAS		List price	With PAS
Appraisal Committee preferred base case (BSC, £348.22; non-responder, £225)								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Inpatient days for BSC based on HES data (3.5 days) (BSC, £274.16; non-responder, £150.94)								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Inpatient days for BSC based on HES data, in hospitalized population (10.74 days) (BSC, £453.50; non-responder, £330.28)								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Post-biologic Fonia costs[5] for non-responders								

(BSC, £348.22; non-responder, £45.04)								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Zero costs for non-responders (BSC, £348.22; non-responder, £0)								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Equal wastage assumed for apremilast and biologics								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					
Zero monitoring for toxicity assumed for apremilast								
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator sequence	[redacted]	[redacted]	[redacted]					

Treatment sequences as follows unless stated otherwise: Apremilast sequence: apremilast → adalimumab → etanercept → BSC; Comparator sequence: adalimumab → etanercept → BSC

BSC, best supportive care; HES, Hospital Episode Statistics; ICER, incremental cost-effectiveness ratio; NA, not available; QALY, quality-adjusted life-year

Figure 6 Scenario analyses at the list price and with PAS for key uncertainties of the model as identified by the Appraisal Committee

The scenario analyses presented in Table 8 address the 4 key Appraisal Committee concerns expressed in TA368, namely:

1. BSC resource use cost (hospitalization)

The base case, consistent with the Appraisal Committee's preferred assumptions for decision-making in TA368, includes BSC resource use based on Fonia et al.(2010).[5]

The Appraisal Committee states that:

The Committee recalled its consideration in section 4.11 that the costs associated with BSC are likely to be even lower than those estimated by the ERG from Fonia et al. (2010) and accounting for this would increase the ICER.

Celgene has explored this uncertainty further. In the first sensitivity analysis, a lower hospitalization rate has been assumed based on all patient data from the Hospital Episode Statistics (HES) data source presented during consultation. It should be noted that basing the number of inpatient days associated with BSC on overall HES data should be interpreted with caution and is highly likely to be an under estimate of the number of inpatient days as required in the economic model, and thus underestimate the total cost of BSC. These data contain patients with a range of stages of disease and severity and cannot be generalised to the modelled population of "severe" psoriasis patients. Further, the sample is likely to include a proportion of patients who are adequately controlled on therapy and may be on biologics and thus may not represent a true BSC cohort as described in the economic model. For both

of these reasons, the resource use data is expected to be an underestimate, if used to inform BSC resource use for a severe psoriasis population.

Indeed, section 4.11 of TA368 states:

"The clinical experts agreed that the hospital episode statistics data underestimated length of hospitalization"

Thus, Celgene considers that using data from the overall HES population is highly conservative and represents a "worst-case" scenario. Incremental QALYs remain the same as the base case [redacted] but incremental costs are increased from [redacted] to [redacted] owing to a greater relative reduction in the overall costs of the comparator sequence. Despite this, the ICER for this scenario is [redacted] /QALY (with PAS) indicating that, even assuming a highly conservative estimate for BSC resource use, apremilast is likely to be considered a cost-effective use of NHS resource and provides added reassurance for the decision-maker.

Celgene considers that a more appropriate assumption may be to use the average length of stay (LOS) in the subgroup of patients that receive any inpatient care. This gives an average LOS of 10.74 days per year (section 4.11 in TA368). In the second sensitivity analysis, the scenario using an average LOS of 10.74 days per year in the BSC definition produced an ICER of [redacted]/QALY (with PAS), [redacted] a WTP threshold range of £20,000-£30,000/QALY.

2. Non-responder cost

The non-responder cost in the model refers to the cost applied to patients who have failed on active treatment (primary or secondary non-response) and then move on to the trial period of another active treatment in the sequence. In the Appraisal Committee's base case, it is assumed this cost is equal to BSC (minus double counting) and is applied to 100% of patients. Celgene agree that removal of double-counting is appropriate however consider that the applying this cost to 100% of patients may overestimate the resource use for patients initiated on biologic therapy.

The Appraisal Committee noted that there was some uncertainty as to the proportion of patients to which this cost should be applied (section 4.12 of TA368). Celgene have explored this uncertainty further. In the first sensitivity analysis, it is assumed that this cost is applied to 0% of patients in the trial period of active treatments to reflect the likelihood that a significant proportion of patients are likely to achieve an early response (within the trial period) following initiation of biologic treatment, consistent with clinical trial data[6-9] The resultant ICER is

improved to [redacted]/QALY (with PAS), [redacted] a WTP threshold range of £20,000-£30,000/QALY.

In the second sensitivity analysis, it is assumed that 12-month post biologic Fonia costs are applied (non-responder cycle cost=£45.04). These data may be more appropriate as the proportion of responder/non-responder mix may be more reflective of those patients who are initiated on biologic therapy, i.e. a greater proportion of responders to non-responders. The ICER for this scenario is [redacted]QALY (with PAS).

3. Wastage associated with apremilast treatment

The base case conservatively assumes a 14-day wastage assumption for apremilast at non-response but no similar wastage assumption for biologic therapy. This disadvantages the cost-effectiveness against apremilast as an additional £275.00 (14-days at list price) is added to the apremilast sequence. Clinical experts and pharmacy procurement specialists have advised that NHS wastage is equally likely, if not more likely, with biologic therapy as Homecare services often deliver a 3-month supply of biologic therapy to patients and biologic therapy is subject to specific storage requirements. Thus the potential for drug waste due to patients discontinuing therapy within this 3-month period or drug spoilage is likely to be higher for injection-based biologics than for apremilast tablets, which are likely to be dispensed at monthly intervals according to NHS pharmacists consulted.

In this scenario analysis, an equal wastage assumption is assumed for apremilast and biologic therapy, set to be equal to zero. By removing the wastage assumption, the total cost in the apremilast sequence is reduced marginally from [redacted] in the base case to [redacted], resulting in an improved ICER of [redacted] (with PAS).

4. Monitoring associated with apremilast treatment

The SPC for apremilast does not contain any requirements for screening at treatment initiation or routine blood monitoring for toxicity with ongoing treatment. This is in contrast to requirements for biologic therapy. Thus, the base case assumption of equal monitoring requirements with biologic therapy is considered to be conservative and disadvantages the cost effectiveness against apremilast. In this scenario analysis, laboratory monitoring associated with apremilast treatment was set to zero. The total cost in the apremilast sequence compared to the base case is reduced slightly resulting in an improved ICER of [redacted]/QALY (with PAS). Celgene would like to further add that this scenario analysis may still not fully capture the wider benefits of obviating the need for routine blood monitoring. For example, the opportunity cost of reducing nurse time may free up resource to be utilised in other dermatology services and the impact of patients not having to travel to hospital (time off

work/daily activities, travel fees, parking, carer/family burden etc.) to have such tests is not incorporated in the calculation. Thus, the result is highly conservative.

Celgene have explored the four key areas of uncertainty highlighted by the Appraisal Committee in a series of scenario analyses. In conclusion, Celgene considers that the results for apremilast with the PAS in these scenario analyses around BSC resource use costs and other key uncertainties highlighted by the Appraisal Committee, indicate that there can be a high degree of certainty that apremilast, as a pre-biologic therapy in severe psoriasis, is a cost-effective use of NHS resources at a willingness to pay of £20,000-£30,000/QALY.

Apremilast vs. BSC

A further analysis considers apremilast as therapy for patients with severe psoriasis who are inappropriate for biologic therapy. This scenario compares:

- Apremilast sequence: Apremilast → BSC
- Comparator sequence: BSC

The clinical effectiveness data for this population has been taken from the company network meta-analysis for the overall population based on the consistent treatment effect observed across a variety of pre-specified sub-groups presented in the original company submission (section 6.5.3).

In this scenario the ICER is less than [redacted] /QALY for apremilast with the PAS and hence can be considered as a cost-effective use of NHS resources. (Table 9).

Table 9 Results of scenario analyses for apremilast at the list price and with PAS versus BSC (using Appraisal Committee preferred assumptions in TA368)

Technologies	**Total costs (£)**		**Total QALYs**	**Incremental costs (£)**		**Incremental QALYs**	**ICER (£) incremental (QALYs)**	
	List price	With PAS		List price	With PAS		List price	With PAS
Apremilast → BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,879	[redacted]
BSC	[redacted]	[redacted]	[redacted]					

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Apremilast as an innovative therapy providing additional benefits for patients not included in the QALY

Note: All data presented in this section has been presented previously during NICE TA368. This section does not contain any new data

Apremilast treatment has been shown to significantly improve Difficult To Treat (DTT) nail and scalp psoriasis and pruritus (itch),[10, 12] a frequently reported bothersome symptom of psoriasis.[13] Apremilast provided rapid and sustained improvement in pruritus and skin discomfort/pain, symptoms not typically captured in psoriasis assessments (e.g., PASI) but which contribute significantly to disease severity and patients' perceptions of their HRQoL.[14]

Apremilast, being an oral therapy, may support patient preferences for route of administration. Empirical research indicates that many patients with psoriasis have a preference to avoid injectable medications for their condition. For example in the MAPP study,[13, 15] half of patients in the UK who had received injectable biologic therapies indicated that these therapies were burdensome, primarily because of AEs, inconvenience and anxiety associated with injections and preparation for self-injection. A preference for an oral route of administration compared to injectable therapy is not captured into the QALY calculation.

Apremilast also reduces the impact of psoriasis on productivity loss and work limitations (as presented in section 6.5.2 p85 of STA submission). The impact of apremilast treatment on work limitations and productivity were assessed using the Work Limitations Questionnaire (WLQ)-25. In a pooled analysis of the Phase 3 RCTs, PSOR-008 and PSOR-009, statistically significant reductions in productivity loss and work limitation scores were observed at Week 16 with apremilast 30 mg bid in contrast to increases seen with placebo suggesting a benefit of apremilast therapy on the wider societal impact of psoriasis.[16] These wider societal benefits were conservatively not incorporated into the economic evaluation.

The additional benefits highlighted in this section relating to the impact of apremilast on DTT symptoms, the potential disutility of injectable biologic therapy and the wider societal benefit of apremilast treatment on work productivity are not captured in the base case QALY calculation. Thus the estimates of cost-effectiveness of apremilast presented in this submission can be considered as conservative.

Overall Conclusion

The analyses presented within this submission show that apremilast, at the fixed PAS price, when used within its licensed indication as a pre-biologic treatment for severe psoriasis, is highly likely to represent a cost-effective use of NHS resources at a WTP threshold of

£20,000-£30,000/QALY in England and Wales. This conclusion is robust to a series of extensive sensitivity and scenario analyses based on varying key parameters identified by the Committee in TA368, including those scenarios which are based on a set of highly conservative assumptions.

4.11 **If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.**

Not relevant

Impact of patient access scheme on ICERs

4.12 **For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.**

This information is presented in section 4.12.

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ERG review of the PAS submission of apremilast for the treatment of severe plaque psoriasis

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1 Introduction

Following the decision not to recommend apremilast for the treatment of moderate to severe plaque psoriasis (TA368, November 2015), Celgene (the Company) has proposed a Patient Access Scheme (PAS). The PAS only applies to patients with *severe* psoriasis receiving apremilast. Severe psoriasis is defined in the company submission as patients with a Psoriasis Area and Severity Index (PASI) score of 10 or more and a Dermatology Life Quality Index (DLQI) score of more than 10. This is a subgroup of the moderate to severe chronic plaque psoriasis population covered by the product's marketing authorisation. The subgroup of patients with moderate psoriasis (i.e. PASI of 10 or more and DLQI of 10 or less) is not included within the proposed PAS and submission. The company also included a revised economic analysis to address areas of uncertainty identified by the Appraisal Committee (AC) in TA368.

The Evidence Review Group (ERG) was requested by NICE to provide additional commentary and validity checks on the PAS submission. Due to the limited resource available, the additional work undertaken by the ERG does not constitute the same level of formal critique that was applied to the original submission. The ERG review should be read in conjunction with the company's PAS submission.

2 PAS Implementation

2.1 PAS scheme

Apremilast is administered orally. The recommended dosage is 30 mg twice daily after an initial titration schedule. A single 10-mg dose is given on the first day of treatment; this is titrated to 30 mg twice daily over 5 days (see the summary of product characteristics for the dose titration schedule). The company has proposed a simple fixed price PAS be applied to the purchase price of the 14-day

treatment initiation pack (27 tablets; 4 x 10 mg, 4 x 20 mg, 19 x 30 mg) and the 28-day pack (56 x 30 mg). The fixed PAS prices for the 14-day treatment initiation and the 56-tablet pack have been proposed at [redacted] and [redacted], respectively. The PAS represents a [redacted] discount from the NHS list price (excluding VAT; British National formulary [BNF] online, accessed May 2016). The fixed price is applied at the point of invoicing to the NHS. The Department of Health (DH) has approved that the fixed price within the PAS is to remain confidential, as is covered by the standard NHS terms and conditions.

2.2 Administration costs

The company has argued that due to the financial simplicity of the PAS discount, applied at the point of invoicing, the NHS will not incur any additional administration costs. Additionally, no rebates are applicable for the proposed scheme.

3 Model changes based on NICE Appraisal Committee's deliberations

The revised model included the proposed PAS scheme and several amendments to the base case analysis to reflect the preferred AC assumptions stated in relation to the most plausible ICER presented for decision making in TA368.

Table 1 summarises the separate models previously produced for TA 368, alongside the company's new PAS submission. The summary highlights the main changes that have occurred during the appraisal process, together with the base case (deterministic) ICERs from each model. Two key changes were made between the ERG alternative base case presented in the initial ERG report and the revised analyses presented to the AC at a subsequent meeting (denoted 'FAD' in Table 1). These changes were motivated by the AC preferred assumptions and are summarised in TA368, which reported:

1) *The Committee concluded that there was considerable uncertainty about the actual costs associated with starting a new therapy if a person's disease has previously not responded to another therapy in the model, but concluded that the ERG's estimate of £225 per cycle was the most plausible of those presented.* (FAD paragraph 4.12)
2) *The Committee considered that it would be reasonable to account for some treatment waste with apremilast. It noted the company's revised model, which included an assumption of 14 days' wasted treatment; it heard from the ERG and experts that this was plausible.*(FAD paragraph 4.14)

These two changes have been included within the base case of the company's PAS submission together with the PAS scheme. No other structural or parameter changes have been proposed by the company within the base case analysis of their PAS submission. The company also undertook a series

of scenario analysis to reflect the AC's concerns regarding uncertainties and possible impact on the most plausible ICER reported for decision making in TA368. These uncertainties related to the following factors:

- Monitoring costs;
- The amount of drug wasted through patients discontinuing therapy;
- The costs associated with BSC; and
- The costs of non-responders during the trial period of therapy with a new agent.

The key results presented by the company are summarised by the ERG in the following section.

Table 1: Key parameter estimates applied in TA368 and the new PAS submission

Parameter	**Original company submission (TA 368)**	**ERG original base-case (TA 368)**	**FAD (revised analysis taking into account AC recommendations and EQ5D error; TA368)**	**Company PAS submission**
Cost of BSC per 28 day cycle	£888.00	£348.22	£348.22	£348.22
Cost of non-responders	£462.56	£348.22	£225.00	£225.00
Source of utility estimates	Woolacott et al.	Apremilast trial data	Apremilast trial data	Apremilast trial data
Efficacy of BSC	None	NCGC model	NCGC model	NCGC model
Efficacy of active treatments	Network meta-analysis *excluding* PSOR-010 study	Network meta-analysis *including* PSOR-010 study	Network meta-analysis *including* PSOR-010 study	Network meta-analysis *including* PSOR-010 study
Wastage of apremilast	None	Up to 3 months	2 weeks	2 weeks
Physician visits differential	Fewer apremilast physician visits	Same number of visits for all active treatments	Same number of visits for all active treatments	Same number of visits for all active treatments
UK/US EQ5D value set	US value set	UK value set*	UK value set	UK value set
Price of apremilast	List price	List price	List price	xx discount on list price
Base-case ICER	Apremilast sequence dominant	£32,204 per QALY (£46,941 with 3 months of apremilast wastage)	£30,300 per QALY	[redacted] per QALY

**the erroneous use of the US value set was identified after the first AC meeting.*

4 The company's PAS submission

The company presented deterministic and probabilistic sensitivity analysis (PSA) results for a specific base case. The base case was stated to correspond with the AC's preferred assumptions and compared the following two treatment sequences in patients with *severe* psoriasis (PASI≥10 and DLQI >10):

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

Table 2 summarises the company's base case deterministic cost-effectiveness results with and without the PAS discount applied.

Table 2: Base case company results with and without the PAS

	List price		PAS discount applied ([redacted])	
	Apremilast sequence	**Comparator sequence**	**Apremilast sequence**	**Comparator sequence**
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£)	£30,310	NA	[redacted]	[redacted]

Based on list prices, the ICER of the apremilast sequence is £30,310 per QALY. The proposed PAS reduces the total cost of the apremilast sequence from [redacted] to [redacted] and reduces the difference in total costs between the sequences to [redacted]. The lower incremental cost difference between the sequences reduces the deterministic ICER of the apremilast sequence to [redacted] per QALY.

A number of univariate deterministic sensitivity analyses are presented, with and without the PAS. These are reported in detail in Tables 5 and 6 of the company's PAS submission (p16-20 and associated tornado plots in Figures 1 and 2). Based on the PAS results, all but one of these analyses results in an ICER for the apremilast sequence of less than £20,000 per QALY (ranging between [redacted] and [redacted] per QALY). The exception is the univariate analysis based on a lower estimated monthly

cost of BSC (£261.17 compared to £348.22 which is applied in the base case) which represents an arbitrary 25% reduction of the base case cost estimate. This analysis results in an ICER of [redacted] per QALY for the apremilast sequence.

The company additionally conducted PSA on the base case, reporting results with and without the PAS discount. The company reports that the probabilistic ICER without the PAS is £28,556 per QALY compared to the deterministic ICER of £30,310. The probabilistic ICER with the PAS scheme is [redacted] per QALY, compared to the deterministic ICER of [redacted]. The company reported that the similarity of the deterministic and probabilistic ICERs indicated no significant issues with non-linearity in the model.

The PSA results for the base case suggest that at the list price apremilast has a [redacted]% probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY, increasing to [redacted]% when the PAS scheme is applied. These probabilities rise to [redacted]% (list price) and [redacted]% (PAS scheme) at a threshold of £30,000 per QALY.

The company also presented results from a range of scenario analyses which correspond to those presented in their original submission for TA386. These are reported in full in Table 7 of the company's PAS submission (p26-31) and relate to:

- alternative treatment sequences and length of sequences;
- apremilast positioning within the sequence
- time horizon;
- decline in efficacy of biologic therapy after failure on first biologic therapy or on apremilast;
- alternative utility estimates for BSC;
- employing a 24-week trial period length for apremilast; and
- using alternative assumptions for the apremilast long-term withdrawal probability.

The ICER for the apremilast sequence was reported to be below £20,000 per QALY for all scenarios based on the PAS. Included within these scenarios are a number of variations on the sequence of biologic therapies included in the base case (which includes two biologics in the apremilast and comparator sequence; adalimumab and etanercept). These scenarios included:

1) Alternative biologic treatment sequences of the same length (i.e. replacing etanercept with ustekinumab in both the apremilast and comparator sequences);

2) Alternative biologic sequences of different length (i.e. 1 biologic [adalimumab only] or 3 biologics [adalimumab, etanercept and ustekinumab]);

3) A comparison of apremilast positioning (pre biologic vs post biologic).

In summary, the impact on the base case ICER for these was (PAS results only):

- The ICER based on an alternative biologic sequence of the *same* length reduced the ICER of the apremilast sequence to [redacted] per QALY.
- The ICER based on an alternative biologic sequence of a *shorter* length increased the ICER of the apremilast sequence to [redacted] per QALY.
- The ICER based on an alternative biologic sequence of a *longer* length resulted in the apremilast sequence dominating the comparator sequence.
- The ICER based on a comparison of apremilast positioning (pre vs post biologic) resulted in the pre-biologic apremilast sequence dominating the post-biologic apremilast sequence.

The result of a separate analysis was also presented for patients with severe psoriasis who are inappropriate for biologic therapy (Table 9, p38; PAS submission). In this scenario, the company compares:

- Apremilast sequence: Apremilast → BSC
- Comparator sequence: BSC

The ICER for apremilast with the PAS was reported to be [redacted] per QALY in this separate analysis.

The results of the scenarios addressing the key uncertainties identified by the AC relating to the costs of BSC and non-responders and wastage/monitoring are presented in Table 8 of the company's submission (p33-34). When the PAS scheme is applied, all bar one of scenarios results in an ICER below £20,000 per QALY for the apremilast sequence. In the scenario where the inpatient days for BSC were based on HES data (3.5 days; BSC=£274.16 and non-responder=£150.94), the ICER for the apremilast sequence was [redacted]. However, it should be noted that in TA368 it was reported that:

The clinical experts agreed that the hospital episode statistics data (estimated 3.5 days per year) underestimated length of hospitalisation. The Committee agreed with this, but considered that the most plausible estimate would be lower than the ERG and company assumptions of 6.49 and 26.6 days per year.(paragraph 4.11)

The company concludes in their submission that apremilast at the fixed PAS price, when used as a pre-biologic therapy in severe psoriasis patients, is highly likely to represent a cost-effective use of NHS resources at conventional thresholds of £20-30,000 per QALY. The company also reports that this conclusion is robust to extensive sensitivity and scenario analyses, including scenarios based on conservative assumptions.

4.1 ERG verification checks

The ERG undertook a series of verification checks in relation to the inclusion of the PAS scheme and the proposed model amendments. The ERG is satisfied that the company appropriately implemented the PAS scheme and the specific recommendations of the AC. The ERG successfully replicated the base case results using two different versions of the model, including: (i) the revised model submitted by the company, and (ii) the original model submitted for TA368 with the same proposed changes (PAS scheme and model amendments to reflect the AC recommendations) implemented by the ERG.

One minor technical issue identified by the ERG was that the updated model did not appear to accurately incorporate the additional cost of wastage. The submitted model applied wastage as a lump sum cost (14 days of apremilast subject to PAS discount) to all patients in the apremilast treatment arm. The ERG considers that the correct approach would be to apply it at the model time point at which patients cease treatment with apremilast, allowing for the impact of mortality before discontinuation of apremilast and appropriate discounting. However, when the ERG rectified this issue, the ERG obtained the same cost-effectiveness results as those reported by the company in their PAS submission. The ERG believes that this is likely due to the small difference that the two methods would have on the resulting cost estimates resulting from a low level of mortality prior to failure on apremilast and the limited effect of discounting.

Due to time constraints the ERG did not attempt to replicate all the individual univariate sensitivity analyses reported in Table 5 of the company's submission. Instead the ERG focused on replicating and verifying the scenario analyses reported in Tables 7-9 of the company's submission. The ERG successfully replicated these results with two exceptions:

- In a scenario reported by the company in Table 7 (p28, PAS submission) where alternative positioning was explored by comparing apremilast pre biologic vs post biologic, the ERG could not replicate the company's result. Instead of finding that apremilast positioned pre biologic dominated apremilast positioned post biologic, the ERG found that the pre biologic positioning of apremilast was both less effective and less costly than the post biologic positioning. As a result, the pre biologic positioning fell within the SW quadrant of the cost-effectiveness plane and the relevant ICER in this quadrant is [redacted] per QALY. This refers to the ICER between the lowest cost sequence (apremilast pre biologic) with the more costly and effective sequence (apremilast post biologic).
- In the separate analysis for apremilast versus BSC (Table 9, p38; PAS submission), the ERG could not replicate the reported ICER of [redacted]. The estimate the ERG obtained was [redacted]. The ERG has not been able to establish the reason for this difference, which appears to be driven by a very minor difference in the mean cost differences reported by the company, compared those estimated by the ERG using the company model.

To further assist in verifying the results of the company's PAS submission, the ERG also conducted a series of additional analyses using the original version of the company's submission for TA368 with the ERG implementing the same changes to reflect the PAS and the AC preferred assumptions. The original model contained full details of the Markov analyses and thus allowed the ERG the required level of access to check and conduct further independent analyses. The ERG successfully replicated the manufacturer base-case analysis using this approach and a sample of the key scenarios.

Summary of verification

The ERG is satisfied that the revised model has appropriately incorporated the PAS and the AC preferred assumptions. The ERG successfully replicated the company's base case using the revised model and with the same amendments made by the ERG using the company's original model. The ERG also successfully replicated the majority of the scenarios presented by the company, with two exceptions. In one of these, the ERG believes that an error may have been made by the company when reporting the results. That is, the pre biologic positioning of apremilast has been incorrectly reported to dominate the post biologic positioning. The error appears to be in reporting of the incremental difference in QALYs i.e. the company incorrectly reporting this as a positive QALY difference in favour of the pre biologic positioning. In the other scenario (apremilast vs BSC), the ERG's estimate of the ICER was marginally different from the company estimate (a difference of £50). The ERG could not identify the reason for this minor difference. Aside from a minor technical issue regarding the approach to modelling the cost of wastage, which subsequently appeared to make no material difference to the results, no other errors were found in the company's submitted results.

4.1 ERG further validation and critique

Although the ERG is satisfied that the company appropriately implemented the PAS scheme and the specific recommendations of the AC, the ERG has significant concerns regarding other aspects of the model results and associated validity. The ERG identified two key aspects of the company's conclusions which warrant further consideration and critique. The ERG has underlined these two aspects in relation to the overall conclusion provided by the company:

"apremilast, at the fixed PAS price, when used within its licensed indication as a pre-biologic treatment for severe psoriasis, is highly likely to represent a cost-effective use of NHS resources at a WTP threshold of £20,000-£30,000/QALY in England and Wales. This conclusion is robust to a series of extensive sensitivity and scenario analyses based on varying key parameters identified by the Committee in TA368, including those scenarios which are based on a set of highly conservative assumptions" (*p39-40, Company PAS submission*).

Issue 1: Apremilast a pre-biologic treatment

The ERG notes that the submission primarily focuses on the positioning of apremilast as a *pre-biologic* in a severe population with a PASI score of 10 or more and a DLQI score of more than 10. The ERG considers that the results presented by the manufacturer are partial in terms of the sequences and positions evaluated and hence cannot be used to determine the optimal position of apremilast in clinical pathway. The ERG considers these to be partial in relation to two aspects:

(i) the company only presented results based on sequences where apremilast is assumed to extend the comparator sequence (i.e. displacement of an existing therapy in the treatment pathway is not considered);

(ii) the company only presents results for 2 comparator sequences at any given time and, as a minimum, a simultaneous comparison of 3 sequences are required to inform positioning (i.e. a sequence with apremilast used pre biologic, post biologic or not at all). Hence, while the manufacturer results appear robust to a wide range of sensitivity and scenario analyses, the ERG does not consider that the partial analyses that have been presented are sufficient to establish that the optimal positioning of apremilast is as a pre-biologic treatment.

The ERG acknowledges that restricting sequences to those where apremilast is assumed to extend the current treatment pathway appeared to be supported by the clinical experts in TA368:

"The clinicians also considered that patients unable to take biological therapies might be offered apremilast but that, in general, apremilast would not displace a biological therapy in the treatment pathway." (FAD, paragraph 4.4).

The ERG considers it important to note that, while this would appear to be the general view, this does not rule out the possibility that apremilast could displace an existing biologic therapy in the treatment pathway. Further analyses supporting the positioning of apremilast as a pre-biologic treatment based on displacement sequences would have provided a more complete assessment. However, the ERG considers that the focus of the submission of apremilast as a pre-biologic treatment and the restriction in the model to assessing two comparator sequences at any given time to represent more significant limitations, particularly given the uncertainties expressed by clinicians in TA368:

"The Committee considered the potential positioning of apremilast in the treatment pathway in clinical practice. It noted that the marketing authorisation for apremilast allows it to be positioned before, instead of, and after biological therapies. The Committee heard from a clinical expert that apremilast would generally be prescribed in people who had already tried biological therapies because apremilast is less effective than biological therapies"..."The clinicians agreed that the

positioning of apremilast (either before or after biological therapy) would be driven largely by patient choice and intolerance or contraindications to biological therapy such as serious infections" (FAD, paragraph 4.4).

The company presented only a single scenario which assessed an alternative positioning for apremilast. This scenario compared the use of apremilast as a pre biologic (Apremilast → adalimumab → etanercept →BSC) versus as a post biologic (Adalimumab → etanercept → apremilast→ BSC). The results of this scenario reported that the use of apremilast as a pre biologic dominated its use a post biologic.

The ERG does not consider that this single scenario is a sufficient basis for determining the optimal position of apremilast and also identified a possible error in the company results for this scenario. The ERG also notes that the interpretation of the results from this scenario needs to be carefully considered. Assuming the time horizon is sufficient that all patients would have progressed to BSC, the ERG would expect that the difference between these sequences to be driven entirely by the impact of discounting (i.e. undiscounted costs and QALYs should be identical). Examining the model results, this appears to be the case. Consequently, any considerations made in relation to the cost-effectiveness of pre and post biologic positioning, employing the key structural assumption used in the base case (i.e. that there is no interaction between the positioning of apremilast and other elements of the sequence, such that the same number, ordering and/or effectiveness of existing treatments applies regardless of apremilast's positioning), relate entirely to issues of time preference and discounting. That is, a consideration of whether individual patient time preferences/discounting are appropriately reflected by the discount rate being applied, as opposed to any clinical meaningful differences (and related cost and QALY differences).

In addition to the theoretical arguments concerning the partial nature of the sequencing analyses and the company's emphasis on the pre biologic positioning of apremilast, the ERG has more serious concerns regarding the logic and validity of the sequencing model itself. These concerns raise questions concerning the face/external validity of the results of any of the sequence analyses which include an existing biologic treatment. Similar concerns were previously identified by the ERG in TA368 (pages 127-129, original ERG report), although the implications are now more evident within the revised model with the proposed changes applied.

The basis for the ERG concerns is clearly illustrated by presenting the results of each treatment individually versus BSC (i.e. not as part of an apremilast or comparator sequence). These results are summarised in Table 3 for apremilast and for the three individual biologic treatments that the company includes within the range of sequences considered in the base case and scenario analyses (adalimumab, etanercept and ustekinumab).

Table 3: Cost-effectiveness of each treatment vs BSC (ERG analysis using company PAS model)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Apremilast					
Apremilast→BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			
Adalimumab					
Adalimumab→BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			
Etanercept					
Etanercept→BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			
Ustekinumab					
Ustekinumab→BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			

As is evident from Table 3, all the three biologic treatments have ICERs compared to BSC that exceed the conventional £20,000-30,000 per QALY threshold range. Although the company has only presented a partial set of sequencing strategies, it logically follows from Table 3 that any sequence which excludes the alternative biologic treatments (i.e either by displacement and/or by not including in the pathway) would be more cost-effective than a sequence which includes them, based on conventional cost-effectiveness thresholds. By implication, since there is only one cost-effective treatment (apremilast), there can only be one cost-effective sequence amongst the entire set of plausible sequences that the model could consider (i.e. different lengths and ordering of the biologics and including possible displacement strategies). This is apremilast followed by BSC.

The external validity of the results of the sequencing analysis and for the other biologic therapies appear highly questionable since all three biologics have previously been appraised by NICE and considered to be cost-effective at the conventional £20,000-30,000 per QALY. The partial nature of the sequencing strategies means that the cost-effectiveness estimate of any comparison including a biologic therapy inappropriately leads to a more favourable ICER for the apremilast sequence being assessed. This is clearly demonstrated within the company's scenario analyses reported in Table 7 (p27-28, Company PAS submission), where the ICER of the apremilast sequence is shown to be less favourable for a shorter biologic sequence is and more favourable for a longer biologic sequence.

This issue was not raised by the company and the issues of external validity and possible implications within the sequencing results were not highlighted and justified. In the absence of any justification provided by the company, the ERG considers that only the results of apremilast reported versus BSC

to have sufficient face validity to inform decision making and that the sequencing results including biologic treatments should be discarded and/or ignored.

The ERG does not consider that these external validity concerns impact on the comparison of apremilast versus BSC and that the manufacturer's model and subsequent implementation appear appropriate for this comparison.

The ERG concludes that the appropriate base case ICER should therefore be [redacted] per QALY (and not [redacted]), which represents the ICER of a sequence of apremilast→BSC vs BSC alone.

Issue 2: Robustness of the results to sensitivity and scenario analyses

The company PAS submission presents a detailed set of results, including univariate and probabilistic sensitivity analyses and scenario analyses. Across the majority of these, the apremilast sequence was routinely reported to be below £20,000 per QALY. While the ERG acknowledges the apparent robustness of the results, the partial nature of the comparisons and the significant concerns noted regarding the validity of the sequencing results means that these findings provide an insufficient basis to demonstrate robustness.

To address this issue, the ERG has presented a set of additional univariate, probabilistic scenario analyses based on the only sequence it considers valid (apremilast→BSC vs BSC alone). These results are based on the same analyses and scenarios presented by the company in their PAS submission.

Given the limited time available, the ERG restricted the univariate analyses to those which appeared most influential in the company's tornado plot (Figure 2, p 20; Company PAS submission). These are reported in Table 4.

Table 4: Univariate sensitivity analysis of apremilast vs BSC (ERG analysis using company PAS model)

	Input values		Apremilast ICER with PAS	
Input parameters	**Low value**	**High value**	**Low value**	**High value**
Efficacy				
PASI-75 – Apremilast (base-case 29.00%)	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal probabilities				
Long-term drop-out probability – Apremilast (base-case 20.00%)	[redacted]	[redacted]	[redacted]	[redacted]

	Input values		Apremilast ICER with PAS	
Input parameters	**Low value**	**High value**	**Low value**	**High value**
Utilities				
Utility – PASI-75 90 - All treatments (base-case 0.16)	[redacted]	[redacted]	[redacted]	[redacted]
Utility – PASI-50 - All treatments (base-case 0.02)	[redacted]	[redacted]	[redacted]	[redacted]
BSC				
Monthly cost of BSC (base-case £348.22)	[redacted]	[redacted]	[redacted]	[redacted]
Inpatient days associated with BSC (base-case 6.49)	[redacted]	[redacted]	[redacted]	[redacted]

The range for the univariate (deterministic) sensitivity analysis at the fixed PAS price was [redacted] to [redacted] per QALY (compared to the range [redacted] to [redacted] reported by the company).

Table 5 reports the results of the PSA undertaken by the ERG. The probabilistic ICER with the PAS is [redacted] per QALY, compared to the deterministic ICER of [redacted]. Across the threshold range of £20,000-£30,000, apremilast has a probability of being cost-effective of [redacted] % to [redacted] %.

Table 5: PSA results of apremilast vs BSC (ERG PAS analysis using company PAS model)

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Probability cost-effective £20,000/QALY	Probability cost-effective £30,000/QALY
Apremilast versus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6 summarises the results of the scenario analyses undertaken by the ERG. Given time restrictions, the ERG has only undertaken scenarios on the cost of BSC and not the additional wastage and monitoring scenarios presented by the company. The scenarios presented by the company for non-responders are not relevant since these costs are only applied in scenarios where a subsequent biologic therapy is assumed. The range for the scenario (deterministic) analysis at the fixed PAS price was [redacted] to [redacted] per QALY (compared to the range [redacted] to [redacted] reported by the company for the comparable scenarios).

Table 6: Results of the scenario analysis of apremilast vs BSC (ERG PAS analysis using company PAS model)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Appraisal Committee preferred base case (BSC, £348.22; non-responder, £225)					
Apremilast alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC alone	[redacted]	[redacted]			
Inpatient days for BSC based on HES data (3.5 days) (BSC, £274.16; non-responder, £150.94)					
Apremilast alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC alone	[redacted]	[redacted]			
Inpatient days for BSC based on HES data, in hospitalized population (10.74 days) (BSC, £453.50; non-responder, £330.28)					
Apremilast alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC alone	[redacted]	[redacted]			

Finally the ERG investigated whether the same validity concerns still applied across these scenarios for the three alternative biologic treatments. Table 7 summarises the ICERs for apremilast and the alternative biologic treatments. In each scenario the ICER for each of the alternative biologic treatments exceeded the conventional threshold range of £20,000-30,000. This further reinforced the ERG's concerns, indicating that the same issues appear to be present across these scenarios.

Table 7: Results of the scenario analysis of apremilast and the alternative biologic treatments vs BSC (ERG PAS analysis using company PAS model)

Scenarios	Treatment			
	Apremilast vs BSC	Adalimumab vs BSC	Etanercept vs BSC	Ustekinumab vs BSC
Appraisal Committee preferred base case (BSC, £348.22; non-responder, £225)	[redacted]	[redacted]	[redacted]	[redacted]
Inpatient days for BSC based on HES data (3.5 days) (BSC, £274.16; non-responder, £150.94)	[redacted]	[redacted]	[redacted]	[redacted]
Inpatient days for BSC based on HES data, in hospitalized population (10.74 days) (BSC, £453.50; non-responder, £330.28)	[redacted]	[redacted]	[redacted]	[redacted]

5 ERG summary

The ERG is satisfied that the company appropriately implemented the PAS scheme and the specific recommendations of the AC. The ERG successfully replicated the manufacturer base and the majority of scenarios. Two exceptions were identified by the ERG. The ERG identified significant concerns regarding other aspects of the model results and associated validity and only considered the ICER for apremilast vs BSC to be sufficiently valid for the purposes of decision making. The base case deterministic ICER for this comparison with the PAS scheme applied was estimated by the ERG to be [redacted] per QALY ([redacted] based on the PSA).

The ERG conducted a restricted set of unvivariate and scenario analyses drawn from those presented by the manufacturer based on the only valid comparison presented. Across these analyses the ICER of apremilast vs BSC ranged between [redacted] and [redacted] per QALY.