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Evidence Review Group Report
Apremilast for treating moderate to severe plaque psoriasis

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Ros Wade wrote the clinical effectiveness sections of the report, with assistance from Huiqin Yang. Sebastian Hinde wrote the cost effectiveness sections of the report and conducted the economic analyses. Melissa Harden wrote the sections on the search strategies. Stephen Palmer provided advice and commented on drafts of the report. Eldon Spackman wrote drafts of the report and took overall responsibility for the cost effectiveness sections of the report. Nerys Woolacott commented on drafts of the report and took overall responsibility for the clinical effectiveness sections of the report.

Note on the text

All commercial-in-confidence (CIC) and academic-in-confidence (AIC) data have been highlighted in black.

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List of abbreviations

AE	Adverse event
AIC	Academic-in-confidence
BAD	British Association of Dermatologists
bid	Twice daily
biw	biweekly (once every 2 weeks)
BSA	Body surface area
BSC	Best supportive care
cAMP	Cyclic adenosine monophosphate
CEA	Cost-effectiveness analysis
CG	Clinical Guideline
CHE	Centre for Health Economics
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIC	Commercial-in-confidence
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DMARDs	Disease-modifying anti-rheumatic drugs
dPGA	dynamic Physician's Global Assessment
EMA	European Medicines Agency
ERG	Evidence Review Group
FAS	Full analysis set
FDA	Food and Drug Administration
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IL	Interleukin
LOCF	Last observation carried forward
mg	milligram
MS	Manufacturer's submission
MTC	Mixed treatment comparison
NAPSI	Nail Psoriasis Severity Index
NAPSI-50	50% improvement in NAPSI score
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
NRI	Non-responder imputation
PASI	Psoriasis Area and Severity Index
PASI-50	50% or greater improvement in PASI score
PASI-75	75% or greater improvement in PASI score
PASI-90	90% or greater improvement in PASI score
PDE4	Phosphodiesterase-4 enzyme
PGA	Physician's Global Assessment
PsA	Psoriatic arthritis
PSA	Probabilistic sensitivity analysis
PSOR-001	Psoriasis study 001
PSOR-003	Psoriasis study 003
PSOR-004	Psoriasis study 004
PSOR-005	Psoriasis study 005
PSOR-008	Psoriasis study 008
PSOR-009	Psoriasis study 009
PSOR-010	Psoriasis study 010
PSS	Personal social services
PUVA	Psoralen and ultraviolet A light
QALY	Quality-adjusted life year
qd	Once daily
qw	Once weekly
RCT	Randomised controlled trial
SPC	Summary of product characteristics
ScPGA	Scalp Physician's Global Assessment
SE	Standard error
SF36	36-item Short-Form Health Survey
SF36 MCS	36-item Short-Form Health Survey Mental Component Summary
sPGA	static Physician's Global Assessment
STA	Single Technology Appraisal
TA	Technology Appraisal
TB	Tuberculosis
TEAE	Treatment-emergent adverse event

TNF	Tumour necrosis factor
TNFα	Tumour necrosis factor alpha
URTI	Upper respiratory tract infection
UVA	Ultraviolet A light
UVB	Ultraviolet B light
VAS	Visual analogue scale
WLQ	Work Limitations Questionnaire
WLQ-25	Work Limitations Questionnaire 25
WPAI	Work Productivity and Activity Impairment Questionnaire
WTP	Willingness to pay

1 Summary

1.1 Critique of the decision problem in the manufacturer's submission

Apremilast (Otezla®) is an oral, small molecule, targeted phosphodiesterase-4 enzyme (PDE4) inhibitor. A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was adopted in November 2014 for the use of apremilast 30 mg twice daily (bid) in "adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA)".[1]

In their submission and clarification response the manufacturer states that apremilast provides an additional step in the treatment pathway for patients with severe psoriasis who are considered to be potential candidates for biological therapies (i.e. those with Psoriasis Area Severity Index [PASI] score ≥10, Dermatology Life Quality Index [DLQI] score >10), which may delay or prevent the need to proceed to biological therapies, and also that it provides an additional therapy for patients who are not eligible for biological therapies because they have a DLQI score ≤10.

The population in the manufacturer's submission (MS) matched that specified in the NICE scope, namely "adults with moderate to severe plaque psoriasis". However, reflecting their preferred positioning of apremilast, the MS considers mainly a subgroup of patients naïve to prior biological therapy. Given the licensed indication wording, it was appropriate to consider this subgroup, but it cannot be assumed without full analysis that this is the most appropriate subgroup for apremilast use: the licence does not preclude use in biologic-experienced patients.

The NICE scope listed the comparators as systemic non-biological therapies, systemic biological therapies and best supportive care, but the comparators in the MS were restricted to systemic biological therapies (in the clinical evidence section) and best supportive care, reflecting the licensed indication wording. However, the economic model presented in the MS reflected only the positioning of apremilast in the treatment pathway selected by the manufacturer, and compared different treatment sequences with apremilast as an additional line of therapy, rather than replacing an existing biological therapy in the sequence. The ERG asked the manufacturer to provide results where apremilast replaces an existing biological therapy in the sequence; in response the manufacturer sent a model that allowed apremilast to replace existing biologic therapy but stated that the modelling approach originally used is considered the most appropriate to address the decision problem and accurately reflect current treatment pathways in severe psoriasis, and the likely positioning of apremilast within future treatment pathways.

A separate submission has been made to NICE for apremilast as treatment for psoriatic arthritis (PsA), therefore, apremilast for the treatment of PsA will not be included in this appraisal.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

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

Four RCTs were included in the review: two Phase III trials PSOR-008[2] and PSOR-009[3], which both compared apremilast at the licensed dose with placebo; a Phase II trial, PSOR-005,[4] which compared three different dosages of apremilast with placebo, and PSOR-010,[5] which compared the licensed dose of apremilast with etanercept (50 mg once per week) and placebo.

The MS focussed on two of the four RCTs; PSOR-008 and PSOR-009.[2, 3] These two RCTs, individually and when their results were pooled, demonstrated that apremilast significantly reduced the severity of psoriasis and its impact on physical, psychological and social functioning, compared with placebo: a statistically significant difference was found between apremilast and placebo for the majority of outcomes at 16 weeks, including PASI-75 response (primary outcome; 31.7% versus 5.5%), sPGA score of 0 or 1 (21.3% versus 4.1%), PASI-50 response (57.7% versus 17.9%), PASI-90 response (8.7% versus 0.7%) mean change in PASI score from baseline (-51.6% versus -16.5%), mean change in psoriasis-affected BSA (-48.0% versus -6.8%), mean change in DLQI score from baseline (-6.6 versus -2.3), DLQI decrease of ≥5 points (70.4% versus 36.6%), mean change in baseline SF-36 Mental Component Summary (MCS) score (2.5 versus -0.7), mean change in pruritis VAS score from baseline (-32.2 versus -8.9), mean change in NAPSI score from baseline for patients with nail psoriasis (-24.6% versus 2.1%) and ScPGA score 0 or 1 for patients with scalp psoriasis (44.7% versus 17.4%). These findings were supported by those of the other two RCTS (PSOR-005 and PSOR-010).[4, 5] The PSOR-010 trial also demonstrated statistically significant improvements in psoriasis severity and impact with etanercept 50 mg once weekly (qw) over placebo (PASI-75 response 48.2% versus 11.9%); the ERG calculated odds ratio for apremilast versus etanercept was 1.41, 95% CI 0.76 to 2.61, indicating apremilast is slightly less effective than etanercept, though the result from this one small trial was not powered for this comparison.

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

In the pooled analysis of safety data from PSOR-008 and PSOR-009 more patients receiving apremilast experienced at least one adverse event, compared with placebo (68.9% versus 57.2%). The most frequently reported adverse events in patients receiving apremilast were diarrhoea (17.8%), nausea (16.6%), upper respiratory tract infections (8.4%), nasopharyngitis (7.3%), tension headache (7.3%) and headache (5.8%). The proportion of patients reporting severe adverse events or serious

adverse events was low and was similar between treatment groups. In terms of the short-term withdrawal rates due to adverse events, the pooled analysis of PSOR-008 and PSOR-009 showed that compared to placebo, apremilast had a slightly higher withdrawal rate due to adverse events at 16-weeks (apremilast 5.4% vs. placebo 3.8%). Similar adverse events results were seen in the PSOR-005 and PSOR-010 trials. As reported in the clinical study report for the PSOR-010 trial, more patients receiving apremilast experienced at least one adverse event (69.9%), compared with placebo (59.5%) or etanercept 50 mg qw (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.

Network meta-analysis of apremilast, adalimumab, etanercept, infliximab and ustekinumab
A network meta-analysis (NMA) was presented to compare the efficacy of apremilast with adalimumab, etanercept, infliximab and ustekinumab, based on the short-term efficacy data from individual trials.

The NMA presented in the MS did not include the PSOR-010 trial, but on request the manufacturer provided an updated NMA of 24 RCTs, including PSOR-010, as well as another trial excluded in error (Gottlieb, 2003). The updated NMA appears to have included all the relevant trials of apremilast and biological therapies for the treatment of psoriasis. Most of the 24 included RCTs were rated good or excellent quality. Insufficient details of the patient characteristics from the trials were presented in the MS, however, the manufacturer provided further details on request. The characteristics and study design of the trials included in the NMA appeared similar enough to be pooled.

The results of the NMA demonstrated that, of the active treatments, apremilast achieved the lowest absolute probability of achieving a PASI response (PASI-50, 75 and 90). Infliximab achieved the highest probability of PASI response, followed by ustekinumab, adalimumab, etanercept, then apremilast. The mean absolute probability of a PASI-75 response was [redacted] with apremilast, compared with between 43% and 85% for the various biological therapies and 6% for placebo.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The MS included a systematic review that does not appear to have missed any relevant RCTs. The four included RCTs were good quality and the results are likely to be reliable. However, the MS focussed on two of the four RCTs; only reporting minimal details of study methods and results, with no apparent assessment of study quality, for the other two RCTs, which were presented as 'supporting evidence'.

The PSOR-010 trial was the only trial to assess both apremilast and a biological therapy (etanercept) against placebo; the other three RCTs only compared apremilast with placebo.

Patients included in the PSOR-008 and PSOR-009 trials may not be representative of the licensed population or those who might be eligible for apremilast in NHS practice, as not all patients in the trials had failed (or even received) conventional systemic therapy: less than 40% of patients had received prior conventional systemic therapy. The manufacturer provided data for a number of subgroups including those patients who had failed two or more conventional systemic therapies or are contraindicated to systemic therapy and are biologic naïve, which reflects the population for their preferred positioning of apremilast in NHS practice, but made up only 19% of the PSOR-008 trial population. The results were similar to the main analysis; 23/68 (33.8%) patients in the apremilast group and 2/42 (4.8%) patients in the placebo group achieved a PASI-75 response. Results for patients who have failed at least one biologic were also similar but based on even smaller samples (From CSRs [redacted]).

The Bayesian NMA was appropriate to pool trial results and compare the treatments available for moderate to severe psoriasis. The NMA included the PASI (PASI-50, PASI-75, PASI-90) outcomes, reflecting the economic model. The manufacturer included 24 RCTs in their updated NMA and chose to synthesise outcome data measured between Week 10 to 16. The results were presented as the probabilities of achieving the specific cut-offs of improvement. On request the manufacturer provided odds ratios for comparisons between apremilast and other active treatments for PASI-50, PASI-75 and PASI-90 response, in addition to the comparisons with placebo. The WinBUGS code was not provided in the MS or in the clarification response despite a specific request and so this has not been checked by the ERG. In the response to clarification the appropriate diagnostic statistics for the updated NMA were provided. The submission included only the results for the random-effects model and so the ERG requested those for the fixed effect also: these were provided and the results were very similar.

A sensitivity analysis was undertaken using PASI outcomes data from only a biologic-naïve subgroup of patients; data from 15 trials considered to include patients naïve to biological therapy were included. The ERG questions the validity of this analysis due to the uncertainty around the 'biologic-naïve' status of the population across the trials.

1.4 Summary of cost effectiveness evidence submitted by the manufacturer

No previous cost-effectiveness studies of apremilast for moderate to severe psoriasis were identified by the manufacturer. Therefore, a de novo analysis to estimate the cost-effectiveness of a sequence including apremilast in two separate populations was submitted by the manufacturer, distinguished by

DLQI>10 or DLQI≤10, both populations considered have PASI≥10. The cost-effectiveness models submitted are based on the structure presented in the original cost-effectiveness analysis of biologics by the York Assessment Group. The York model structure was extended by the manufacturer to evaluate sequences of biologics. The base-case analysis for the DLQI>10 population compares two sequences, with the presentation of apremilast as a pre-biologic additional line of treatment:

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

The DLQI≤10 population analysis only considers apremilast followed by BSC versus BSC alone due to the ineligibility of patients in this population to receive biologic therapies under current NICE guidance. In both models a cycle length of 28 days and a time period of 10 years is applied. Health states are defined by the PASI improvement from baseline considered in five states: PASI0, PASI0-50, PASI50-75, PASI75-90 and PASI90-100.

All of the treatments in the sequence are made up of a 'trial period', the initial 10 to 16 week period over which initial response to the treatment is assessed, and a period of continued use of the treatment. All patients are assumed to complete the full trial period for each biologic, unless they die from other causes (no psoriasis related mortality is considered). At the end of the trial period, patients stay on that line of treatment if they have had a PASI improvement of 75% or more. Response parameters are informed by the manufacturer's NMA. If an inadequate response occurs patients move to the next line of treatment or BSC if at the end of the sequence. During the continued use period of each biologic, patients are assumed to stay in the same health state unless they die or withdraw from that treatment. Withdrawal is applied as a fixed rate per cycle and assumed to be the same for all active treatments. The position of a biologic in the sequence does not impact its effectiveness, or the effectiveness of any subsequent treatments.

In the DLQI>10 population model health related quality of life (HRQoL) scores are applied to the five modelled health states independent of treatment. The manufacturer uses HRQoL values from the original York model[6] which are applied to the four PASI improvement health states (i.e. not PASI0). In the DLQI≤10 model EQ-5D scores observed directly from the PSOR-008 trial are used to inform the four PASI improvement health states.

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

A major driver of both of the population models is the approach taken to BSC. The manufacturer assumes no treatment effect from BSC. All patients are assumed to be in the PASI0 health state and receive the baseline HRQoL. This assumption is based on clinical opinion. The cost associated with BSC is very high, including an average of 26.6 days of hospitalisation per year for all patients and the provision of cyclosporine and methotrexate in 45% of patients. The resultant cost for BSC is £11,543 per year, making it more expensive than apremilast, adalimumab, etanercept or ustekinumab. The cost of BSC is based on the highest cost presented in CG153.

Validation of the model was carried out, with the model structure and assumptions validated by a clinical expert. A range of one way scenarios and deterministic sensitivity analyses were presented by the manufacturer for the DLQI>10 population model as well as a probabilistic sensitivity analysis (PSA). The manufacturer reports apremilast arms being dominant in both the DLQI>10 and ≤10 population models with cost savings of £3,226 and £5,911 and QALY gains of 0.14 and 0.05 respectively. The results of the PSA are reported for the DLQI>10 population, finding 100% probability of the apremilast arm being cost-effective for all cost-effectiveness thresholds.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The original model submitted by the manufacturer was inflexible, initially only allowing the ERG to consider the use of apremilast as a pre-biologic additional line of therapy. The ERG considered the base-case sequence proposed by the manufacturer represented a limited set of potentially relevant sequences. The ERGs concern was that the proposed use and position of apremilast within an existing comparator sequence (i.e. whether apremilast might replace an existing therapy or extend a sequence and its position within an extended sequence) should be formally demonstrated rather than simply stated. The ERG considered that the manufacturer's base-case cost-effectiveness results were not necessarily a sufficient basis to inform the most efficient use and position of apremilast. The ERG was also concerned that uncertainties surrounding the cost-effectiveness of the comparator sequence and any implications for the cost-effectiveness of apremilast had not been robustly demonstrated by the manufacturer, since only partial comparisons were made.

The ERG has a number of concerns about the approach taken in the models presented by the manufacturer. Of most importance are the assumptions made with regards to the cost and effectiveness of BSC. The manufacturer applies BSC costs from CG153. These costs appear to represent a high need to very high need population that would be hospitalised for on average 26.6 days each year. The ERG acknowledges that there may be a subpopulation of very high need patients who are more likely to fail on multiple lines of biologics and incur very high BSC costs, however, the manufacturer did not undertake an analysis in this population and it is not clear how these patients could be identified prior to initiation of a biologic. Furthermore, it is not clear that apremilast would

be appropriate as first line treatment for this very severe population. In the absence of any formal attempt to consider particular subgroups (aside from the 2 DLQI populations) the ERG considers the BSC costs reported in Fonia et al[7] provides a more appropriate basis. Furthermore, the patient characteristics reported in Fonia et al are similar to those reported in the apremilast trials. While the manufacturer argued that Fonia was not a good representation of BSC costs after multiple lines of biologic treatment, the ERG considers that the manufacturer is potentially conflating the failure of multiple treatment with a higher need subgroup. Since the manufacturer models psoriasis as a non-progressive disease, it is unclear to the ERG why the costs from Fonia et al are not an appropriate basis for estimating the costs of BSC for an 'average' patient who would be eligible for biologic therapy. Ultimately all patients will progress to BSC in the manufacturer's model and hence using the BSC costs for an 'average' patient seems more appropriate to the ERG. The manufacturer also assumed the same costs of high need patients for BSC in patients with DLQI≤10. The ERG considered these costs even less generalizable to this population.

In addition, the manufacturer assumed no effectiveness of BSC; patients in BSC were assumed to have the baseline health related quality of life. Alternatively, the CG153 analysis assumed that patients on BSC would have the placebo response of patients in second line biologic trials, and all patients would at least have a 0.05 improvement in HRQoL. Observational data of patients receiving BSC reported up to 83% of patients achieving PASI-50 improvements. The ERG considered this an important issue for further exploration.

The ERG concluded that the manufacturer's approach to HRQoL was subject to several unnecessary assumptions. The HRQoL used by the manufacturer were based on an unjustified algorithm mapping DLQI scores from an etanercept trial. The ERG considers the most appropriate approach would have been to use the direct EQ-5D estimates from the trials as was done for the DLQI≤10 population.

Of additional concern to the ERG was that the network meta-analysis used to inform the efficacy for both populations failed to include the full range of available data, excluding the PSOR-010 apremilast trial data. The manufacturer also failed to incorporate any consideration of wastage of apremilast in the models submitted, despite the assumption that patients on apremilast would only visit a physician once a year and might require large prescriptions at each visit. Finally, the ERG considered that the manufacturer's application of a constant rate of long-term withdrawal to be the same across all biologics failed to make use of the available evidence from the apremilast trials.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The clinical evidence presented was appropriately based on a systematic review and the evidence for apremilast was derived from four good quality RCTs. The comparison with the biologic therapies was based on an appropriate NMA, after it was updated to include the PSOR-010 and Gottlieb trials.

A de novo model based on previous NICE technology appraisals was developed. The revised model submitted in response to the points for clarification allowed apremilast to be considered at different positions in the sequence.

1.6.2 Weaknesses and areas of uncertainty

The trials of apremilast, and those of the biologics were not specific to the licensed population for the treatment of moderate to severe psoriasis. In particular few data were available for the specific population proposed by the manufacturer (those who had failed two or more conventional systemic therapies or are contraindicated to systemic therapy and are biologic naïve). Even smaller subgroup samples were available to populate biologic experienced analyses.

The submission did not present data on patients' response to biological therapies after having received apremilast, therefore, it is unclear whether subsequent treatment effectiveness is affected by prior use of apremilast.

Longer-term safety data for apremilast are required as currently the safety data only extends to one year.

The cost-effectiveness model submitted did not allow multiple sequences to be compared simultaneously. This limited the usefulness of the probabilistic sensitivity analysis.

The costs of BSC were very high compared to previous technology appraisals, it was assumed that patients would be hospitalised 26.6 days each year when not on apremilast or biologics. It was also assumed that treatment with BSC did not improve the patient's condition.

The use of external health-related quality-of-life data was not well justified given the availability of trial data.

It was assumed that apremilast had the same withdrawal rate as biologics despite the differences in mode of administration and effectiveness.

The manufacturer did not consider the potential costs of wastage or non-compliance of apremilast, nor did they consider the costs of adverse events.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a range of exploratory analyses to assess the uncertainties raised in the review and critique of the manufacturer's clinical and cost-effectiveness evidence. The ERG's exploratory analyses focussed on: the issues and potential approaches to sequencing, the costs associated with BSC, the effectiveness of BSC in improving PASI score, and different approaches to HRQoL. Where appropriate all exploratory analyses were conducted on both the DLQI>10 and DLQI≤10 populations.

The ERG considered the manufacturer's approach taken to the placement of apremilast and the associated comparators to be excessively restrictive and failing to represent the NICE scope. While the ERG does not believe that any alternative sequence explored represents a more clinically likely scenario than the base-case presented by the manufacturer, the consideration of such additional sequences is a vital part of understanding the economic model submitted by the manufacturer, and the evaluation of apremilast within its licenced indication as required by the NICE scope. The ERG focused on two approaches to demonstrate the implications of different sequencing approaches in the DLQI>10 model: a comparison of all treatments as a single line of therapy, and the use of apremilast at different positions within a sequence. The main finding of these exploratory analyses was the inconsistency of results generated from the manufacturer's model to those previously reported in the literature, specifically previous TAs. The ERG also found that the sequence presented as the base-case by the manufacturer was the most cost-effective of a range of sequences containing apremilast at different positions.

The implications of the high cost of BSC was explored by the ERG through a number of exploratory analyses focussing on: the use of an alternate, cheaper, form of cyclosporine, applying different scenarios around the required rate of hospitalisation while on BSC, and the use of direct evidence from the literature on the cost of BSC.[7] These scenarios were applied to both the DLQI>10 and DLQI≤10 populations. The ERG found that there was a significant level of variability in the estimate of the cost of BSC with the cost per year varying from a maximum of £11,543 as applied by the manufacturer to a minimum of £3,395 when no hospitalisations were assumed. The ERG considered the use of direct evidence collected by Fonia et al.[7] to be the most indicative of the decision problem presented, which was associated with an annual cost of £4,581. The cost-effectiveness of the apremilast arm in both populations was highly sensitive to these different assumptions. The result of dominance over the comparator in both populations changed to a maximum ICER of £27,934 per QALY in the DLQI>10 population and to £121,875 in the DLQI≤10 population when patients were assumed to have no hospitalisations. The application of the Fonia cost resulted in an ICER of £17,859 and £85,538 in the respective populations.

The ERG applied additional exploratory analyses to the manufacturer's base case, considering a range of BSC effectiveness results and the use of different HRQoL scores. However, none of these additional analyses when applied to the manufacturer's base-case changed the conclusion of dominance of the apremilast arm in either population.

The ERG therefore constructed a preferred analysis which layered the different exploratory analyses together. The exploratory analyses chosen were: the use of the NMA results including the PSOR-010 trial (for the DLQI>10 population only), the use of BSC and non-responder costs from Fonia,[7] the use of HRQoL scores from the EQ-5D observed directly from the apremilast trials, and the application of the BSC effectiveness data from the CG153 base-case. The ERG preferred analysis resulted in an ICER of £39,391 for the DLQI>10 population and £87,908 for the DLQI≤10 population.

The incorporation of additional exploratory analysis to the ERG preferred analyses considering the implications of wastage and withdrawal estimates from the apremilast trials further increased the ICERs in both populations.

1.8 Conclusions

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

The cost-effectiveness of apremilast is dependent on optimistic assumptions about the costs and effectiveness of BSC. The ERG did not consider that the cost approach taken represented the appropriate BSC for the average patient who would otherwise be taking apremilast. Using evidence from UK clinical practice the ICER of apremilast increased above £20,000 per QALY in both patient populations of interest.

2 Background

2.1 Critique of manufacturer's description of underlying health problem

The description of the underlying health problem in the manufacturer's submission (MS) is appropriate and relevant to the decision problem under consideration.

Psoriasis is a chronic immune-mediated inflammatory skin disease, estimated to affect between 1.3 to 2.6% of the adult population in the UK.[8] Psoriasis typically follows a remitting-relapsing course and can have a major negative impact on health-related quality of life (HRQL). The most common form of psoriasis is chronic plaque psoriasis (psoriasis vulgaris), characterised by thickened, red, scaly plaques, typically found on the elbows, knees and scalp. Psoriasis is often graded using the Psoriasis Area Severity Index (PASI), which measures the percentage of skin area affected and the severity (erythema [redness], induration [thickness] and desquamation [scaling]). A score is calculated ranging from 0 (no disease) to 72 (maximal disease); around 20% of patients have moderate to severe disease (often defined as a PASI score of 10 or more).[9]

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's overview of current service provision is generally appropriate and relevant to the decision problem under consideration.

NICE clinical guideline 153 (2012) describes the care pathway for patients with psoriasis.[10] The care pathway was adequately summarised in the MS (Figure 2). Initially patients are managed with topical treatments, including emollients, coal tar, corticosteroids and vitamin D analogues (first line therapy). Patients whose disease is not controlled with topical treatments alone may be offered phototherapy (narrow-band ultraviolet B (UVB) light). For patients whose psoriasis cannot be controlled with first line therapy and who have extensive disease that has a significant impact on physical, psychological and social functioning (which can be measured using the Dermatology Life Quality Index (DLQI)), systemic non-biological therapies should be offered, such as methotrexate, ciclosporin, acitretin and psoralen and ultraviolet A light (PUVA) (second line therapy). For patients whose disease is not controlled by, or who are intolerant or contraindicated to second line therapy, systemic biological therapy is recommended; adalimumab, etanercept or ustekinumab for patients with a PASI score ≥10 and a DLQI score >10, or infliximab for patients with a PASI score ≥20 and a DLQI score >18 (third line therapy). Very recently (January 2015) an additional biologic systemic therapy, secukinumab, has been given marketing authorisation and because of its particularly favourable effects it is approved for use in all patients eligible for systemic therapy, not just in those who have failed on conventional systemic therapy.[11] Secukinumab for the treatment of psoriasis is currently being appraised by NICE.

The MS included a section on problems associated with the use of biologic therapies (p31 MS) and suggests that there is an unmet clinical need for effective treatments without adverse effects. However, the ERG's clinical advisor stated that with the accumulation of long term data in biologic registries, the limitations of biologic therapy and their side effect profiles are well known and the concerns over potential adverse effects have been somewhat alleviated. Furthermore, there is a large population of patients whose disease is well controlled with methotrexate or biological therapies. Importantly, the implicit comparison made in the background section of the MS between apremilast and other therapies does not take into account the actual evidence from apremilast trials, which does not favour apremilast. This is discussed further in Section 4. The PSOR-010 trial demonstrates more frequent adverse events in the apremilast arm than in the etanercept arm. The MS refers to discontinuation of biologics as a problem but cites the results of a recently published survey[12] of patients with psoriasis and psoriatic arthritis, "that the commonest reason for drug discontinuation was treatment ineffectiveness", suggesting more effective therapies are needed.

The ERG's clinical advisor commented that the MS may overstate the problems with biological therapies. The MS states that "currently only 50% of patients who satisfy the NICE eligibility criteria to receive biologic therapy for their psoriasis in England and Wales receive therapy suggesting that a significant proportion of patients are undertreated and may be suboptimally managed in clinical practice". The ERG's clinical advisor commented that if this statement refers to patients who would be offered biological therapies in practice, then 50% seems a high estimation, as, in his experience, there are not many patients who refuse treatment with a biological therapy because of potential adverse events or the mode of delivery. The source that the manufacturer cites for this statistic is a UK conjoint-analysis study undertaken by the manufacturer; limited study details were presented in Section 4.1.3 of the MS. The study was an online survey of the preferences of 300 patients with moderate to severe psoriasis. The mean BSA of participants was only [redacted], which is considerably lower than that of patients included in the apremilast trials. Insufficient study details were provided to allow an assessment of the validity of the study; therefore, the results of this study may not be reliable or applicable to patients with more extensive psoriasis. Etanercept is administered once or twice a week, adalimumab every two weeks, and ustekinumab is administered in hospital by intravenous injection once every three months. Whilst some patients may prefer an oral therapy to an injection, others may consider a less frequent injection to be less onerous than taking a tablet twice a day; missed doses may affect both the clinical effectiveness and cost of treatment.

The MS states that "there is a significant unmet need in patients who fail on or are contraindicated to conventional systemic non-biologic therapy but do not meet the eligibility criteria for biologic therapy due to disease severity". The ERG's clinical advisor commented that there is not a large population

of patients who have a PASI score ≥10 and a DLQI score ≤10; generally PASI and DLQI scores correlate.

Technology under appraisal

In December 2013 the manufacturer submitted an application to the European Medicines Agency (EMA) for apremilast for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The EMA commented that as an active comparator study with a conventional systemic therapy such as methotrexate was not conducted, it was difficult to rank this product with other first line systemic conventional therapies. A justification that the efficacy and safety data support a broad indication in patients in need of systemic therapy was considered inadequate. The manufacturer therefore agreed to amend the indication to a narrower population: "adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA)". A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was adopted in November 2014.[1]

The manufacturer also submitted an application to the EMA for apremilast, alone or in combination with disease-modifying anti-rheumatic drugs (DMARDs), as treatment for active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant of a prior DMARD therapy. A separate submission has been made to NICE for this indication, therefore, apremilast for the treatment of PsA will not be included in this appraisal.

Apremilast (Otezla®) is an oral, small molecule, targeted phosphodiesterase-4 enzyme (PDE4) inhibitor. The MS described the mechanism of action of apremilast.

The manufacturer states that apremilast provides an additional step in the treatment pathway for patients with severe psoriasis, who are considered to be potential candidates for biological therapies (PASI score ≥10, DLQI score >10), which may delay or prevent the need to proceed to biological therapies. It also provides an additional therapy for patients who are not eligible for biological therapies because they have a DLQI score ≤10.

3 Critique of manufacturer's definition of decision problem

3.1 Population

The population in the MS matched that specified in the NICE scope, namely "adults with moderate to severe plaque psoriasis". However, the MS considers mainly a subgroup of patients naïve to prior biological therapy. Given the licensed indication wording, it was appropriate to consider this subgroup. However, it cannot be assumed without full analysis that this is the most appropriate subgroup for apremilast use: the licence does not preclude use in biologic-experienced patients.

The CHMP positive opinion recommended the granting of a marketing authorisation for apremilast 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 cyclosporine, methotrexate or PUVA.[1] Moderate to severe chronic plaque psoriasis was not defined in the CHMP positive opinion, however in NICE guideline CG153 biological therapies are recommended for the treatment of adults with severe psoriasis, defined by a total PASI score of 10 or more and DLQI score more than 10.[10] The evidence presented in the MS was derived from clinical trials whose inclusion criteria were adults with moderate to severe plaque psoriasis, defined by a PASI score of 12 or more, body surface area (BSA) affected 10% or more and static Physician's Global Assessment (sPGA) score of 3 or more. DLQI was not an inclusion criterion in the trials.[2, 3]

3.2 Intervention

The intervention in the MS matched that specified in the NICE scope. The clinical trials that provided the clinical effectiveness evidence used the recommended dose of apremilast: 30 mg twice daily (bid), after titration period (treatment is initiated with a dose of 10 mg on day 1 and is titrated to 30 mg bid over five days).

3.3 Comparators

The NICE scope listed the comparators as "systemic non-biological therapies (including acitretin, ciclosporin, methotrexate, phototherapy with or without psoralen), systemic biological therapies (including etanercept, infliximab, adalimumab and ustekinumab) and best supportive care". However, in line with the product licence, the statement of the decision problem presented in the MS excluded systemic non-biological therapies and included only systemic biological therapies (including etanercept, infliximab, adalimumab and ustekinumab) and best supportive care. The most recently licenced biological systemic agent, secukinumab is an obvious omission from both the NICE scope and the MS. Although, owing to the timeframe of licensing for this new therapy, it is appropriate that it was not included in the MS.

Whilst the clinical effectiveness section of the MS included a network meta-analysis (NMA) to compare the efficacy of apremilast with biological therapies, the economic model presented in the MS only compared different treatment sequences with apremilast as an additional line of therapy (apremilast-adalimumab-etanercept-BSC vs adalimumab-etanercept-BSC), rather than replacing an existing biological therapy in the sequence. The ERG asked the manufacturer to provide results where apremilast replaces an existing biological therapy in the sequence; the manufacturer responded that the modelling approach used is considered the most appropriate to address the decision problem and accurately reflect current treatment pathways in severe psoriasis, and the likely positioning of apremilast within future treatment pathways. It is not Celgene's expectation that apremilast will displace an existing biologic treatment option, but rather will be positioned prior to the existing sequence of biologic treatments, as an additional line of therapy. The ERG believes that it cannot be assumed without full analysis that this is the most appropriate use for apremilast.

3.4 Outcomes

The outcomes presented in the manufacturer's decision problem matched the NICE scope and were appropriate. The outcomes assessed included PASI response, Physician's Global Assessment of disease activity, time to loss of PASI-75 response, other complications of psoriasis (such as pruritis and nail and scalp outcomes), health related quality of life (assessed using DLQI and SF-36) and adverse effects of treatment.

4 Clinical Effectiveness

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results. The ERG's conclusions on the clinical effectiveness of apremilast for the treatment of moderate to severe chronic plaque psoriasis are presented at the end of this section.

4.1 Critique of the methods of review(s)

The MS described a systematic review evaluating the clinical effectiveness and tolerability of apremilast for the treatment of moderate to severe plaque psoriasis. Four RCTs were identified; Psoriasis study 008 (PSOR-008)[2] and Psoriasis study 009 (PSOR-009)[3] both compared apremilast at the licensed dose against placebo, Psoriasis study 005 (PSOR-005; a phase 2b study)[4] compared three different dosages of apremilast against placebo, and Psoriasis study 010 (PSOR-010; a phase 3b study)[5] compared the licensed dose of apremilast against placebo and etanercept (50 mg once per week) against placebo. PSOR-008 and PSOR-009 were described in detail in the MS, with PSOR-005 and PSOR-010 presented as supporting evidence.

Additional non-RCT evidence was presented; Psoriasis study 001 (PSOR-001; a pilot study),[13] Psoriasis study 003 (PSOR-003; a phase 2 study)[14] and Psoriasis study 004 (PSOR-004; a phase 2 study).[15] These three trials either did not include the relevant population or did not assess apremilast at the licensed dose, so are of limited relevance.

4.1.1 Search strategy

The MS described the search strategies used to identify relevant clinical effectiveness studies on the use of apremilast for the treatment of moderate to severe plaque psoriasis. The search strategies were briefly described in the main body of the submission and full details were provided in the Appendices.

The electronic databases MEDLINE, MEDLINE In Process, EMBASE and the Cochrane Library (including the Cochrane Database of Systematic Reviews [CDSR], the Database of Abstracts of Reviews of Effects [DARE], the Cochrane Central Register of Controlled Trials, the Cochrane Methodology Register [CMR] and the NHS Economic Evaluation Database [NHS EED]) were searched on 23 May 2014. The search strings used for each database were reported in Appendix 2, Section 10.2.4 of the MS. The manufacturer also searched ClinicalTrials.gov for relevant clinical trials. In addition the proceedings of six conferences from January 2012 to May 2014 were hand searched using the same search criteria reported for the electronic searches; International Society for Pharmacoeconomics and Outcomes Research (ISPOR), American Academy of Dermatology (AAD), British Association of Dermatologists (BAD), European Academy of Dermatology and Venerology

(EADV), European League Against Rheumatism (EULAR), American College of Rheumatology (ACR).

The methods used to identify both published and unpublished studies for the systematic review were appropriate and for the most part well reported. There were some minor details missing from the reporting of the searches in Appendix 2, Section 10.2, however the manufacturer supplied further details in their response to the ERG's Points for Clarification.

All of the NICE required databases were searched together with sources for unpublished and ongoing studies. The search strategies contained in Appendix 2, Section 10.2, were appropriate and would result in a sensitive search. The drug name, brand name, drug identification number and relevant subject headings were included in the strategies. The correct fields have been searched and the search lines have all been combined appropriately.

In the original submission it was stated that the searches were not limited by date, language or study design, which is appropriate. However, the manufacturer clarified that a limit to English language studies and human studies was applied to the searches of MEDLINE and EMBASE. This could have led to relevant foreign language papers not being identified by the search. In addition, the limit to human studies has limited the retrieval to those studies indexed as human. However there are some records in the databases that have not yet been indexed as human and therefore these could have been missed.

The search strategy for ClinicalTrials.gov provided by the manufacturer did not contain the brand name otezla. However, after testing this, it was found that the omission of the brand name would not have resulted in any ongoing trials being missed from the search of this register.

4.1.2 Inclusion criteria

Studies of any design, that assessed apremilast in patients with psoriasis, PsA or any other form of psoriasis and measured any clinical or HRQL outcomes were eligible for inclusion. Only studies reported in English were eligible for inclusion; non-English language publications, editorials, non-systematic reviews and letters were excluded.

The inclusion criteria were generally appropriate, although the systematic review searches and study selection stages of the review were undertaken to identify studies for both this appraisal and the separate appraisal of apremilast for PsA. The studies of patients with PsA were subsequently excluded from this review.

Study reports for the two main RCTs described in the MS (PSOR-008 and PSOR-009)[2, 3] were provided by Celgene, rather than identified by the searches. The study report for the RCT PSOR-010[5] was provided by Celgene in October 2014, after the searches had been performed, so was not included in the PRISMA flow diagram of the study selection process (Figure 5 of the MS).

The MS states that disputes as to eligibility were referred to a third party (project lead), however, the number of reviewers undertaking each stage of study selection was not stated, therefore, it is unclear whether appropriate methods were used to reduce the potential for reviewer bias and error. The reasons for exclusion of studies excluded at the full paper stage were not reported. The exclusion of non-English language publications increases the potential for language bias. However, despite these limitations, it is unlikely that any relevant studies of apremilast were excluded.

The following trials were included in the review:

PSOR-008 (phase 3; also called the ESTEEM 1 trial)[2]
PSOR-009 (phase 3; also called the ESTEEM 2 trial)[3]
PSOR-005 (phase 2b)[4]
PSOR-010 (phase 3b)[5]
PSOR-004 (phase 2)[15]
PSOR-003 (phase 2)[14]
PSOR-001 (phase 2 pilot study)[13]

The PSOR-010 trial was the only trial to assess both apremilast and a biological therapy against placebo; the other three RCTs only compared apremilast with placebo. The phase 2 studies compared apremilast with a different dose of apremilast, or had no comparator.

4.1.3 Data extraction

The MS does not state how many reviewers undertook data extraction, only that data were extracted and entered directly into tables. Therefore, it is unclear whether appropriate methods were used to reduce the potential for reviewer bias and error.

Adequate data from the PSOR-008 and PSOR-009 trials were presented in the MS. The PSOR-010, PSOR-005, PSOR-004, PSOR-003 and PSOR-001 trials were presented as supporting evidence, with limited study details reported. Trials PSOR-010 and PSOR-005 both assessed apremilast at the licensed dose, therefore, further details should have been provided for these two trials that met the inclusion criteria for the review.

4.1.4 Quality assessment

Quality assessment results were only presented for trials PSOR-008 and PSOR-009 (in Appendix 3 of the MS). The quality of these two RCTs was assessed using appropriate criteria specific to RCTs; the trials were good quality. The quality assessment results were checked by the ERG.

It is unclear whether there was any quality assessment of the PSOR-010, PSOR-005, PSOR-004, PSOR-003 and PSOR-001 trials.

4.1.5 Evidence synthesis

The results of trials PSOR-008 and PSOR-009 were presented separately and a pooled analysis of efficacy and safety data was undertaken (Appendix 16 and Section 6.9 of the MS). The two trials had similar patient and study characteristics; therefore, pooling their results was appropriate. However, the results were merely pooled together, rather than using statistical methods to calculate a weighted average of the trials. In view of the similarity in methods between the two studies, this is acceptable and the pooled result is likely to be reliable.

A NMA was carried out to compare the efficacy of apremilast with adalimumab, etanercept, infliximab and two different dosages of ustekinumab (45 mg and 90 mg). The NMA is described in Sections 4.3 and 4.4 of this report.

4.1.6 Conclusions from critique of systematic review methods

The search strategy for RCT evidence was adequate; no relevant studies of apremilast appear to have been missed. The inclusion criteria were appropriate (after the exclusion of studies of patients with PsA from this appraisal). The methods used for study selection, data extraction and quality assessment were not reported; therefore it is unclear whether they were susceptible to error and bias. The PSOR-010 trial was the only trial to assess both apremilast and a biological therapy against placebo; the other three RCTs only compared apremilast with placebo. The phase 2 studies compared apremilast with a different dose of apremilast, or had no comparator.

The MS focussed on trials PSOR-008 and PSOR-009, whilst trials PSOR-010 and PSOR-005 were only presented as supporting evidence. Trials PSOR-010 and PSOR-005 both met inclusion criteria for the systematic review and assessed apremilast at the licensed dose, therefore, further details of their methods and results should have been presented.

The review presented adequate study details and quality assessment results for trials PSOR-008 and PSOR-009; the trials were good quality. Limited details were presented, and no apparent assessment of study quality was undertaken, for PSOR-010 and PSOR-005, or the additional three phase 2 trials that were included as supporting evidence.

The efficacy and safety results of trials PSOR-008 and PSOR-009 were pooled, which was appropriate in view of the similarities between the trials. In addition, a NMA was presented to compare the efficacy of apremilast with adalimumab, etanercept, infliximab and ustekinumab, described in Sections 4.3 and 4.4 of this report.

4.1.7 Ongoing studies

The open-label long term extension phase of the PSOR-008, PSOR-009 and PSOR-010 trials is still ongoing. Sixteen week data from the PSOR-010 trial were made available for the MS. In addition, the ERG identified the following ongoing study of apremilast:

- Efficacy and safety study of two doses of apremilast in Japanese subjects with moderate-to-severe plaque-type psoriasis (PSOR-011). The estimated completion date is December 2015.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Trials included in the review

Four RCTs of apremilast at the licensed dose were included in the review; PSOR-008, PSOR-009, PSOR-005 and PSOR-010. The PSOR-008 and PSOR-009 trials were described in detail, whilst the PSOR-005 and PSOR-010 trials were presented as supporting evidence in Section 6.8 of the MS. The reason stated for presenting PSOR-005 as supporting evidence only, rather than in sections 6.3, 6.4 and 6.5 of the MS, along with PSOR-008 and PSOR-009, was that PSOR-005 had a shorter follow-up than PSOR-008 and PSOR-009. However, the follow-up extended to 24 weeks, so was long enough to capture the primary outcome of PASI-75 response at Week 16. The MS did not state a reason for presenting the PSOR-010 trial as supporting evidence, rather than in detail, alongside PSOR-008 and PSOR-009.

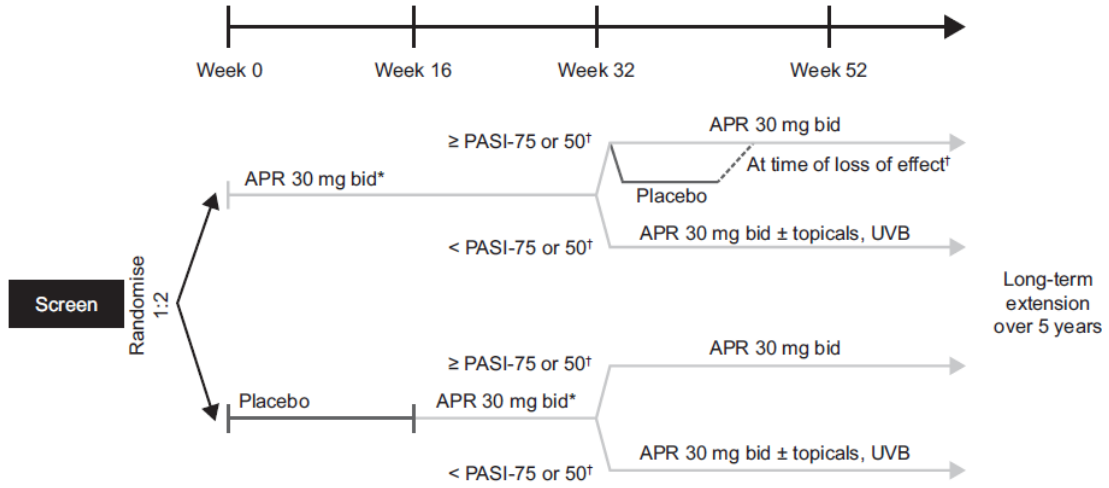
The MS also described three phase 2 trials; PSOR-001, PSOR-003 and PSOR-004. However, these trials did not assess apremilast at the licensed dose, so they were appropriately presented only as supporting evidence in Section 6.8 of the MS.

4.2.1.1 RCT evidence

PSOR-008 and PSOR-009 were both multicentre double-blind parallel-group RCTs of apremilast compared with placebo. During the initial 16-week placebo-controlled phase of the trials patients with moderate to severe psoriasis were randomised 2:1 to either apremilast 30 mg bid or placebo. At Week 16, patients receiving placebo switched to apremilast 30 mg bid for the 16-week maintenance phase, therefore, the randomised comparison with placebo was only until Week 16. At Week 32, patients entered the 20-week treatment withdrawal phase, whereby patients who had received apremilast for the entire trial and were responders (achieved PASI-75 in PSOR-008 or PASI-50 in

PSOR-009) were randomised 1:1 to continue on apremilast or switch to placebo. Patients then entered a 4-year long-term extension phase (weeks 52 to 260) which is still ongoing; data from this phase of the trials were not available at the time of the submission. Figure 1 summarises the complex trial design for PSOR-008 and PSOR-009 (Figure 6 of MS).

Figure 1: Trial design for PSOR-008 and PSOR-009 trials



APR, apremilast; bid, twice daily; PASI, Psoriasis Area and Severity Index; PASI-50/75, 50/75% or greater improvement in PASI score; UVB, ultraviolet B light.

Trial PSOR-005 was a 24 week double-blind parallel-group RCT of apremilast compared with placebo. Patients with moderate to severe psoriasis were randomised 1:1:1:1 to placebo or apremilast at one of three different dosages (10 mg bid, 20 mg bid or 30 mg bid). At week 16, patients receiving placebo were re-randomised to apremilast 20 mg or 30 mg bid for the 8-week active treatment phase, whilst those on apremilast continued with their allocated treatment. Therefore, the randomised comparison with placebo was only until Week 16.

Trial PSOR-010 is a multicentre double-blind parallel-group RCT of apremilast compared with etanercept and placebo. During the initial 16-week placebo-controlled phase of the trial patients with moderate to severe psoriasis were randomised 1:1:1 to placebo tablet + placebo injection, or apremilast (30 mg bid) tablet plus placebo injection, or etanercept (50 mg once weekly (qw)) injection plus placebo tablet. At week 16, all patients were switched to apremilast 30 mg bid for the 88-week apremilast extension phase of the trial;

[redacted]. The long-term extension phase of this trial is still ongoing. Sixteen week data from the PSOR-010 trial were made available for the MS. The study design, eligibility criteria and participant baseline characteristics of the PSOR-008, PSOR-009, PSOR-005 and PSOR-010 trials are summarised in Tables 1, 2 and 3, respectively (details for

PSOR-008 and PSOR-009 are presented as Tables 8, 9, 10 and 93 of the MS, details for PSOR-005 are from the MS and the trial publication and details for PSOR-010 are from the MS and the trial CSR).

Table 1: Methodological details of PSOR-008, PSOR-009, PSOR-005 and PSOR-010 trials

Study details	PSOR-008	PSOR-009	PSOR-005	PSOR-010
Location	72 sites in Australia, Belgium, Canada, France, Germany, Italy, UK and USA	45 sites in Austria, Canada, Denmark, France, Germany, Italy, Spain, Switzerland and USA	35 sites in the USA and Canada	65 sites in the USA, Canada, Belgium, Czech Republic, Estonia, Germany, UK, Hungary, Latvia, Netherlands and Australia
Design	Phase 3, double-blind, placebo-controlled, randomised, multicentre study that included these phases: a) placebo-controlled phase (Weeks 0–16) b) maintenance phase (Weeks 16–32) c) randomised treatment withdrawal phase (Weeks 32–52) long-term extension phase (Weeks 52–260 [years 2–5])		Phase 2b, double-blind, placebo-controlled, randomised, multicentre study that included these phases: a) placebo-controlled phase (Weeks 0-16) b) active treatment phase (Weeks 16-24)	Phase 3b, double-blind, placebo-controlled, randomised, multicentre study that included these phases: a) placebo-controlled phase (Weeks 0-16) b) apremilast extension phase (Weeks 16-104) [redacted]
Duration of core study	52 weeks		24 weeks	104 weeks
Method of randomisation	Patients were assigned to APR 30 mg bid or placebo (2:1) through a centralised IVRS		Patients were assigned to APR 30 mg bid, APR 20 mg bid, APR 10 mg bid or placebo (1:1:1:1) through a centralised IVRS	Patients were assigned to APR 30 mg bid, etanercept 50 mg qw or placebo (1:1:1) [redacted]
Method of blinding	Double-blind – blinding was maintained until all patients completed Week 52		Double-blind	Double-blind
Intervention and comparator	APR 30 mg bid Placebo (2:1 ratio)		APR 30 mg bid, APR 20 mg bid, APR 10 mg bid, Placebo (1:1:1:1 ratio)	APR 30 mg bid Etanercept 50 mg qw Placebo (1:1:1 ratio)
Primary outcome	Proportion of patients receiving APR achieving PASI-75 at Week 16			
Secondary outcomes (including scoring methods and timings of assessments)	Proportion of patients achieving sPGA score of 0 (clear) or 1 (almost clear) with ≥2-point reduction from baseline at Week 16 Other secondary endpoints: • Percent change from baseline in the psoriasis-affected BSA (%) at Week 16 • Percent change from baseline in the PASI score at Week 16 • Proportion of patients who achieved PASI-50 at Week 16 • Change from baseline in the pruritus VAS at Week 16 • Change from baseline in the DLQI score at Week 16 • Change from baseline in the SF-36 MCS score at Week 16 Time to loss of PASI-75 response (loss of effect) during the randomised treatment withdrawal phase		Proportion of patients achieving PASI-75 at Week 24, PASI-50 at Week 16 and PASI-90 at Week 16; time to achieve PASI-50 or PASI-75 (Weeks 0-16); percentage change from baseline PASI after 24 weeks; percentage change from baseline in affected BSA at Week 16; change from baseline in DLQI and SF-36 at Weeks 16 and 24; systemic exposure of apremilast at Weeks 14 and 24.	Proportion of patients receiving etanercept or placebo achieving PASI-75 at Week 16 Other secondary endpoints (comparison of APR vs placebo and etanercept vs placebo): • Proportion of patients achieving a sPGA score of clear (0), almost clear (1) with at least 2 points reduction at Week 16 (sPGA response) • Percent change from baseline in the psoriasis-affected BSA (%) at Week 16 • Proportion of patients who achieved PASI-50 at Week 16 • Change from baseline in the DLQI score at Week 16 • Change from baseline in the SF-36v2 MCS score at Week 16 • Proportion of patients with a LS-PGA score of clear (0) or almost clear (1) at Week 16
Duration of follow-up for reported analysis	52 weeks		24 weeks	16 weeks
Criteria for crossover from placebo to APR (Week 16)	At Week 16, all patients randomised to placebo were switched to APR 30 mg bid; all patients originally randomised to APR 30 mg bid continued on APR 30 mg bid		At Week 16, all patients randomised to placebo were randomly assigned (in a 1:1 ratio) to APR 20 mg bid or APR 30 mg bid; all patients originally randomised to APR continued on APR	At Week 16, all patients randomised to etanercept or placebo were switched to APR 30 mg bid; all patients originally randomised to APR 30 mg bid continued on APR 30 mg bid

Study details	PSOR-008	PSOR-009	PSOR-005	PSOR-010
Criteria for continuing treatment at Week 32 (treatment withdrawal phase)	Patients randomised to APR 30 mg bid at baseline and achieving ≥ PASI-75 vs baseline (responders and partial responders) at week 32 were re-randomised (1:1, blinded) to continue APR 30 mg bid or to placebo (withdrawal patients) Subsequently, if PASI-75 was lost in withdrawal patients, they were permitted to resume APR 30 mg bid before Week 52. All patients resumed treatment with APR 30 mg bid by Week 52, regardless of whether or not they lost PASI-75 At week 32, patients initially randomised to APR 30 mg bid and not achieving ≥ PASI-75 at week 32 were given the option of adding topical therapies or phototherapy (at Week 32 only) Patients initially randomised to placebo and switched to APR 30 mg bid at Week 16 continued APR treatment. Patients in this cohort who had not achieved ≥ PASI-75 at Week 32 were given the option of adding topical therapies or phototherapy	Patients randomised to APR 30 mg bid at baseline and achieving ≥ PASI-50 vs baseline (responders and partial responders) at week 32 were re-randomised (1:1, blinded) to continue APR 30 mg bid or to placebo (withdrawal patients) Subsequently, if PASI-50 was lost in withdrawal patients, they were permitted to resume APR 30 mg bid before Week 52. All patients resumed treatment with APR 30 mg bid by Week 52, regardless of whether or not they lost PASI-50 At week 32, patients initially randomised to APR 30 mg bid and not achieving ≥ PASI-50 at week 32 were given the option of adding topical therapies or phototherapy (at Week 32 only) Patients initially randomised to placebo and switched to APR 30 mg bid at Week 16 continued APR treatment. Patients in this cohort who had not achieved ≥ PASI-50 at Week 32 were given the option of adding topical therapies or phototherapy	N/A	N/A
Criteria for continuing treatment into long-term extension phase	Patients completing 52 weeks and wishing to continue		N/A	All patients were to maintain this dosing through Week 104

APR, apremilast; bid, twice daily; BSA, body surface area; DLQI, Dermatology Life Quality Index ; IVRS, interactive voice response system; MCS, mental component summary; PASI, Psoriasis Area and Severity Index; PASI-50/75, 50/75% or greater improvement in PASI score; SF-36, 36-item Short-Form Health Survey; sPGA, static Physician Global Assessment; VAS, visual analogue scale

Table 2: Eligibility criteria in PSOR-008, PSOR-009, PSOR-005 and PSOR-010 trials

Key inclusion criteria for PSOR-008, PSOR-009 and PSOR-010	**Key exclusion criteria for PSOR-008, PSOR-009 and PSOR-010**
• Aged ≥18 years • Chronic plaque psoriasis for ≥12 months prior to screening • Moderate to severe plaque psoriasis, defined by: ▪ PASI score ≥12; ▪ BSA affected ≥10%; and ▪ sPGA ≥3 (moderate) • Candidate for phototherapy and/or systemic therapy • WBC count ≥3000/mm^3 (≥3.0 x 10^9/L) and <14 000/mm^3 (<14 x 10^9/L) • Platelet count ≥ 100 000/μL (≥100 x 10^9/L) • Serum creatinine ≤1.5 mg/dL (≤132.6 μmol/L) • AST and ALT ≤2 x ULN • Total bilirubin ≤2 mg/dL (34 μmol/L) • Hb ≥9 g/dL (≥5.6 mmol/L) • HbA1c ≤9.0% • FCBP had negative pregnancy test at screening and baseline • (There was no minimum DLQI score requirement at baseline) Additional criteria for PSOR-010: • Had no prior exposure to biologics for treatment of psoriatic arthritis or psoriasis	• History of any other clinically significant disease • Severe renal impairment • Active or incompletely treated TB • Significant infection, or psoriasis flare or rebound within 4 weeks of screening • Clinically significant abnormality on 12-lead ECG at screening • Positive hepatitis B or C at screening • HIV infection or other immunodeficiency disease • AST or ALT >1.5 x ULN • Total bilirubin >ULN • Albumin <LLN • Use of phototherapy or systemic therapy within 4 weeks prior to randomisation • Topical therapy within 2 weeks of randomisation (except for limited use of low-dose corticosteroids)
Key inclusion criteria for PSOR-005 (reported in trial publication)	**Key exclusion criteria for PSOR-005 (reported in trial publication)**
• Aged ≥18 years • Chronic plaque psoriasis for ≥6 months prior to screening • Moderate to severe plaque psoriasis, defined by: ▪ PASI score ≥12; ▪ BSA affected ≥10%; and • Candidate for phototherapy and/or systemic therapy	• History of any other clinically significant disease, including *Mycobacterium tuberculosis* or HIV infection • Positive hepatitis B or C at screening • Pregnant or breastfeeding • Use of phototherapy or systemic therapy within 4 weeks prior to randomisation • Topical therapy within 2 weeks of randomisation • Use of adalimumab, etanercept, efalizumab or infliximab within 12 weeks • Use of alefacept within 24 weeks

AST, aspartate transaminase; ALT, alanine transaminase; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; FCBP, females of childbearing potential; Hb, haemoglobin; HbA1c, glycated haemoglobin; HIV, human immunodeficiency virus; LLN, lower limit of normal; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment; TB, tuberculosis; ULN, upper limit of normal; WBC, white blood cell

Table 3: Baseline characteristics of participants in PSOR-008, PSOR-009, PSOR-005 and PSOR-010 trials

Characteristic	PSOR-008		PSOR-009		PSOR-005*		PSOR-010		
	APR 30 mg bid (n = 562)	Placebo (n = 282)	APR 30 mg bid (n = 274)	Placebo (n = 137)	APR 30 mg bid (n=88)	Placebo (n=88)	APR 30 mg bid (n=83)	Etanercept (n=83)	Placebo (n=84)
Age, years, Mean ± SD	45.8 ± 13.07	46.5 ± 12.72	45.3 ± 13.05	45.7 ± 13.38	44.1 ± 14.7	44.1 ± 13.7	46.0 ± 13.59	47.0 ± 14.07	43.4 ± 14.91
Male, n (%)	379 (67.4)	194 (68.8)	176 (64.2)	100 (73.0)	50 (57)	53 (60)	49 (59.0)	49 (59.0)	59 (70.2)
Duration of plaque psoriasis, years since diagnosis, Mean ± SD	19.75 ± 13.04	18.68 ±12.36	17.94 ±11.37	18.68 ±12.09	19.2 ± 12.0	19.6 ± 11.6	19.73 ± 12.74	18.14 ± 11.75	16.62 ±12.07
PASI score Mean ± SD	18.74 ± 7.18	19.37 ± 7.39	18.93 ± 7.06	20.04 ± 8.00	19.1 ± 7.1	18.1 ± 5.7	19.3 ± 7.03	20.3 ± 7.88	19.4 ± 6.80
BSA, Mean ± SD	24.4 ± 14.72	25.34 ±14.65	25.46 ± 5.42	27.58 ±15.82	25.0 ± 15.3	21.0 ± 11.2	27.1 ± 15.61	28.4 ± 15.69	27.3 ± 16.12
Pruritis (itch), VAS mm	66.2 ± 25.52	65.2 ± 24.79	NR	NR	NR	NR	NR	NR	NR
sPGA 2 (mild)	0	1 (0.4)	1 (0.4)	0	NR	NR	0	1 (1.2)	0
3 (moderate)	401 (71.4)	192 (68.1)	198 (72.3)	88 (64.2)	NR	NR	66 (79.5)	69 (83.1)	61 (72.6)
4 (severe)	161 (28.6)	89 (31.6)	75 (27.4)	49 (35.8)	NR	NR	17 (20.5)	13 (15.7)	23 (27.4)
Presence of nail psoriasis at baseline, n (%)	363 (64.6)	195 (69.1)	182 (66.4)	96 (70.1)	NR	NR	NR	NR	NR
ScPGA ≥3, n (%)	374 (66.5)	189 (67.0)	176 (64.2)	93 (67.9)	NR	NR	54 (65.1)	54 (65.1)	58 (69.0)
DLQI, mean ± SD	12.7 ± 7.05	12.1 ± 6.67	12.5 ± 7.13	12.8 ± 7.06	NR	NR	NR	NR	NR
DLQI ≤10, n (%)	[redacted]		123 (43.6)	119 (43.4)	58 (42.3)	NR	NR	NR	NR
Prior systemic therapy (conventional and/or biologic), n (%)	301 (53.6)	150 (53.2)	157 (57.3)	73 (53.3)	47 (53)	39 (44)	66 (79.5)**	58 (69.9)**	70 (83.3)**
Prior conventional systemic therapy, n (%)	212 (37.7)	102 (36.2)	106 (38.7)	53 (38.7)	NR	NR	66 (79.5)	58 (69.9)	70 (83.3)
Prior biologic therapy, n (%)	162 (28.8)	80 (28.4)	92 (33.6)	44 (32.1)	NR	NR	N/A**	N/A**	N/A**
≥1 prior biologic therapy failed, n (%)	37 (6.6)	19 (6.7)	24 (8.8)	11 (8.0)	NR	NR	N/A**	N/A**	N/A**
Prior phototherapy, n (%)	176 (31.3)	88 (31.2)	83 (30.3)	31 (22.6)	NR	NR	24 (28.9)	20 (24.1)	24 (28.6)

Note: Data are mean (SD) or n (%). * Baseline characteristics only presented for APR 30 mg bid group (licensed dose) and placebo group.
** Patients had to have no prior exposure to biologics for treatment of psoriatic arthritis or psoriasis to be eligible for inclusion in the trial.
APR, apremilast; bid, twice daily; BSA, body surface area; DLQI, Dermatology Life Quality Index; N/A, not applicable; NR, not reported; PASI, Psoriasis Area and Severity Index; ScPGA, scalp Physician Global Assessment; SD, standard deviation; sPGA, static Physician Global Assessment

As shown in Table 1, trials PSOR-008 and PSOR-009 had the same trial design and methods, except that the definition of response used in a treatment withdrawal phase differed between the trials (PASI-75 in PSOR-008 and PASI-50 in PSOR-009); further details are presented under 'Randomised treatment withdrawal phase' in Section 4.2.3.1. The eligibility criteria were the same for both trials (Table 2) and baseline characteristics were similar between trials and between treatment groups within trials (Table 3). Trial PSOR-008 was a larger trial, including 844 participants from 72 sites (including patients from the UK), whilst PSOR-009 included 411 participants from 45 sites (not including the UK).

Inclusion criteria for PSOR-005 appear to have been similar to those for PSOR-008 and PSOR-009. A total of 352 patients were randomised from 35 sites in the USA and Canada. Baseline characteristics appear to have been similar between treatment groups and between this trial and PSOR-008 and PSOR-009, although limited data were reported in the MS, making it hard to assess comparability. In view of the different study design and doses used in this study, it appears to have been appropriate to exclude it from the meta-analysis of PSOR-008 and PSOR-009.

Inclusion criteria for PSOR-010 were similar to those for PSOR-008 and PSOR-009, except that patients had to have had no prior exposure to biologics for the treatment of psoriatic arthritis or psoriasis to be eligible for inclusion. Therefore, exposure to prior biological therapy differed between this trial and the other trials. In addition, a much higher proportion of patients in this trial had received prior conventional systemic therapy (range 69.9 to 83.3% between treatment groups) than in the other trials (range 36.2 to 38.7%).

[redacted]

The primary endpoint was the same in all four trials; PASI-75 response at Week 16.

Patients included in the PSOR-008 and PSOR-009 trials may have had less severe disease than those eligible for apremilast in NHS practice, as not all patients in the trials had failed (or even received) conventional systemic therapy: less than 40% of patients had received prior conventional systemic therapy. The proportion of patients who had received prior conventional systemic therapy in PSOR-010 was more reflective of patients seen in practice, but still slightly low. The proportion of patients who had received prior conventional systemic therapy was not reported for PSOR-005.

Patients with a more severe phenotype are more likely to fail treatment; therefore, the inclusion of systemic treatment-naïve patients may mean the inclusion of patients with a less severe phenotype than those likely to be seen in practice. Therefore, the clinical effectiveness of apremilast may be higher in the trials than would be seen in routine NHS practice, where patients eligible for apremilast would have to have failed to respond to or have a contraindication to, or be intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA. The ERG requested subgroup analysis data for patients in the PSOR-008 trial who had failed two or more conventional systemic therapies and were biologic naïve. The manufacturer provided data for patients who had failed 2 or more conventional systemic therapies or are contraindicated to systemic therapy and are biologic naïve, which reflects the population likely to be eligible for apremilast in NHS practice.

In addition, patients were excluded from the trials if they had a history of other clinically significant disease, significant infection, or psoriasis flare or rebound within four weeks of screening, amongst other exclusion criteria. Patients seen in practice may have other clinically significant disease or significant infection prior to therapy, as these are not listed as contraindications in the Summary of Product Characteristics (SPC). The MS states that moderate to severe psoriasis is associated with a number of comorbidities including joint disease, metabolic syndrome, depression and cardiovascular morbidity.

4.2.1.2 Phase 2 trial evidence

The 'non-RCT' evidence consisted of three phase 2 trials that did not assess apremilast at the licensed dose, so they were included as supporting evidence. Brief study details are presented in Table 4 (Table 7 of the MS).

PSOR-001 was a single-arm pilot study that assessed apremilast 20 mg once daily (qd) in 19 patients with severe psoriasis. PSOR-003 was a multicentre double-blind parallel-group RCT of apremilast 20 mg qd or 20 mg bid compared with placebo in patients with moderate to severe psoriasis. PSOR-004 was a small multicentre open-label study that assessed apremilast 20 mg bid in 30 patients with recalcitrant psoriasis who were intolerant or unresponsive to standard systemic or biologic therapies. After 12 weeks, responders (≥PASI-75) continued on apremilast 20 mg bid, whilst non-responders had their dose escalated to 30 mg bid; only 7 patients received apremilast 30 mg bid.

Table 4: Brief study details of relevant phase 2 trials

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
PSOR-004 (NCT00521339) Phase 2, multicentre, open-label study	APR 20 mg bid APR 30 mg bid	Patients with plaque psoriasis Diagnosis for ≥6 months; BSA affected ≥10%; WBC count > 3000–20,000/μL; platelet count > 100,000/μL; serum creatinine ≤ 1.5 mg/dL; AST and ALT ≤ 2 times ULN	To assess the efficacy, tolerability and pharmacodynamics of APR in patients with recalcitrant plaque psoriasis	Gottlieb *et al*.[15] *J Drugs Dermatol* 2013;12:888–97	Provides information on the biological and clinical activity of APR and supports further studies of APR 30 mg bid
PSOR-003 (NCT00606450) Phase 2 study	APR 20mg qd APR 20mg* bid Placebo	Patients with moderate to severe plaque psoriasis for ≥6 months; PASI score ≥10; BSA affected ≥10%	To compare the clinical efficacy of APR 20 mg once daily and 30 mg bid with PBO, and to evaluate APR safety and tolerability.	Papp *et al*. *J Eur Acad Dermatol Venereol* 2013;27:e376–83.[14]	Provides information on clinical efficacy and safety of APR
PSOR-001 (NCT00604682) Phase 2, open-label, single-arm study	APR 20 mg qd	Patients with severe plaque psoriasis ≥6 months; BSA affected ≥15%; had undergone photo/systemic therapy	To evaluate the reduction in epidermal thickness after 29 days of treatment with APR 20 mg Assess the clinical and biological activity of APR in patients with severe plaque-type psoriasis	Gottlieb *et al*.[13] *Curr Med Res Opin* 2008;24:1529–38	Provides information about clinical response and immunomodulatory role for APR in patients with severe plaque psoriasis

* Corrected using trial publication, in Table 7 of the MS this is incorrectly stated as APR 30mg bid
ALT, alanine aminotransferase; APR, apremilast; AST, aspartate aminotransferase; bid, twice daily; BSA, body surface area; PASI, Psoriasis Area and Severity Index; PBO, placebo; qd, once a day; ULN, upper limit of normal; WBC, white blood cell

4.2.2 Summary of the quality of the included trials

4.2.2.1 RCT evidence

Results of the quality assessment for PSOR-008 and PSOR-009 were presented in Appendix 3 of the MS. Both trials were large well-conducted double-blind RCTs; randomisation and concealment of treatment allocation were adequate, the treatment groups were generally similar at baseline, outcome measures were appropriate, follow-up was adequate, an appropriate intention-to-treat analysis (called the full analysis set) was performed and there were no unexpected imbalances in drop-outs between treatment groups. The ERG requested further information about the proportion of patients for whom data were missing, and 'last observation carried forward' (LOCF) imputation was used. The manufacturer provided additional data showing that whilst there was a reasonably high proportion of patients for whom PASI-75 response data were missing at Week 16 (10.8% and 13.5% in the apremilast groups and 12.4% and 19.0% in the placebo groups of the PSOR-008 and PSOR-009 trials, respectively) the vast majority of imputations did not result in apremilast patients being considered PASI-75 responders; 4.9% and 5.4% for PSOR-008 and PSOR-009, respectively. The manufacturer also conducted a sensitivity analysis using a non-responder imputation (NRI) for all missing patients. Therefore, the ERG was satisfied that the imputation of missing data did not bias the primary outcome (PASI-75 response) or main secondary outcome (sPGA 0/1) results in favour of apremilast. Week 32 data presented in Table 15 of the MS for the outcome 'mean change in PASI score from baseline' used the observed data, excluding patients who had dropped out. Therefore, this result is likely to be more favourable to apremilast.

No quality assessment was reported in the MS for trials PSOR-005 and PSOR-010, but an assessment of the quality of trial PSOR-010 was presented in the manufacturer's response to the ERG's Points for Clarification document.

Based on the information available to the ERG it can be seen that trial PSOR-005 was an adequately powered double-blind RCT; randomisation and concealment of treatment allocation were adequate, the treatment groups were generally similar at baseline, outcome measures were appropriate, follow-up was relatively short (24 weeks) but it was adequate for assessing the primary outcome of PASI-75 response at Week 16, an appropriate intention-to-treat analysis was performed and there were no unexpected imbalances in drop-outs between treatment groups.

Trial PSOR-010 is an adequately powered double-blind RCT; randomisation and concealment of treatment allocation were adequate.

[redacted]

[redacted] Outcome measures were appropriate. Only 16 week data were available at the time of this assessment, as later stages of this trial are ongoing, however, this was adequate for assessing the primary outcome of PASI-75 response at Week 16.

[redacted]

4.2.2.2 Phase 2 trial evidence

No quality assessment appears to have been undertaken for trials PSOR-001, PSOR-003 and PSOR-004.

Based on the information available to the ERG it can be seen that PSOR-001 was a small, short-term (29 day), single-arm pilot study with only 19 participants, none of which received apremilast at the licensed dose. PSOR-003 was a short-term (12 week) multicentre double-blind parallel-group RCT; however none of the included patients received apremilast at the licensed dose. PSOR-004 was a small, longer-term, open-label study with only 30 participants, only 7 of which received apremilast at the licensed dose, after having received apremilast at a lower dose for the previous 12 weeks.

4.2.3 Summary of the results of the included trials

4.2.3.1 RCT evidence

Efficacy

Trials PSOR-008 and PSOR-009

16 week time point

Table 7 presents the efficacy results for trials PSOR-008, PSOR-009 and the pooled analysis of PSOR-008 and PSOR-009. Both trials demonstrated a statistically significant difference between apremilast and placebo for Week 16 comparisons for the majority of outcomes, including PASI-75 response (primary outcome), sPGA score of 0 or 1, PASI-50 response, PASI-90 response, mean change in PASI score from baseline, mean change in psoriasis-affected BSA, mean change in DLQI score from baseline, mean change in SF-36 MCS score from baseline, mean change in pruritis VAS score from baseline, mean change in NAPSI score from baseline for patients with nail psoriasis and ScPGA score 0 or 1 for patients with scalp psoriasis. Apremilast reduced the severity of psoriasis and its impact on physical, psychological and social functioning, compared with placebo.

Results of subgroup analyses for the primary outcome were consistent with those for the main analysis (Figures 10 to 12 of the MS). Although they suggested that patients who had failed ≥2 systemic therapies were less likely to achieve a PASI-75 response than those who had failed 0 or 1

prior systemic therapies. Patients with a history of palmoplantar psoriasis were less likely to achieve a PASI-75 response than those without a history of palmoplantar psoriasis; however, numbers of patients were low in these subgroup analyses (Figures 11 and 12 of the MS).

The ERG requested subgroup analysis data for patients in the PSOR-008 trial who had failed two or more conventional systemic therapies and were biologic naïve. The manufacturer provided data for this subgroup and a number of other slightly different subgroups according to whether patients had experienced or failed treatments and whether or not those who were contraindicated to systemic therapy were included (Table 5).

Table 5: PASI-75 responses at Week 16 (LOCF) by subgroups (FAS, PSOR-008)

	APR 30 mg bid (n = 562)	**PBO (n = 282)**	**Risk Difference (95% CrI)**
experienced 2 or more conventional systemic therapies and are biologic naïve	9/35 (25.7%)	0/19 (0%)	25.7 (11.2–40.2)
experienced 2 or more conventional systemic therapies **or are contraindicated to systemic therapy** and are biologic naïve	30/94 (31.9%)	2/57 (3.5%)	28.4 (17.8, 39.0)
failed 2 or more conventional systemic therapies	2/15 (13.3%)	0/6 (0%)	13.3 (–3.9–30.5)
failed 2 or more conventional systemic therapies **or are contraindicated to systemic therapy**	29/98 (29.6%)	2/60 (3.3%)	26.3 (16.1, 36.4)
failed 2 or more conventional systemic therapies and are biologic naïve	1/7 (14.3%)	0/3 (0%)	14.3 (–11.6–40.2)
failed 2 or more conventional systemic therapies **or are contraindicated to systemic therapy** and are biologic naïve	23/68 (33.8%)	2/42 (4.8%)	29.1 (16.1, 42.0)

Definition of contraindication: Subjects who met one or more of the following six criteria at baseline: 1. Use of alcoholic beverages: >14 drinks per week; 2. AST (SGOT,Aspartate Aminotransferase) and ALT (SGPT, Alanine Aminotransferase) > 1.5xUpper Limit of Normal (ULN); 3. Hemoglobin < 10 g/dL; 4. White blood cell count (Leukocytes) < 3.5x10^9/L; 5. Creatinine Clearance < 60 mL/min; 6. Triglyceride > 300 mg/dL (or 3.39 mmol/L).

These subgroup results from PSOR-008 indicate that the treatment effect of apremilast is fairly consistent across the subgroups and similar to that for the whole trial population. The subgroup proposed by the MS as the most appropriate positioning for apremilast in the treatment pathway is '**failed** 2 or more conventional systemic therapies **or are contraindicated to systemic therapy** and are biologic naïve'; this represents only 13% of the full trial population. As previously stated, the ERG points out that this preferred positioning of apremilast cannot be accepted without first conducting a full analysis to support it. The ERG omitted in error to request the equivalent results from trial PSOR-009.

Further potentially relevant subgroup results for those patients who have failed at least one biologic therapy were available from the CSRs for PSOR-008 and 009 and are presented in Table 6 below.

Table 6: PASI-75 responses at Week 16 (LOCF) by subgroups (taken from CSRs for PSOR-008 and -009)

	Trial PSOR-008 (n=844)			Trial PSOR-009 (n=411)		
	Apremilast 30mg	Placebo	Risk difference (RD) of PASI 75 at 16 wks	Apremilast 30mg	Placebo	Risk difference (RD) of PASI 75 at 16 wks
Number of patients	186/562	15/282	27.8 (95% CI 23.1, 32.5)	79/274	8/137	23.0 (96% CI 16.3, 29.6)
Number of patients who have failed at least one biologic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

These further subgroup results primarily serve to demonstrate the small size of the post-biologic sample in the trials. The results are based on too small a patient sample to reliably indicate whether or not the treatment effect of apremilast is different in this subgroup. Furthermore, this subgroup will not accurately reflect the post-biologic patient in the NHS as many of the trial patients had received biologics without first having failed conventional systemic therapies.

Longer follow-up – 32 to 104 weeks

The mean percentage change in PASI score was significantly improved, compared with placebo, as early as Week 2. PASI-75 response was maintained in the Week 32 analysis. The MS stated that a further analysis at 104 Weeks demonstrated that PASI-75 response was maintained, although the number of patients included in this 'as observed' analysis was considerably lower than in the earlier analyses (data provided in response to the ERG's Points for Clarification): 100/212 (47.2%) patients who had continuously received apremilast achieved a PASI-75 response at Week 104 and 44/99 (44.4%) patients who received placebo followed by apremilast achieved a PASI-75 response at Week 104. Of 844 patients who had ever received apremilast, 311 (36.8%) remained on treatment at Week 104; the primary reasons for discontinuation were lack of efficacy (232/844 [27.5%], withdrawal of consent by patient (108/844 [12.8%]) and adverse event (80/844 [9.5%]). This 'as observed' result is likely to be more favourable to apremilast than using LOCF or NRI analysis, as patients who did not respond to apremilast or withdrew due to adverse events were not included in the analysis.

Randomised treatment withdrawal phase

In trials PSOR-008 and PSOR-009, patients who were randomised to apremilast at baseline and achieved a PASI-75 response in PSOR-008 or a PASI-50 response in PSOR-009 were re-randomised to placebo or to continued apremilast during a treatment withdrawal phase (Weeks 32 to 52). If response was lost during the treatment withdrawal phase, they were permitted to resume apremilast before week 52. In PSOR-008, [redacted] in the placebo group and [redacted] in the continued apremilast group lost PASI-75 response at some point

during the treatment withdrawal phase, i.e within 20 weeks. The median time to first loss of PASI-75 response was 5.1 weeks in patients re-randomised to placebo and 17.7 weeks in patients re-randomised to apremilast. In PSOR-009, 35/62 patients (56.5%) in the placebo group and 7/61 patients (11.5%) in the continued apremilast group lost 50% of their Week 32 PASI improvement at some point during the treatment withdrawal phase. The median time to a loss of 50% of the improvement in PASI score obtained at Week 32 compared to baseline was 12.4 weeks in patients re-randomised to placebo and 21.9 weeks in patients re-randomised to apremilast. Patients who were treated with placebo in the randomised treatment withdrawal phase showed significant responses following re-treatment with apremilast.

These results suggest that treatment benefit is not fully maintained in a substantial proportion of patients; [redacted] of patients continuing apremilast treatment in the PSOR-008 trial lost PASI-75 response between Week 32 and Week 52.

Trials PSOR-005 and PSOR-010

Details and results for PSOR-010 were provided on request to the ERG. Table 8 presents the efficacy results for trials PSOR-005 and PSOR-010, alongside the pooled analysis of trials PSOR-008 and PSOR-009, for comparison. Both trials demonstrated a statistically significant difference between apremilast 30 mg bid and placebo at Week 16 for the primary outcome of PASI-75 response, as well as sPGA score of 0 or 1, PASI-50 response, PASI-90 response, mean change in psoriasis-affected BSA, mean change in DLQI score from baseline and mean change in pruritis VAS score from baseline. Apremilast reduced the severity of psoriasis and its impact on physical, psychological and social functioning, compared with placebo. The PSOR-010 trial also compared etanercept with placebo;

[redacted]. There was no direct comparison between apremilast and etanercept reported in the MS. The odds ratios (ORs) calculated by the ERG from numbers in Table 8 for etanercept vs apremilast were for PASI-75 (OR 1.41, 95% CI 0.76 to 2.61), [redacted] and [redacted], indicating that etanercept improved PASI response slightly more than apremilast,

[redacted].

Table 7: Summary of efficacy endpoints at Week 16 and Week 32 for PSOR-008, PSOR-009 and pooled analysis

Outcome	PSOR-008			PSOR-009			Pooled analysis		
	Week 16		Week 32	Week 16		Week 32	Week 16		Week 32
	APR 30 mg bid (n = 562)	Placebo (n = 282)	APR/APR 30 mg bid (n = 562)	APR 30 mg bid (n = 274)	Placebo (n = 137)	APR/APR 30 mg bid (n = 274)	APR 30 mg bid (n = 836)	Placebo (n = 419)	APR/APR 30 mg bid (n = 836)
Primary outcome									
PASI-75, n (%)	186 (33.1)†	15 (5.3)	159 (28.3)*	79 (28.8)†	8 (5.8)	68 (24.8)	265 (31.7)†	23 (5.5)	227 (27.2)
Secondary outcomes									
sPGA score 0 or 1, n (%)	122 (21.7)†	11 (3.9)	135 (24.0)	56 (20.4)†	6 (4.4)	49 (17.9)	178 (21.3)†	17 (4.1)	184 (22.0)
PASI-50, n (%)	330 (58.7)†	48 (17.0)	301 (53.6)*	152 (55.5)†	27 (19.7)	126 (46.0)	482 (57.7)†	75 (17.9)	427 (51.1)
PASI-90, n (%)	55 (9.8)†	1 (0.4)	68 (12.1)	24 (8.8)††	2 (1.5)	26 (9.5)	79 (9.4)†	3 (0.7)	94 (11.2)
Mean change in PASI score from baseline, % (95% CI)	-52.1 (-54.7, -49.4)†	-16.8 (-20.6, -13.0)	-61.9** (-64.6, -59.3)	-50.8 (-55.2, -46.4)†	-16.0 (-22.2, -9.8)	-58.8 (-62.8, -54.7)	-51.6 (SE 1.2)†	-16.5 (SE 1.7)	-61.0 (SD 28.0)
Mean change in psoriasis-affected BSA, % (95% CI)	-47.8 (-51.0, -44.6)†	-6.99 (-11.5, -2.4)	-61.2 (-64.4, -57.9)	-48.4 (-53.6, -43.2)†	-6.3 (-13.5, 1.1)	-55.9 (-60.6, -51.2)	-48.0 (SE 1.4)†	-6.8 (SE 2.0)	-61.0 (SD 33.99)
Patients with nail psoriasis									
Mean change in NAPSI score, % (95% CI)[#]	-22.5 (SD 54.9)†	6.5 (SD 60.6)	-43.6 (-50.3, -36.8)	-29.3 (-38.7, -20.0)††	-6.4 (-19.4, 6.5)	-60.0 (-69.5, -50.5)	-24.6 (SE 2.6)† N=538	2.1 (SE 3.6) N=286	NR
NAPSI-50, n (%)	121 (33.3)†	29 (14.9)	164 (45.2)	78 (44.6)†	17 (18.7)	97 (55.4)	199/538 (37.0)†	46/286 (16.1)	NR
Patients with scalp psoriasis									
ScPGA score 0 or 1, n (%)	174 (46.5)†	33 (17.5)	140 (37.4)	72 (40.9)†	16 (17.2)	57 (32.4)	246/550 (44.7)†	49/282 (17.4)	NR
ScPGA score 0, 1 or 2, n (%)	257 (68.7)†	67 (35.4)	211 (56.4)	118 (67.0)†	39 (41.9)	90 (51.1)	NR	NR	NR
DLQI									
Mean change in DLQI score, n (95% CI)	-6.6 (-7.1, -6.1)†	-2.1 (-2.8, -1.3)	-7.3 (-7.9, -6.7)	-6.7 (-7.5, -6.0)†	-2.7 (-3.7, -1.7)	-7.0 (SD 6.4)	-6.6 (SE 0.2)†	-2.3 (SE 0.3)	-7.2 (SD 6.55)
Patients with baseline DLQI > 5									
DLQI decrease of ≥5 points, n (%)[#]	322 (70.2)†	79 (33.5)	264 (57.5)	160 (70.8)†	51 (42.9)	115 (50.9)	482/685 (70.4)†	130/355 (36.6)	379/685 (55.3)
SF-36 MCS score									
Mean change from baseline, n (95% CI)[$]	2.3 (1.6, 3.0)†	-0.8 (-1.8, 0.2)	3.01 (2.1, 4.0)	2.6 (1.49, 3.71)††	-0.03 (-1.61, 1.55)	3.45 (1.88, 5.02)	2.5 (SE 0.3)†	-0.7 (SE 0.5)	3.2 (SD 10.3)
Pruritis VAS score									

Outcome	PSOR-008			PSOR-009			Pooled analysis		
	Week 16		Week 32	Week 16		Week 32	Week 16		Week 32
	APR 30 mg bid (n = 562)	Placebo (n = 282)	APR/APR 30 mg bid (n = 562)	APR 30 mg bid (n = 274)	Placebo (n = 137)	APR/APR 30 mg bid (n = 274)	APR 30 mg bid (n = 836)	Placebo (n = 419)	APR/APR 30 mg bid (n = 836)
Mean change from baseline, n (95% CI)[#]	-31.5 (-34.1, -29.0)†	-7.3 (-10.9, -3.6)	-34.5 (-37.5, -31.5)	-33.5 (-37.6, -29.4)†	-12.2 (-18.0, -6.4)	-34.7 (-39.4, -30.0)	-32.2 (SD 1.1)†	-8.9 (SD 1.6)	-34.6 (SD 31.7)
Patients who achieved ≥10mm decrease, n/N (%)	397/537 (73.9)†	108/276 (39.1)	325/537 (60.5)	191/270 (70.7)†	59/131 (45.0)	145/270 (53.7)	588/807 (72.9)†	167/407 (41.0)	470/807 (58.2)
WLQ-25									
Mean change from baseline in WLQ-25 index score, n (95% CI)	-0.0035 (-0.008, 0.001)††	0.006 (-0.0002, 0.012)	-0.0055 (-0.02, -0.00)	-0.0053 (-0.011, 0.0003)	-0.0064 (-0.015, 0.0018)	-0.0055 (-0.0124, 0.0014)	-0.0043 (SE 0.002)††	0.0026 (SE 0.003)	-0.006 (SD 0.04)
Mean change from baseline in WLQ-25 productivity loss score, n (95% CI)	-0.32 (-0.7, 0.1)††	0.53 (-0.04, 1.1)	-0.52 (-1.02, -0.014)	-0.50 (-1.02, 0.02)	-0.60 (-1.37, 0.16)	-1.5 (-4.3, 1.2)	-0.40 (SE 0.2)††	0.23 (SE 0.24)	NR
Exploratory outcomes									
PASI-75 in patients with DLQI≤10 at baseline, n (%)	77/230 (33.5)	8/123 (6.5)	71/230 (30.9)	40/119 (33.6)	2/58 (3.4)	34/119 (28.6)	117/349 (33.5)	10/181 (5.5)	105/349 (30.1)

*Non-responder imputation (NRI) method for imputing missing data, rather than last observation carried forward (LOCF), which was used for Week 16 results.
**As observed analysis; patients who had dropped-out were excluded from the analysis.
#Decrease = improvement
$Increase = improvement
†Statistically significant difference for Week 16 comparison ($p<0.0001$)
††Statistically significant difference for Week 16 comparison ($p<0.05$)
NR = Not reported.

Table 8: Summary of efficacy endpoints at Week 16 and Week 32 or 24 (where reported) for pooled analysis, PSOR-005 and PSOR-010

Outcome	Pooled analysis			PSOR-005*			PSOR-010		
	Week 16		Week 32	Week 16		Week 24	Week 16		
	APR 30 mg bid (n = 836)	Placebo (n = 419)	APR/APR 30 mg bid (n = 836)	APR 30 mg bid (n = 88)	Placebo (n = 88)	APR/APR 30 mg bid (n = 88)	APR 30 mg bid (n = 83)	Placebo (n = 84)	Etanercept (n = 83)
Primary outcome									
PASI-75, n (%)	265 (31.7)†	23 (5.5)	227 (27.2)	36 (40.9)†	5 (5.7)	35 (39.8)	33 (39.8)†	10 (11.9)	40 (48.2)†
Secondary outcomes									
sPGA score 0 or 1, n (%)	178 (21.3)†	17 (4.1)	184 (22.0)	29 (33)††	11 (12.5)		NR	NR	NR
sPGA score 0 or 1, with change from baseline of ≥2 points, n (%)	NR	NR	NR	NR	NR	NR	[redacted]	3 (3.6)	24 (28.9)†
PASI-50, n (%)	482 (57.7)†	75 (17.9)	427 (51.1)	53 (60.2)†	22 (25.0)	58 (65.9)	[redacted]	28 (33.3)	69 (83.1)†
PASI-90, n (%)	79 (9.4)†	3 (0.7)	94 (11.2)	10 (11.4)††	1 (1.1)	13 (14.8)	[redacted]	[redacted]	[redacted]
Mean change in PASI score from baseline, % (SE/SD)	-51.6 (SE 1.2)†	-16.5 (SE 1.7)	-61.0 (SD 28.0)	-52.9 (SD 36.4)†	-20.5 (SD 40.9)	NR	[redacted]	[redacted]	[redacted]
Mean change in psoriasis-affected BSA, % (SE/SD)	-48.0 (SE 1.4)†	-6.8 (SE 2.0)	-61.0 (SD 33.99)	-49.4 (SD 37.7)†	-8.4 (SD 51.1)	NR	[redacted]	-16.5 (SD 36.9)	-56.5 (SD 36.1)†
LS-PGA score 0 or 1, n (%)	NR	NR	NR	NR	NR	NR	[redacted]	5 (6.0)	19 (22.9)††
Patients with nail psoriasis									
Mean change in NAPSI score, % (SE)[#]	-24.6 (SE 2.6)† N=538	2.1 (SE 3.6) N=286	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
NAPSI-50, n (%)	199/538 (37.0)†	46/286 (16.1)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Patients with scalp psoriasis									
ScPGA score 0 or 1, n (%)	246/550 (44.7)†	49/282 (17.4)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
ScPGA score 0, 1 or 2, n (%)	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
DLQI									
Mean change in DLQI score, n (SE/SD)	-6.6 (SE 0.2)†	-2.3 (SE 0.3)	-7.2 (SD 6.55)	-4.4 (SD 5.1)††	-1.9 (SD 5.2)	NR	[redacted]	-3.8 (SD 5.6)	-7.8 (SD 6.5)†

Outcome	Pooled analysis			PSOR-005*			PSOR-010		
	Week 16		Week 32	Week 16		Week 24	Week 16		
	APR 30 mg bid (n = 836)	Placebo (n = 419)	APR/APR 30 mg bid (n = 836)	APR 30 mg bid (n = 88)	Placebo (n = 88)	APR/APR 30 mg bid (n = 88)	APR 30 mg bid (n = 83)	Placebo (n = 84)	Etanercept (n = 83)
Patients with baseline DLQI > 5									
DLQI decrease of ≥5 points[#]	482/685 (70.4)†	130/355 (36.6)	379/685 (55.3)	NR	NR	NR	[redacted]	[redacted]	[redacted]
SF-36 MCS score									
Mean change from baseline, n (SE/SD)[$]	2.5 (SE 0.3)†	-0.7 (SE 0.5)	3.2 (SD 10.3)	2.9 (SD 9.2)††	-0.8 (SD 10.0)	2.9 (SD 10.2)	[redacted]	2.6 (SD 9.2)	4.4 (SD 9.6)
Pruritis VAS score									
Mean change from baseline, n (SD)[#]	-32.2 (SD 1.1)†	-8.9 (SD 1.6)	-34.6 (SD 31.7)	-43.7 (SD 46.8)†	-6.1 (SD 76.4)	NR	[redacted]	[redacted]	[redacted]
Patients who achieved ≥10mm decrease, n/N (%)	588/807 (72.9)†	167/407 (41.0)	470/807 (58.2)	NR	NR	NR	NR	NR	NR
WLQ-25									
Mean change from baseline in WLQ-25 index score, n (SE/SD)	-0.0043 (SE 0.002)††	0.0026 (SE 0.003)	-0.006 (SD 0.04)	NR	NR	NR	NR	NR	NR
Mean change from baseline in WLQ-25 productivity loss score, n (SE)	-0.40 (SE 0.2)††	0.23 (SE 0.24)	NR	NR	NR	NR	NR	NR	NR
Exploratory outcomes									
PASI-75 in patients with DLQI≤10 at baseline, n (%)	117/349 (33.5)	10/181 (5.5)	105/349 (30.1)	NR	NR	NR	NR	NR	NR

Results for PSOR-005 are from the trial publication and results for PSOR-010 are from the trial CSR
*Results only presented for APR 30 mg bid group (licensed dose) and placebo group
#Decrease = improvement
$Increase = improvement
†Statistically significant difference for Week 16 comparison compared with placebo ($p<0.001$)
††Statistically significant difference for Week 16 comparison compared with placebo ($p<0.05$)
NR = Not reported.

Adverse events

Safety data for trials PSOR-008 and PSOR-009 were presented separately in Tables 98 and 99 in Appendix 18 of the MS. A pooled analysis of safety data for the placebo-controlled period (Weeks 0 to 16) of trials PSOR-008 and PSOR-009 was presented in Table 28 of the MS. More patients receiving apremilast experienced at least one adverse event, compared with placebo (68.9% versus 57.2%). The most frequently reported adverse events in patients receiving apremilast were diarrhoea (17.8%), nausea (16.6%), upper respiratory tract infections (8.4%), nasopharyngitis (7.3%), tension headache (7.3%) and headache (5.8%); other adverse events were reported in less than 5% of patients. The proportion of patients reporting severe adverse events or serious adverse events was low and was similar between treatment groups. Adverse events leading to treatment discontinuation occurred in 16 (3.8%) patients in the placebo group and 45 (5.4%) patients in the apremilast group. Adverse events leading to treatment interruption occurred in 17 (4.1%) patients in the placebo group and 53 (6.4%) patients in the apremilast group. The MS stated that the majority of gastrointestinal adverse events occurred within the first 15 days of treatment exposure. The ERG asked for data to support this and the company provided the information that across PSOR 008 and 009 combined of 221 diarrhoea events within the first 16 weeks of exposure; 147 (66.5%) occurred within the first 15 days and 172 (77.8%) occurred within the first 30 days. Also of 182 nausea events within the first 16 weeks of exposure, 132 (72.5%) occurred within the first 15 days and 156 (85.7%) occurred within the first 30 days.

During the 16 week double blind treatment period of the PSOR-005 trial, more patients receiving apremilast 30 mg bid experienced at least one adverse event, compared with placebo (81.8% versus 64.8%). The most frequently reported adverse events in patients receiving apremilast 30 mg bid were nausea (18%), upper respiratory tract infections (16%), tension headache (16%), diarrhoea (14%), headache (10%), viral upper respiratory tract infection (8%), nasopharyngitis (6%), gastroenteritis (6%), dyspepsia (5%), vomiting (5%); other adverse events were reported in less than 5% of patients. The proportion of patients reporting serious adverse events was low and was similar between treatment groups (2% in both the placebo group and the apremilast 30 mg bid group). Adverse events leading to treatment discontinuation occurred in five (5.7%) patients in the placebo group and ten (11.4%) patients in the apremilast 30 mg bid group.

During the 16 week placebo-controlled period (Weeks 0 to 16) of the PSOR-010 trial, more patients receiving apremilast experienced at least one adverse event (69.9%), compared with placebo (59.5%) or etanercept 50 mg qw (53.0%). The most frequently reported adverse events in patients receiving apremilast were headache (13.3%), nausea (10.8%), diarrhoea (10.8%), upper respiratory tract infection (7.2%) and tension headache (6.0%); other adverse events were reported in less than 5% of patients. The most frequently reported adverse events in patients receiving etanercept were

nasopharyngitis (9.6%) and headache (6.0%); other adverse events were reported in less than 5% of patients. 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. A similar proportion of patients reported a severe adverse event between groups (3.6% in the apremilast group, 2.4% in the placebo and etanercept groups). Adverse events leading to treatment discontinuation occurred in two (2.4%) patients in the placebo group, two (2.4%) patients in the etanercept group and three (3.6%) patients in the apremilast group. Adverse events leading to treatment interruption occurred in 1 (1.2%) patients in the placebo group, 2 (2.4%) patients in the etanercept group and 8 (9.6%) patients in the apremilast group.

Table 9 presents a summary of adverse event data for the pooled analysis of PSOR-008 and PSOR-009, PSOR-005 and PSOR-010. Data for PSOR-005 and PSOR-010 were not presented in the MS and have been extracted from the trial publication and trial CSR, respectively.

Table 9: Summary of adverse event data (Weeks 0 to 16, safety population) for the pooled analysis of PSOR-008 and PSOR-009, PSOR-005 and PSOR-010

Patients	Pooled analysis		PSOR-005		PSOR-010		
	Placebo n = 418	Apremilast 30 mg bid n = 832	Placebo n = 88	Apremilast 30 mg bid n = 88	Placebo n = 84	Apremilast 30 mg bid n = 83	Etanercept 50 mg qw n = 83
Overview, n (%)							
Any TEAE	239 (57.2)	573 (68.9)	57 (64.8)	72 (81.8)	50 (59.5)	58 (69.9)	44 (53.0)
Any drug-related TEAE	87 (20.8)	330 (39.7)	NR	NR	22 (26.2)	28 (33.7)	21 (25.3)
Any severe TEAE	15 (3.6)	32 (3.8)	NR	NR	2 (2.4)	3 (3.6)	2 (2.4)
Any serious TEAE	11 (2.6)	17 (2.0)	NR (2%)	NR (2%)	0	3 (3.6)	1 (1.2)
Any serious drug-related TEAE	0 (0)	4 (0.5)	NR	NR	0	2 (2.4)	1 (1.2)
Any TEAE leading to drug withdrawal	16 (3.8)	45 (5.4)	5 (5.7)	10 (11.4)	2 (2.4)	3 (3.6)	2 (2.4)
Any TEAE leading to drug interruption	17 (4.1)	53 (6.4)	NR	NR	1 (1.2)	8 (9.6)	2 (2.4)
Any TEAE leading to death	1 (0.2)	1 (0.1)	NR	NR	0	0	0
AEs reported by ≥ 5% of patients in any treatment group, n (%)							
Diarrhoea	28 (6.7)	148 (17.8)	4 (5)	12 (14)	7 (8.3)	9 (10.8)	1 (1.2)
Nausea	28 (6.7)	138 (16.6)	7 (8)	16 (18)	2 (2.4)	9 (10.8)	4 (4.8)
Upper respiratory tract infection	27 (6.5)	70 (8.4)	5 (6)	14 (16)	2 (2.4)	6 (7.2)	2 (2.4)
Nasopharyngitis	29 (6.9)	61 (7.3)	7 (8)	5 (6)	8 (9.5)	4 (4.8)	8 (9.6)
Tension headache	14 (3.3)	61 (7.3)	6 (7)	14 (16)	4 (4.8)	5 (6.0)	3 (3.6)
Headache	14 (3.3)	48 (5.8)	5 (6)	9 (10)	5 (6.0)	11 (13.3)	5 (6.0)

Patients	Pooled analysis		PSOR-005		PSOR-010		
	Placebo n = 418	**Apremilast 30 mg bid n = 832**	**Placebo n = 88**	**Apremilast 30 mg bid n = 88**	**Placebo n = 84**	**Apremilast 30 mg bid n = 83**	**Etanercept 50 mg qw n = 83**
Viral upper respiratory tract infection	N/A	N/A	7 (8)	7 (8)	N/A	N/A	N/A
Gastroenteritis	N/A	N/A	3 (3)	5 (6)	N/A	N/A	N/A
Dyspepsia	N/A	N/A	2 (2)	4 (5)	N/A	N/A	N/A
Arthralgia	N/A	N/A	6 (7)	2 (2)	N/A	N/A	N/A
Vomiting	N/A	N/A	1 (1)	4 (5)	N/A	N/A	N/A

TEAE = treatment emergent adverse event. A TEAE is an AE with a start date on or after the date of the first dose of investigational product and no later than 28 days after the last dose of investigational product.
N/A = Not applicable; not reported by ≥5% of patients in this trial.
NR = Not reported.

A longer term pooled analysis of safety data from PSOR-008 and PSOR-009, including 1184 patients who had received apremilast for any duration up to 52 weeks, was presented in Table 29 of the MS. Eighty percent of patients experienced an adverse event; 8.2% experienced a severe adverse event and 5.7% experienced a serious adverse event. Diarrhoea (17.6%), upper respiratory tract infection (16.9%), nausea (15.9%), nasopharyngitis (15.0%), tension headache (9.2%), headache (6.4%), back pain (5.2%) and vomiting (5.1%) were the most frequently reported adverse events; other adverse events were reported in less than 5% of patients. The most common adverse events leading to treatment discontinuation were diarrhoea, nausea, headache and vomiting; 8.4% patients discontinued treatment due to adverse events, mostly within the first 24 weeks of apremilast treatment. The proportion of patients who had drug interruptions due to adverse events was 10.7%.

Patient compliance with treatment was not reported in the MS.

[redacted]

4.2.3.2 Phase 2 trial evidence

The primary endpoint in trial PSOR-001 was at least a 20% reduction in plaque epidermal thickness from baseline to day 29, which was achieved in 8/15 (53%) patients who had evaluable skin biopsies. At Week 12 of the PSOR-003 trial, significantly more patients receiving apremilast 20 mg bid achieved a PASI-75 response compared with patients receiving placebo (24.4% versus 10.3%). At Week 12 of the PSOR-004 trial, 67% patients had an improvement of 1 point or more in sPGA score, and 30% achieved a PASI-75 response.

4.2.4 Conclusions from critique of trials of the technology of interest

Four large well-conducted double-blind RCTs of apremilast at the licensed dose were included in the review; PSOR-008, PSOR-009, PSOR-005 and PSOR-010. The design of the initial placebo-controlled phase of the four RCTs was similar. The trials were similar in terms of eligibility criteria and baseline characteristics of participants, except that in trial PSOR-010 patients had to have had no prior exposure to biologics to be eligible for inclusion, in addition, a much higher proportion of patients in this trial had received prior conventional systemic therapy (range 69.9 to 83.3% between treatment groups) than in the other trials (range 36.2 to 38.7%)[redacted]

The primary endpoint was the same in all four trials; PASI-75 response at Week 16. All four trials demonstrated a statistically significant difference between apremilast and placebo for Week 16 comparisons for the majority of outcomes, including PASI-75 response (primary outcome), sPGA score of 0 or 1, PASI-50 response, PASI-90 response, mean change in psoriasis-affected BSA, mean change in DLQI score from baseline and mean change in pruritis VAS score from baseline. Apremilast reduced the severity of psoriasis and its impact on physical, psychological and social functioning, compared with placebo. PASI-75 response was maintained in the Week 32 analysis of the PSOR-008 and PSOR-009 trials.

The PSOR-010 trial also compared etanercept with placebo [redacted] There was no direct comparison between apremilast and etanercept reported in the MS. The odds ratios (ORs) calculated by the ERG from numbers in Table 8 for etanercept vs apremilast indicate that etanercept improved PASI response slightly more than apremilast.

More patients receiving apremilast experienced at least one adverse event, compared with placebo. The most frequently reported adverse events in patients receiving apremilast were diarrhoea, nausea, upper respiratory tract infections, nasopharyngitis, tension headache and headache. In the PSOR-010 trial more patients receiving apremilast experienced at least one adverse event, compared with etanercept. The most frequently reported adverse events with etanercept were nasopharyngitis and headache. The proportion of patients reporting severe adverse events or serious adverse events was low and was similar between treatment groups.

Additional non-RCT evidence was presented; PSOR-001, PSOR-003 and PSOR-004. However, these trials did not assess apremilast at the licensed dose, so they were appropriately presented only as supporting evidence in Section 6.8 of the MS.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

A NMA was presented to compare the efficacy of apremilast with the licensed biological therapies adalimumab, etanercept, infliximab and ustekinumab. A systematic review was conducted to identify the trials for inclusion in this NMA. The inclusion criteria appear to have been appropriate, and

appropriate biological therapies were included in the NMA, at their recommended dose. However, ustekinumab is recommended at a dose of 45 mg at Week 0 and 4, followed by subsequent injections every three months. Patients weighing over 100 kg should be given ustekinumab in 90 mg doses. The NMA included ustekinumab at both 45 mg and 90 mg doses, regardless of patient weight.

The MS described the search strategies used to identify RCTs of apremilast, adalimumab, etanercept, infliximab and ustekinumab in adults with psoriasis. The search strategies were briefly described in the main body of the submission and full details were provided in the Appendices. The electronic databases MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and ClinicalTrials.gov were searched on 3 September 2013, with the searches updated in October 2014. Additional manual searching of the reference lists of published systematic reviews, meta-analyses and HTA documents was also carried out.

The methods used to identify both published and unpublished studies for the NMA were appropriate and for the most part well reported. There were some minor details missing from the reporting of the searches in Appendix 4, Section 10.4, however the manufacturer supplied further details in their response to the ERG's Points for Clarification.

All of the NICE required databases were searched together with ClinicalTrials.gov for ongoing studies and reference checking of previous reviews to capture studies that may not have been identified by the database searches. The search strategies contained in Appendix 2, Section 10.2 were appropriate and would result in a fairly sensitive search. However the search terms for psoriasis in EMBASE and CENTRAL were limited to indexing terms only. It would have improved the sensitivity of the search if psoriasis had also been searched in the titles and abstracts of the records. Similarly with the EMBASE search strategy it appears that the drug names were searched for as subject headings only, which could have resulted in missed relevant studies.

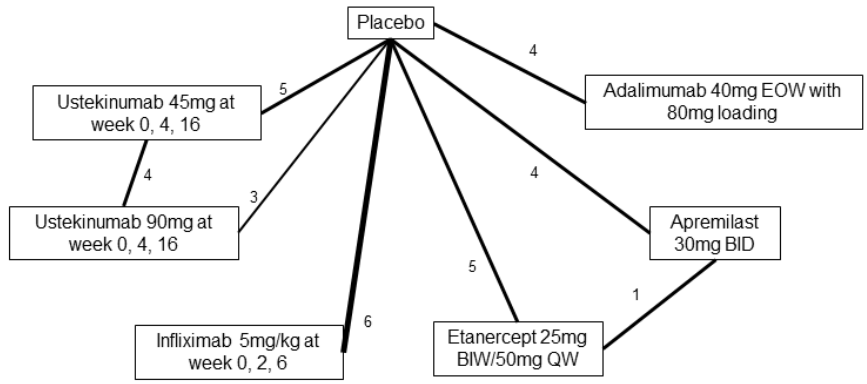
The database searches were limited to English language studies and human studies in MEDLINE and EMBASE. This could have led to relevant foreign language papers not being identified by the search. In addition, the limit to human studies has limited the retrieval to those studies indexed as human. However there are some records in the databases that have not yet been indexed as human and therefore these could have potentially been missed.

Study design limits to restrict retrieval to trials, systematic reviews, or meta-analysis were applied to the searches of MEDLINE and EMBASE. The manufacturer clarified that these limits were provided by the databases. These limits are quite restrictive and could have missed relevant trials or systematic reviews. The use of validated study design search filters for the retrieval of systematic reviews and trials are available and would have resulted in a more sensitive search.

Owing to time constraints, the ERG did not undertake independent searches to check that all relevant studies were included in the NMA. However, a comparison of studies included in this STA with the earlier STA of ustekinumab identified one RCT of etanercept which was excluded from this review in error: Gottlieb, 2003.[16] The excluded trial was presented in Table 83 of the MS (Studies excluded from NMA of current systemic treatments for psoriasis) with the reason for exclusion stated as 'with treatment arm of interest but not recommended dose', however, the trial assessed etanercept at the recommended dose of 25 mg every two weeks.[16] The ERG compared the results of this trial with the three trials of etanercept included in the NMA; the results were similar, suggesting that the exclusion of this trial is unlikely to have biased the results of the NMA against etanercept. The NMA presented in the MS omitted the PSOR-010 trial. The ERG questioned why this trial was excluded and requested a re-estimation of the main NMA including the PSOR-010 trial. The manufacturer responded that results for the primary endpoint at Week 16 were not available at the time the NMA was developed. The manufacturer presented an updated result of the NMA, incorporating both the additional data from trial PSOR-010 and the previously missing Gottlieb trial. Table 83 of the MS was checked for additional relevant studies excluded in error; none were found.

The network diagram of treatments (Figure 23 of the MS) incorrectly stated that six trials were included for the comparison of placebo with etanercept 50 mg biw. In the Points for Clarification document the ERG asked for this figure to be corrected, a new figure was provided by the manufacturer, with the dosage of etanercept corrected to 25 mg biw/50 mg qw, and the number of trials comparing placebo with etanercept correctly reported as five. The corrected network diagram is presented below as Figure 2 (also including the PSOR-010 trial).

Figure 2: Corrected network of treatments for analysis of PASI outcomes



Note: Each node represents a treatment and/or a dosing regimen, and each link connects treatments that have been directly compared in one or more randomized clinical trials. Thicker lines represent higher number of comparisons in the network.
bid, twice daily; biw, biweekly; EOW, every other week; PASI, Psoriasis Area and Severity Index.

The quality of the 22 trials included in the NMA was assessed using an appropriate quality assessment tool for RCTs; full results of the quality assessment were presented and the majority of trials were rated as excellent or good quality.

The MS presented insufficient details of patient characteristics for the trials included in the NMA for the ERG to assess the comparability of patient populations between the trials. The ERG requested further details of patient characteristics. The manufacturer provided a table summarising the patient characteristics in the included trials and a table summarising prior and concomitant use of systemic non biologic and biological therapy in the included trials. In general, the patient characteristics were similar between most trials, although there were a few outliers where patients had more severe disease (in terms of body surface area affected and PASI score) and a higher proportion of patients had received prior conventional systemic therapy. The trials with different patient/prior therapy exposure characteristics were spread across the different therapies assessed, so results were unlikely to be biased against a particular therapy.

The manufacturer acknowledged that there is heterogeneity among the included trials, in terms of patient characteristics and trial methodology, and that owing to the relatively small number of trials available for each individual therapy, the limited ability to adjust for such heterogeneity reduces the degree of certainty associated with the results of the analyses.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 Critique of the methods of the NMA

The ERG used the NICE Decision Support Unit (DSU) Reviewer's Checklist to appraise the NMA; the majority of items were satisfactory and there were no major issues identified. The completed DSU Reviewer's Checklist is presented in Appendix 10.1.

A brief outline of the methods used for the NMA was presented in the MS. In response to a request from the ERG further details of the methods for the NMA were provided by the manufacturer.

Bayesian network meta-analysis (NMA) was conducted to pool trial results. Comparable studies identified by the systematic review were compiled to form a "network", indicating the pairwise comparisons contained within each study. NMA models were programmed in WinBUGS software using a Bayesian statistical framework.[17] Absolute outcome estimates were calculated by estimating the weighted average (i.e., proportional to study sample size) of the outcomes observed in the placebo arm of all of the studies. The absolute estimates for the other treatments were then calculated by combining the absolute placebo estimate and the NMA-derived treatment effect. This means that the pooled overall base estimate will not be exactly the same from the result of any single trial (due to

statistical aggregation), and thus the absolute estimates for the treatment comparators will also differ somewhat from the effects reported in the studies. Fixed- and random-effects models were evaluated and selection was determined by model fit statistics (i.e., deviance information criterion) to identify the best model choice. The submission included only the results for the random-effects model and so the ERG requested those for the fixed effect also: these were provided and the results were very similar.

The NMA included the PASI (PASI-50, PASI-75, PASI-90) outcomes which are ordered outcome categories created based on the continuous PASI scale. To make efficient use of the data for this type of measure, a multinomial model with probit link has been proposed.[18] The model assumes that there is an underlying continuous variable which has been categorised by specifying the cut-offs and that the treatment effect is the same regardless of the different cut-offs in each trial. The results are presented as the probabilities of achieving the specific cut-offs of improvement. The placebo PASI 75 probability was fixed at the observed value for the PSOR-008 and PSOR-009 trials.

This modelling approach to network meta-analysis was considered appropriate by the ERG. The WinBUGS code was not provided in the MS or in the clarification response despite a specific request and so this has not been checked by the ERG.

In the response to clarification it was stated that all model results are the aggregate of 50,000 samples after a 10,000-sample burn-in period and the diagnostic statistics for the updated NMA were provided (Table 10). These statistics demonstrate that there is little to choose between the fixed and random effects models for either the full or subgroup population. The model-fit statistics were not provided for the original NMA models.

Table 10: Model diagnostics for fixed- and random-effects PASI model

Population and model	Model diagnostics	Fixed effect	Random effects
All original			
	sigma	NA	Mean (95% CrI): 0.08 (0, 0.19)
	Res Dev	178.40	173.70
	pD	32.87	37.56
	DIC	211.27	211.26
Biologic naïve original			
	sigma	NA	Mean (95% CrI): 0.18 (0.03, 0.38)
	Res Dev	122.90	114.20
	pD	24.98	31.08
	DIC	147.88	145.28

As stated earlier, the outcomes synthesised were PASI-50, PASI-75 and PASI-90 response. As these are the outcomes included in the economic model this was appropriate. The absolute probabilities and ORs relative to placebo for each treatment for achieving PASI-50, PASI-75 and PASI-90 responses were appropriately presented. The manufacturer included 24 RCTs in their updated synthesis and chose to synthesise outcome data measured between Week 10 to 16. The ERG asked the manufacturer to provide odds ratios for comparisons between apremilast and other active treatments for PASI-50, PASI-75 and PASI-90 response, in addition to the comparisons with placebo. The manufacturer provided the additional results requested.

4.4.2 The results of the NMA

The results of the updated analysis, including trial PSOR-010 and the Gottlieb trial, are presented in Tables 11, 12 and 13; the results are presented as absolute probabilities, odds ratios compared with placebo, and odds ratios for each treatment compared with all others. These results demonstrate that infliximab achieved the highest probability of PASI-75 response, followed by ustekinumab, adalimumab, etanercept, then apremilast. The mean probability of a PASI-75 response was [redacted] with apremilast, and between 43% and 85% for the various biological therapies. The results from the fixed effect model were very similar to those for the random effects model.

Table 11: Results of Updated NMA (Random Effects Model) (Total population) - Absolute probability

	PASI-50		PASI-75		PASI-90	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
Placebo	0.17	(0.12, 0.23)	0.06	(0.04, 0.08)	0.01	(0.01, 0.02)
Apremilast 30mg BID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25mg BIW/ 50 mg QW	0.68	(0.59, 0.77)	0.43	(0.33, 0.54)	0.19	(0.13, 0.27)
Adalimumab 40mg EOW w/ 80mg loading	0.83	(0.75, 0.9)	0.62	(0.51, 0.72)	0.35	(0.25, 0.46)
Ustekinumab 45mg at wk 0, 4 and Q12W	0.91	(0.87, 0.95)	0.77	(0.68, 0.84)	0.51	(0.41, 0.61)
Ustekinumab 90mg at wk 0, 4 and Q12W	0.94	(0.9, 0.96)	0.81	(0.73, 0.87)	0.57	(0.46, 0.67)
Infliximab 5mg/kg at wk 0, 2, 6	0.95	(0.92, 0.98)	0.85	(0.78, 0.91)	0.64	(0.52, 0.74)

Crl, credible interval; PASI-50/75/90, 50%/75%/90% or greater improvement in Psoriasis Area and Severity Index score

Table 12: Results of Updated NMA (Random Effects Model) (Total population) - OR of all treatment comparisons compared with placebo

	PASI-50		PASI-75		PASI-90	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
Apremilast 30mg BID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25mg BIW/ 50 mg QW	10.76	(8.01, 14.43)	13.48	(9.89, 18.22)	22.72	(15.66, 32.43)
Adalimumab 40mg EOW w/ 80mg loading	25.20	(17.07, 35.59)	29.75	(20.62, 41.05)	52.21	(34.43, 75.46)
Ustekinumab 45mg at wk 0, 4 and Q12W	54.47	(38.77, 74.58)	58.29	(43.15, 76.72)	100.20	(70.72, 139)
Ustekinumab 90mg at wk 0, 4 and Q12W	73.64	(49.85, 106.4)	75.15	(53.73, 102.2)	126.50	(87.37, 178.5)
Infliximab 5mg/kg at wk 0, 2, 6	110.90	(66.72, 186.5)	105.30	(69.33, 161.1)	170.70	(110.7, 261)

Crl, credible interval; PASI-50/75/90, 50%/75%/90% or greater improvement in Psoriasis Area and Severity Index score

Table 13: Results of Updated NMA – PASI 75 response - OR of all treatment comparisons

	PASI-75					
	Placebo	Adalimumab 40mg EOW w/ 80mg loading	Apremilast 30mg BID	Etanercept 25mg BIW/ 50 mg QW	Infliximab 5mg/kg at wk 0, 2, 6	Ustekinumab 45mg at wk 0, 4 and Q12W
Placebo						
Adalimumab 40mg EOW w/ 80mg loading	[redacted]	-	-	-	-	-
Apremilast 30mg BID	[redacted]	[redacted]	-	-	-	-
Etanercept 25mg BIW/ 50 mg QW	[redacted]	[redacted]	[redacted]	-	-	-
Infliximab 5mg/kg at wk 0, 2, 6	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ustekinumab 45mg at wk 0, 4 and Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Ustekinumab 90mg at wk 0, 4 and Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time constraints precluded the ERG re-running the NMA. Instead, the ERG checked the NMA results against the data used in the NMA (data from Table 19 of the MS as well as data from the trials of PSOR-010 and Gottlieb, 2003). It showed that the results for each treatment arm were generally consistent across studies for all the drugs, and the results were also fairly consistent with those absolute probabilities generated by the NMA. Furthermore, the results of the NMA were compared with the NMA results presented in the previous ustekinumab STA and were found to be similar, with infliximab having the highest probability of PASI-75 response, followed by ustekinumab 90 mg, ustekinumab 45 mg, adalimumab and finally etanercept having the lowest probability of PASI-75 response of the biological therapies assessed in both appraisals. The ERG therefore conclude that the results from the updated NMA are likely to be reasonably reliable.

A sensitivity analysis was undertaken using PASI outcomes data from only a biologic-naïve subgroup of patients; data from 15 trials considered to only include patients naïve to biological therapy were included. The results were generally consistent with the overall population results. However, the ERG questions the validity of this analysis on the grounds that the 'biologic-naïve' status of the population across the trials is somewhat suspect: the trials included in this subgroup NMA did not consistently report whether patients were naïve to biological therapy; studies that reported data for populations naïve to anti-TNFα therapy were assumed to be naïve for all biological agents; and trials

in which less than 20% of patients were reported to have received prior biological therapy were also included in the biologic-naïve subgroup analysis. Therefore, the results of the subgroup analysis should be interpreted with caution. An updated version of this sensitivity analysis was provided by the manufacturer, including trial PSOR-010 and the missing Gottlieb trial, however these results do not have face validity: the absolute probability of response with placebo was higher than three of the active treatments. Therefore, it appears that the updated sensitivity analysis contains errors.

4.5 Conclusions of the clinical effectiveness section

The MS presented a reasonably well conducted systematic review of apremilast for the treatment of patients with moderate to severe plaque psoriasis, which identified four good quality double-blind, placebo controlled RCTs; PSOR-005, PSOR-008, PSOR-009 and PSOR-010. The search strategy for RCT evidence was adequate and no relevant studies of apremilast appear to have been missed. However, the MS focussed on two of the RCTs (PSOR-008 and PSOR-009), whilst trials PSOR-010 and PSOR-005 were only presented as supporting evidence, with minimal study details and results and no quality assessment results presented. The PSOR-010 trial was the only trial to allow direct comparison of apremilast with a biological therapy (etanercept), although it was not powered for this comparison.

The design of the initial placebo-controlled phase of the four RCTs was similar and the trials were similar in terms of eligibility criteria and baseline characteristics of participants, except that in trial PSOR-010 patients had to have had no prior exposure to biologics to be eligible for inclusion, and in addition, a much higher proportion of patients in this trial had received prior conventional systemic therapy. Patients included in the PSOR-008 and PSOR-009 trials may not be representative of the licensed population nor of those who may be eligible for apremilast in NHS practice, as less than 40% of patients had received prior conventional systemic therapy.

All four trials demonstrated a statistically significant difference between apremilast and placebo for PASI-75 response at Week 16 (primary outcome) and the majority of other outcomes, demonstrating that apremilast reduces the severity of psoriasis and its impact on physical, psychological and social functioning, compared with placebo. The manufacturer provided data from PSOR-008 for a number of subgroups of patients including those who had failed two or more conventional systemic therapies or are contraindicated to systemic therapy and are biologic naïve and for those who had failed biologic therapy. The results were similar to the main analysis but are based on only a small proportion of the full trial population (13% and [redacted] respectively).

The PSOR-010 trial also compared etanercept with placebo. Direct comparison of PASI-75 response for apremilast with etanercept by the ERG indicated that apremilast was slightly less efficacious than etanercept.

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

A NMA was presented to compare the efficacy of apremilast with four biological therapies (adalimumab, etanercept, infliximab and ustekinumab). This was an appropriate analysis in terms of methods and trials except that the original NMA presented in the MS did not include the PSOR-010 trial, because the Week 16 data were not available at the time the NMA was developed. On request from the ERG, the manufacturer provided an updated result of the NMA incorporating the additional data from trial PSOR-010, as well as another trial excluded in error (Gottlieb, 2003). Thus, the manufacturer included 24 RCTs in their updated synthesis and chose to synthesise outcome data measured between Week 10 to 16. The results of the NMA demonstrated that, except for placebo, apremilast achieved the lowest probability of PASI response (PASI-50, 70 and 90). Of the active treatments infliximab achieved the highest probability of PASI response, followed by ustekinumab, adalimumab, etanercept, then apremilast.

Although the manufacturer suggests positioning apremilast before biological therapy in the treatment pathway, no data were presented on patients' response to biological therapies after having received apremilast; therefore, it is unclear whether treatment effectiveness of biologics is affected by prior use of apremilast.

In the short term apremilast is well tolerated. However no evidence has been presented to indicate that apremilast is better tolerated than biologics and data from the one available direct comparison (PSOR-010) suggests adverse events may be more frequent with apremilast. There is still uncertainty about the long term safety of apremilast as current safety data only extends to one year.

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

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the manufacturer and the additional information provided following the ERG points for clarification. The ERG critically reviewed the manufacturer's submission, their response to the points for clarification and three separate electronic versions of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations. Section 6 presents additional work undertaken by the ERG to address key remaining uncertainties.

The manufacturer's original economic submission included:

1. A description of a systematic literature review conducted to identify published evidence on the cost-effectiveness of apremilast and biologic therapies for the treatment of psoriatic arthritis (PsA) or psoriasis (Manufacturer's Submission (MS), Section 7.1, with details provided in a separate appendix (MS Appendix 10, Section 10.10).
2. A report on the de novo economic evaluation conducted by the manufacturer (MS Section 7.2-7.7). The report describes the patient population, model structure and technology in Section 7.2; clinical parameters and relevant assumptions made in Section 7.3; the approach taken to assess health related quality of life (HRQoL) in Section 7.4; the resource use and unit cost assumptions and sources in Section 7.5; the sensitivity analyses conducted in Section 7.6; and the cost-effectiveness results for the base-case and sensitivity analyses in Section 7.7.
3. Two separate economic models developed in Microsoft Excel®. The models addressed the two distinct populations, i.e. DLQI≤10 and DLQI>10, presented as the base-case analyses separately as described in Section 7.2.3.

In response to a number of points for clarification raised by the ERG, the manufacturer further submitted:

4. A response to the points for clarification, including EQ-5D data by DLQI subgroups and additional scenario analyses requested by the ERG to address uncertainties surrounding the BSC costs applied in the base-case analysis based on estimates reported in NICE Clinical Guideline (CG) 153.[10]
5. An updated version of the electronic economic model for the DLQI>10 population. This model incorporated corrections to the effectiveness parameters and allowed apremilast to be assessed at different points in the treatment sequence. No further changes were made to the model presented.

5.1 ERG comment on manufacturer's review of cost-effectiveness and supporting evidence

5.1.1 Searches

The manufacturer undertook a systematic literature search to identify published evidence on the cost-effectiveness of apremilast and biologic therapies for the treatment of PsA and psoriasis. The combined search was conducted to inform both this submission and the separate submission considering apremilast for PsA (ID682). However, only the references relating to the treatment of psoriasis were subsequently considered in the manufacturer's review. The search strategies were described in the main body of the submission, with further details provided in Appendix 10.

The electronic databases Medline®, Medline®In-Process and Embase were searched, and the search was conducted in Ovid. A separate search of the Cochrane Library was also undertaken. Additional searching of congress abstracts from the following meetings was carried out: International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International and European meetings, American Academy of Dermatology (AAD), British Association of Dermatology (BAD), European Academy of Dermatology and Venerology (EADV), European League Against Rheumatism (EULAR), and the American College of Rheumatology (ACR). A supplementary search of NICE technology appraisals was also performed.

The electronic database searches were run on the 30th June 2014 and covered the period 2005 to June 2014. The additional searching of congress abstracts and NICE technology appraisals was carried out June 2014 and covered the period January 2012 to June 2014. An English language limit was applied to the searches of MEDLINE and EMBASE.

Most of the NICE required databases were searched with the exception of EconLIT. The manufacturers clarified that the Cochrane Library was searched via the Wiley interface. However, the strategy reported in Appendix 10 does not have the correct search syntax for the Wiley interface and would not have run correctly.

The search strategies for MEDLINE and EMBASE combine terms for psoriasis and terms for apremilast or biological therapies. The strategies incorporate correct use of text word searches, synonyms and relevant subject heading searches. All of the drug names are included in the strategies: apremilast, etanercept, adalimumab, infliximab, golimumab and ustekinumab. Searches for brand names for each drug have also been included. The correct fields have been searched, truncation has been used appropriately and the search lines have all been combined correctly.

The search strategies for the electronic databases all include a section limiting results to cost-effectiveness studies. The manufacturers clarified that this section of the strategy was a bespoke strategy, designed to limit results to cost-effectiveness studies. Although not a validated study design filter, this part of manufacturers strategy is fit for purpose, with a variety of search terms, both text word and subject headings, relating to cost-effectiveness methods. However, the search of the Cochrane Library, which includes the NHS Economic Evaluations Database (NHS EED), also contains this bespoke cost-effectiveness strategy. It is unnecessary to limit searches of NHS EED to cost-effectiveness studies as this database only contains economic evaluations. Therefore, the search of NHS EED could have potentially missed relevant cost-effectiveness studies.

A limit to English language studies was applied to the searches of MEDLINE and EMBASE, therefore relevant foreign language papers may have been missed by the search. In addition, retrieval was limited to human studies in MEDLINE and EMBASE, therefore only those studies indexed as human would have been found. However, there are some records in these databases that have not yet been indexed as human and therefore these could potentially have been missed.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion and exclusion criteria used by the manufacturer are provided in Table 88 (p 241) of the MS. In addition to these criteria all duplicate studies were removed. The ERG considers the inclusion and exclusion criteria to be reasonable and would be expected to identify all relevant studies.

5.1.3 Studies included and excluded in the cost effectiveness review

1,094 study references were identified from the electronic searches, 87 of which were duplicates and were removed, resulting in 1,007 being applied to the inclusion/exclusion criteria. 940 were excluded by the application of the inclusion/exclusion criteria to their respective title/abstract. The remaining 67 studies were further considered together with 2 conference abstracts and 9 NICE TAs.

Of these 78 studies, a further 42 studies were subsequently excluded based on review of the full paper.

Data from 36 publications was thus summarised and subject to data extraction. Of these 19 reported the cost-effectiveness of treatment for psoriasis as a cost per QALY; and 17 reported the cost-effectiveness of treatments for PsA and as such are not relevant to this submission so also excluded from analysis.

9 of the 19 studies considered relevant to this submission reported cost-utility analyses from a UK perspective of biological therapies for moderate-to-severe psoriasis. A narrative summary of the results of these was provided by the manufacturer in Section 7.1.2 of the MS. A further 10 studies

presenting cost–utility analyses of biologic therapies in countries other than the UK were summarised separately in Appendix 10 of the MS. None of the 19 studies considered the cost-effectiveness of apremilast for the treatment of psoriasis. No additional studies relevant to this evaluation were identified by the ERG.

5.1.4 Conclusions of the cost effectiveness review

In the absence of any previously published economic evaluations of apremilast for psoriasis, the de novo cost-effectiveness analysis reported in Section 7.2 of the MS is the most relevant source of evidence to inform the decision problem for apremilast. However, the ERG considers that the review of previous cost-utility analyses of biological therapies in the UK (and particularly previous NICE TAs) was relatively superficial, focusing largely on describing the interventions and comparators, populations and subsequent ICER estimates. A more detailed investigation of differences in modelling approaches, key structural and parameter assumptions and sources of input data would have provided a useful basis to identify any key differences between the approach applied in the de-novo analyses and those applied in previous NICE TAs. Such a review could therefore have provided an important basis for subsequent validation i.e. identifying the extent to which the cost-effectiveness of the biological comparators was consistent with estimates reported in previous studies.

5.1.5 Review of supporting evidence

The manufacturer conducted two additional reviews to identify evidence on utility values, and costs and resource use associated with the management of psoriasis in the UK. The same approach was taken as for the review of existing cost-effectiveness evidence.

For the utilities search the ERG noted that in general the searches were well reported but a few issues were noted with the search strategies. Most of the NICE required databases were searched, however EconLIT was not searched. The search strategies for the electronic databases included search terms for psoriasis combined with terms for EQ-5D. Relevant synonyms and subject headings have been used along with text word searches, which is appropriate. Truncation and field searches have been used appropriately. An error combining search lines has been made with the Cochrane Library search strategy at line 28. This line should be combining lines #26 AND #27, however the wrong line numbers have been entered (#22 AND #23). This means that the results from lines 19-21 and lines 24-26 have not been included in the final results, so it is possible that relevant studies from the Cochrane Library have been missed. However, no errors combining search lines have been made in the searches of EMBASE and MEDLINE.

For the costs and resource use review the ERG noted that the searches were appropriate and are well reported. Most of the NICE required databases were searched with the exception of EconLIT. The

search strategies for all of the databases combine terms for psoriasis and terms for costs. The results are limited by the final part of the strategy to UK studies. Appropriate text word searches, synonyms and relevant subject heading searches have been included in all of the searches. The correct fields have been searched, truncation has been used appropriately and the search lines have all been combined correctly.

5.2 ERG's summary and critique of manufacturer's submitted economic evaluation

The manufacturer submitted separate electronic models for the economic evaluation of the two separate populations of interest which differed by DLQI. Due to the similarity of the model structures across these separate populations, the ERG's summary and critique primarily focuses on the population as defined by PASI≥10 and DLQI>10. However, in each section the ERG note how the submitted evaluation is different, if at all, (i.e. comparators, structural, parameter inputs, etc.) for the population with a PASI≥10 and DLQI≤10. An overall summary of the manufacturer's approach and signposts to the relevant sections in the MS are reported in Table 14 below.

Table 14: Summary of the Manufacturer's economic evaluation

Element of HTA	Approach	Source/Justification	Location in MS
Model structure	A Markov model was employed for the cost-effectiveness analysis	The structure was similar to that used previously and sought to reflect the pattern of care in the NHS in a UK setting.	Sections 7.2.2 to 7.2.6 (p131-135)
Population	The main population considered was adults with moderate to severe plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant to other systemic non-biologic therapies and a PASI≥10 and a DLQI>10. An additional base-case population is considered who have PASI≥10 and DLQI≤10.	The population is based on the CHMP for the placement as a post conventional systemic therapy, expert opinion, and CG153[10] for the differentiation of the two populations based on DLQI.	Section 7.2.1 (p131) and Section 7.2.7 (p136-137)
Interventions and comparators	The main analysis (PASI≥10 and a DLQI>10) population compares a sequence of 2 anti-TNFs (adalimumab, etanercept) followed by BSC with and without apremilast as an additional therapy added at the beginning of the sequence. The additional base-case analysis in the PASI≥10 and DLQI≤10 population compares apremilast followed by BSC to BSC alone.	The use of apremilast as an additional, pre-biologic, line of therapy is based on clinical opinion, presented in the MS and further in B1 of the points for clarification. The main analysis comparators are based on CG153.[10] The additional analysis assumes the lack of NICE guidance on those in the population DLQI≤10 indicates an unserved treatment need.	Section 7.2.7 (p136-137)
Perspective, time horizon and discounting	The NHS and PSS perspective was taken. A time horizon of 10 years applied, and an annual rate of 3.5% was used for both costs and health effects.	In accordance with the NICE Guide to the Method of Technological Appraisal and previous studies in psoriasis.[19]	Section 7.2.6 (p135)
Treatment effectiveness and extrapolation	Results from the NMA are used to inform the probability of response to treatment, by PASI response, during the trial period of each treatment. Long term withdrawal of patients from each drug is assumed at a fixed 1.70% probability per cycle (28 days). Withdrawal incorporates failure of treatment due to lack of efficacy in addition to other reasons for withdrawal (e.g. adverse events, patient preference).	The NMA was used to take into account all available evidence on the response to treatments considered, and address the lack of head to head trial data for apremilast. The long term withdrawal rate is consistent with previous evaluations for the TNF-inhibitors.	Section 7.3.1 (p138), Section 7.3.6 (p140-144), and Section 7.7.6 (p171-172)
Health related quality of life (HRQoL)	DLQI>10 population utility increments are based on previously published estimates by PASI response categories for TNF-inhibitors. The DLQI≤10 analysis uses utility increments from the PSOR-008 and 009 trials.	The main justifications presented for the approach taken in the DLQI>10 population are to maintain consistency with previous submissions, and data showing the same HRQoL response in apremilast as an anti-TNF (etancercept). No clear justification is provided why a different approach is taken in the DLQI≤10 analysis.	Section 7.4.3 to 7.4.13 (p147-152)
Resources and costs	Costs are categorised in three forms: treatment and administrative costs; monitoring and laboratory costs; hospitalisations costs	Sources of data include the NHS Reference Costs 2012/13[20], BNF,[21] EMA,[1] Psoriasis Costing Report[22] and CG153[10]	Section 7.5 (p152-161)
Best Supportive Care (BSC)	In both populations the manufacturer assumes a cost of BSC based on the base-case presented in the CG153 analysis.[10] The base-case analysis assumes no efficacy of BSC, such that all patients have a PASI0 (i.e. no change from initial presentation).	The cost of BSC is selected to maintain consistency with the CG153 analysis.[10] The assumption of no BSC effectiveness is based on clinical advice.	Section 7.5.6 (p162-163) and Section 7.4.9 to 7.4.14 (p152-154)

5.2.1 Model structure

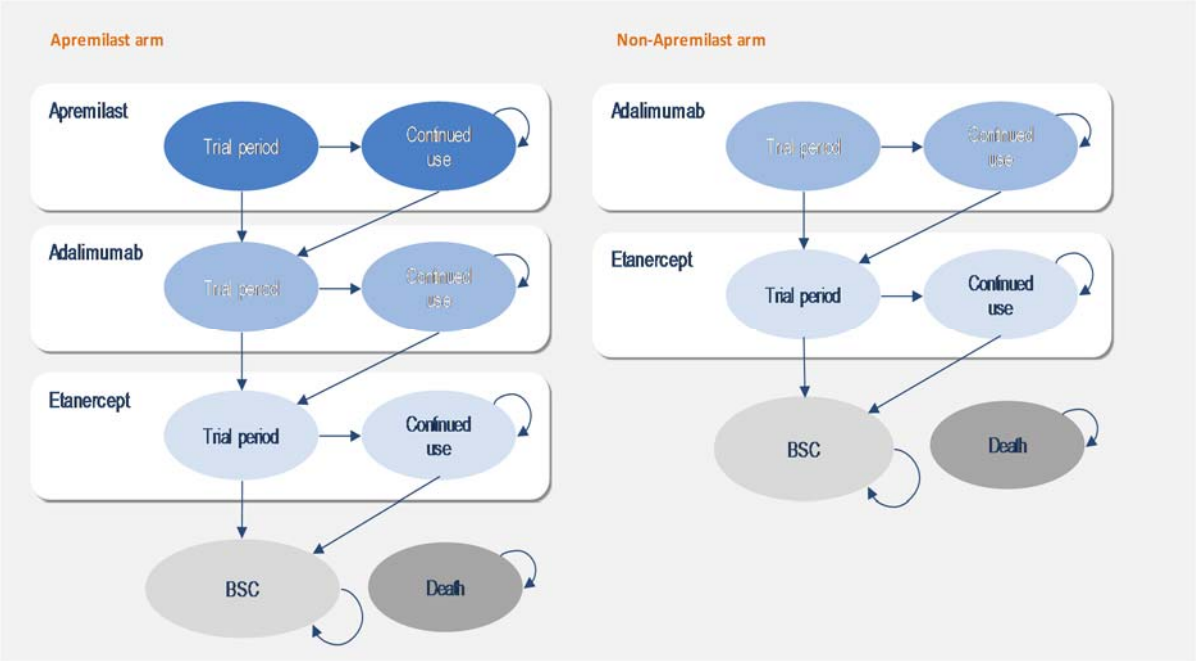
In the absence of previously published cost-effectiveness analyses of apremilast for the treatment of moderate to severe plaque psoriasis the manufacturer undertook a de novo economic evaluation using a Markov state transition cohort model. The model projects expected clinical and economic outcomes. The model is used to estimate costs, life years gained (LYG) and quality adjusted life years (QALYs).

The model structure chosen is based on that developed by the University of York Assessment group in that it consists of trial and treatment (or continued use) periods.[6] This type of model structure has been applied in previous TAs for psoriasis.[23-26] However, this model structure is different from previous analyses in that it allows a comparison of treatment sequences, with up to five lines of treatment.

Figure 3 provides a simplified schematic of the manufacturer's sequential model used for the PASI≥10 and DLQI>10 population. In this base-case the apremilast treatment sequence patients are assumed to progress through four lines of treatment. These four lines of treatment are, apremilast, two lines of biologic therapy (assumed to be adalimumab and etancercept in the base-case model) and BSC. In the comparator sequence, patients are assumed to be allowed to progress through the same two lines of biologic therapy and BSC. Patients progress through the different lines of therapy due to non-response and withdrawal.

The cycle length of the model is 28 days with a time horizon of 10 years. The cycle length was chosen to be sufficient to account for the different lengths of trial periods preceding the continued use of biologic therapies. The time horizon was selected to maintain consistency with the CG153 analysis[10] and as the majority of patients in both arms of the base-case are on BSC by the end of 10 years.

Figure 3: Markov model structure



Transition to the death health state is allowed from all health states in the model (arrows not displayed in the figure); BSC, Best Supportive Care

During each line of treatment, patients are assumed to start in a trial period and may transition to a continued use period. The trial period represents a fixed period of time (10 to 16 weeks depending on the treatment) over which the efficacy of the treatment is monitored. At the end of the trial period, if an adequate response to the treatment is reported patients move to continuous use of the treatment and stay at the PASI response level they achieved until they discontinue. If the response is inadequate patients move into the trial period of the next line of treatment or to BSC if at the end of the treatment sequence.

Table 15 provides a summary of the health states and their definitions. Within each treatment state in the Markov model patients can be in a number of different health states i.e. at different PASI levels with correspondingly different HRQoL and costs. This is described further in Sections 5.2.7 and 5.2.8 below.

Table 15: Summary of model health states

State	Definition
Trial period (apremilast, biologic therapy)	10–16 weeks (depending on the treatment), after which treatment response is assessed for all patients, based on PASI-75 response
Continued use (apremilast, biologic therapy)	Continued use of treatment for patients having responded to treatment according to achievement of PASI-75 response at the end of the trial period
BSC	Last treatment strategy for patients having failed all other treatment options
Death	Background mortality

BSC, best supportive care; PASI, psoriasis area and severity index.

In the original model submitted by the manufacturer the alternative sequences are limited both by the structure of the model and the number of sequences permitted. In particular, the apremilast sequence only allows apremilast to be considered as the first treatment in the sequence. Furthermore, while the model is flexible to compare up to four lines of biologic treatment followed by BSC, the apremilast sequence is always compared to the same sequence but without apremilast included. Consequently, the original model does not permit apremilast to be considered in any other point of the sequence except first, and only compares treatment sequences where apremilast represents an additional line of therapy.

The manufacturer stated in their submission that the comparator treatment sequence reflected established clinical practice in England and Wales, according to their clinical experts' opinion and was stated to be in accordance with current NICE guidance and NICE CG153.[19] The base-case analysis was based on a treatment sequence that included adalimumab and etanercept which was justified based on a recent publication suggesting these are the most widely used biologics for plaque psoriasis in the UK and Eire.[27] However, all biologic therapies recommended by NICE for the treatment of psoriasis in the UK were included as user options in the model and a sensitivity analysis included the anti-IL-12/23 agent ustekinumab as the second-line biologic.

As part of their clarification responses the manufacturer provided further justification for only comparing treatment sequences with apremilast as an additional line of therapy in their original submission. The manufacturer stated that this reflected the most likely positioning of apremilast within future treatment pathways and that they did not expect apremilast to displace an existing biologic treatment, citing the chronic nature of psoriasis and the alternative mode of action of apremilast. Furthermore, the manufacturer argued that a direct displacement of biologic(s) was not considered to be the strategy with the largest clinical benefit (i.e. health maximising) over a patient's lifetime. The manufacturer also cited a written statement from Dr Anthony Bewley, a consultant

dermatologist at Whipps Cross University Hospital and the Royal London Hospital, to support this approach and to further justify the position of apremilast as the first therapy in the sequence.

Although the ERG acknowledge the justification provided by the manufacturer, it is our view that this represents an important restriction from a cost-effectiveness perspective. That is, an appropriate assessment of cost-effectiveness requires a comparison against all relevant and feasible options which clearly could encompass different positions for apremilast and a comparison of sequences where apremilast either extends a proposed sequence or displaces a therapy. Clearly some of the feasible sequences may not be consistent with a health maximising strategy over a patient's lifetime. However, the ERG considers that it is important to assess the relative cost-effectiveness of these different sequences since the most efficient (i.e. cost-effective) use and position of apremilast needs to be formally demonstrated rather than simply assumed. Furthermore, while some of the feasible sequences involving apremilast may not represent the sequence which maximises health benefits over the lifetime of a patient with psoriasis, this clearly does not obviate the need to demonstrate that the health maximising sequence is itself cost-effective.

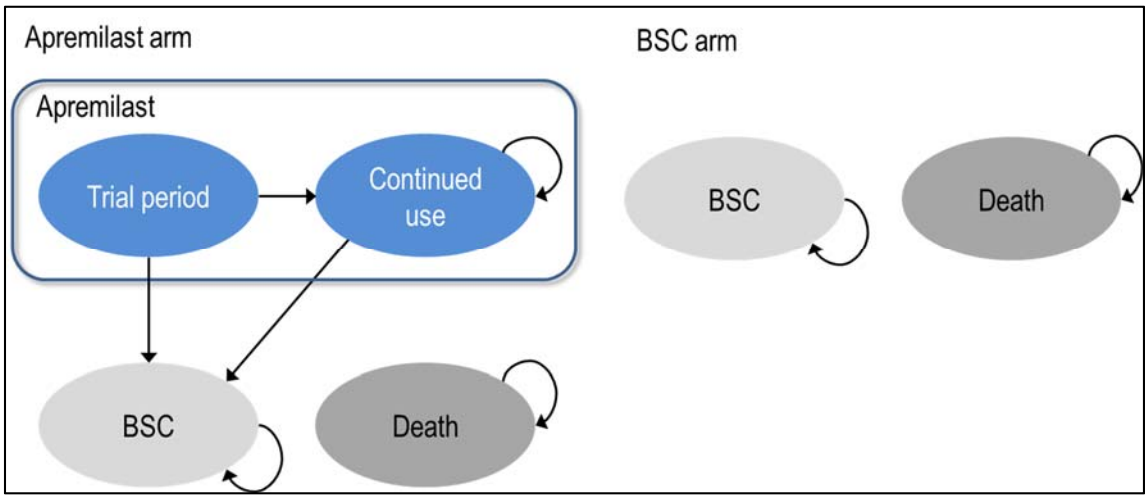
The lack of flexibility of the original model to assess the cost-effectiveness of apremilast at different points in the sequence did not allow the ERG to assess all relevant and feasible sequences, or even to verify the separate scenario analyses presented by the manufacturer where a comparison of a sequence using apremilast as the first and last lines of active therapy was presented. Furthermore, the ERG considered these restrictions appeared contrary to the NICE methods guide and the economic evaluation principle of including all relevant comparators.[19] As part of the points for clarification the ERG requested that the model be allowed to compare apremilast at different points in the treatment sequence and that the model be allowed to consider comparisons for which apremilast replaces an anti-TNF or ustekinumab. The manufacturer provided a more flexible model in their response to the points for clarification. While the updated model was more flexible in its ability to consider the full range of sequences requested by the ERG it was less flexible in other respects. For example, the Markov traces were removed from the original, and many of the spreadsheet calculations were replaced with Visual Basic code.

The analyses undertaken using this updated model are discussed further in Section 6.

<u>DLQI ≤ 10 model differences</u>

The manufacturer employed a similar model structure in the DLQI ≤ 10 population. The primary difference of structure is the approach to sequencing; the model used for this analysis is limited to a single comparator, BSC. This model structure is shown in Figure 4.

Figure 4: DLQI ≤ 10 base-case Markov model structure



The ERG considered BSC to be the appropriate comparator given current NICE recommendations.

5.2.2 The manufacturer's economic evaluation compared with the NICE reference case checklist

Table 16: NICE reference case checklist

Element of HTA	NICE Reference Case	Consistent in MS	Comment on whether de novo evaluation meets requirements of NICE reference case
Defining the decision problem	The scope developed by NICE	In part	The evaluation appropriately considers the use of apremilast within its licensed indication for treating moderate to severe plaque psoriasis, as in the scope. However, a restricted decision problem is presented as the base-case of apremilast as an additional first line of therapy prior to biologics.
Comparator(s)	As listed in the scope developed by NICE	In part	In the base-case analysis apremilast was compared in a sequence followed by adalimumab, etanercept and BSC (which incorporated methotrexate, cyclosporine and NBUVB) to the same sequence without apremilast. Scenarios were presented which included the biologic ustekinumab. The biologic infliximab and the non-biologic acitretin were not included in the evaluation. In a sequence approach all treatment positions should be considered as comparator strategies.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes	QALY benefits to treated individuals were taken into account. No impact on carers was considered.
Perspective on costs	NHS and PSS	Yes	NHS and PSS costs were taken into account
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes	
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	The base-case analysis followed a 10 year time horizon at which point 75% of the apremilast arm and 83% of the comparator arm were on BSC or dead. Additional scenarios changed the time horizon to 1, 5 and 40 years.
Synthesis of evidence on health effects	Based on systematic review	In part	A systematic review of clinical effectiveness was conducted. Trials that met the review criteria were synthesised via an NMA. The results of this analysis were used to inform the cost-effectiveness model. However, a pivotal trial (PROR-010) was not included in the NMA due to its time of publication. The population considered by the NMA is not always indicative of its use in the model.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of Health related quality of life in adults	Yes	Health effects are expressed as QALYs throughout. EQ-5D questionnaires were completed during the apremilast trials (PSOR-008, 009 and 010), however these were only used in the DLQI≤10 base-case, and a DLQI>10 scenario. The DLQI>10 base-case applied HRQoL decrements from published literature. These scores were originally calculated by mapping the change in DLQI associated with PASI responses for anti-TNF inhibitors to EQ-5D scores in HODaR.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	All additional QALYs are given the same weight.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	All costs relate to NHS and PSS resources.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes	Costs and health effects are discounted at 3.5% per annum.

5.2.3 Population

The MS evaluated the cost-effectiveness of apremilast in patients with moderate to severe plaque psoriasis who have failed to respond to or who have a contraindication to, or are intolerant to other systemic non-biologic therapies and who have a PASI ≥ 10. Two base-case populations are considered, those with DLQI > 10 and those with DLQI ≤ 10. As both models only consider the PASI ≥ 10 population (only differing in the DLQI score) future reference to the two populations will be made as either the 'DLQI > 10' or the 'DLQI ≤ 10' population.

The manufacturer does not define the disease severity of the modelled population nor do they present patient characteristics for the 'DLQI > 10' or 'DLQI ≤ 10' populations separately in the MS. However, the efficacy data used in the model came from populations described in the manufacturer's response to points for clarification A4 and summarized below (Table 17).

Table 17: The range of population characteristics reported for the trials used in the NMA

Studies	Number of studies	Range of % Male	Range of Mean Age (years)	Range of Psoriasis Duration (years)	Range of %BSA affected	Range of PASI score
All	24	54.3%-89.1%	35-51	11.1-23	21%-50.2%	14.5-33.1
Apremilast	5	56.8%-73.0%	43.3-47.0	16.6-19.8	21.0%-28.4%	18.1-20.3

The ERG considers, in the light of the CHMP opinion, it is appropriate to limit the patient population to those who have failed to respond to or who have a contraindication or intolerance to other systemic non-biologic therapies. The ERG also considers it appropriate to separately evaluation the two base-case populations given the differences in comparators that are appropriate for each population.

<u>DLQI ≤ 10 model differences</u>

The patient population in the additional base-case analysis presented by the manufacturer only differs in that they must have a DLQI ≤ 10. Such that they are those with moderate to severe plaque psoriasis who have failed to respond to or who have a contraindication to, or are intolerant to other systemic non-biologic therapies; a PASI ≥ 10; and a DLQI ≤ 10.

The manufacturer reports that 41.75% of patients in the PSOR-008 and 009 trials have a DLQI ≤ 10. However, it is unclear how many of these patients fulfil the full criteria outlined by the manufacturer as only 36% of patients in PSOR-008 and 38% in PSOR-009 had received prior conventional systemic therapies of any form. As such the generalisability of the trial data to the modelled population is uncertain.

5.2.4 Interventions and comparators

As discussed in Section 5.2.1, a treatment sequencing approach is taken to evaluate apremilast. The NICE scope required three forms of comparators to be considered:

- Systemic non-biological therapies (including acitretin, ciclosporin, methotrexate, phototherapy with or without psoralen);
- Systemic biological therapies (including etanerceptt, infliximab, adalimumab and ustekinumab);
- Best supportive care.

In the base-case analysis a single pairwise comparison of apremilast was considered. Apremilast was not considered versus systemic non-biological therapies nor was it compared directly against systemic biological therapies, but only in addition to a sequence. The ERG do not consider that the MS base-case analysis is consistent with the NICE scope.

The base-case cost-effectiveness evaluated apremilast in two distinct positions:

1. as an additional line of therapy before biologic therapy followed by a biologic therapy sequence and BSC for the management of patients with severe psoriasis as defined by a PASI ≥10 and DLQI >10:
    - **Apremilast sequence**: apremilast → adalimumab → etanercept → BSC
    - **Comparator sequence**: adalimumab → etanercept → BSC

2. as an additional line of therapy before BSC for patients with a PASI≥10 and DLQI ≤ 10 (and hence ineligible to receive biologic therapy under current NICE guidance):
    - **Apremilast sequence**: apremilast → BSC
    - **Comparator sequence**: BSC

All treatments considered in the model (with the exception of those considered part of BSC) are associated with an initial trial period as discussed in Section 5.2.1. The trial period represents the initial period over which a treatment is administered before a patient is deemed to respond or not. Table 18 reports the length of trial period for all of the treatments presented. A scenario analysis is presented in which the trial period of apremilast is extended from 16 weeks to 24 weeks. The ERG note that the trial duration of infliximab (10 weeks) is not perfectly divisible by the 28 day (4 week) cycle length used in the model presented.

Table 18: Lengths of trial period by treatment

Drug	Duration	Source
Apremilast	16 weeks	Celgene
Adalimumab (Humira®)	16 weeks	NICE(2008)[25] TA146
Etanercept (Enbrel®)	12 weeks	NICE(2006)[23] TA103
Infliximab (Remicade®)	10 weeks	NICE(2008)[24] TA134
Ustekinumab (Stelara®)	16 weeks	NICE(2009)[26] TA180

In addition to the base-case sequence the manufacturer presented a range of scenarios considering different sequences and comparators:

- Replacing etanercept in the sequence with ustekinumab (45mg subcutaneously every 12 weeks) in both arms;
- Removing etanercept from the sequence in both arms such that only one TNF (adalimumab) is included in the sequence;
- Adding ustekinumab as an additional line of therapy prior to BSC in both arms such that the sequence apremilast is added to consists of three biologics;
- Comparing the sequence with apremilast as a pre-biologic to the same sequence with it post-biologic.

The justification provided by the manufacturer for the proposed sequences and positioning of apremilast and the ERG concerns were previously discussed in Section 5.2.1. The ERG considered the base-case sequences proposed by the manufacturer represented a limited set of potentially relevant sequences and that the manufacturer's base-case cost-effectiveness results were not a sufficient basis to inform the most efficient use and positioning of apremilast. In particular the ERG was concerned with the following aspects:

1. The exclusion of sequences where apremilast might replace an existing therapy (or therapies) within an existing sequence;
2. The lack of flexibility in the original model to consider the use of apremilast at alternative points within a proposed sequence;
3. The restriction to a comparison of only two mutually exclusive strategies simultaneously.

The lack of flexibility and the restriction of only being able to directly compare two sequences simultaneously were considered by the ERG to be important limitations meaning that only partial assessments of cost-effectiveness could be provided.

The approach taken by the manufacturer raises an important issue with regards to treatment sequencing in psoriasis. The original 'York model'[6] only considered single lines of treatments, such

that once a patient had failed to respond to the treatment they were moved to BSC, this is also true of the analyses presented in subsequent TAs on psoriasis. The only analysis of systemic biologics used as second line treatment was undertaken by the NICE guidelines development group (CG153).[10] Within this guideline evidence on the effectiveness of ustekinumab and infliximab was meta-analysed and used to represent the second line use of all systemic biologics, since no second line data was available for adalimumab or etanercept. The meta-analysis of second line use showed that ustekinumab and infliximab were not as effective as in first line use. The guidelines development group also undertook a number of scenario analyses particularly on the cost and effectiveness of BSC, because of the uncertainty and influence of these parameters.

Although the ERG recognises that the use of a sequence of treatments for the treatment of psoriasis is reflective of the recommendations from the NICE Guideline,[19] the ERG is concerned that the manufacturer's base-case cost-effectiveness results are based on one specific comparator sequence (and use select scenarios to explore pairwise comparisons of others) without any formal demonstration that this specific comparator sequence is itself cost-effective and consideration of any implications for the cost-effectiveness of apremilast.

The ERG considered that additional flexibility in the model would allow a more formal evaluation of whether the length and/or position of treatments in the comparator sequence makes any material difference or not to the cost-effectiveness of apremilast. While such an analysis could provide a more appropriate assessment of the optimal position of apremilast, the ERG's initial interest was driven largely by the desire to understand the logic of the case presented by the manufacturer as well as any unintended consequences that might arise from the exclusion of particular sequences.

These concerns can be simply illustrated. Taking the TNF comparator sequence proposed by the manufacturer (adalimumab>etanercept>BSC). If one assumes that these 2 TNFs could actually be used in any order and apremilast could be positioned before or after the TNFs; then there are 6 relevant sequences which need to be compared:

- **Apremilast sequence 1**: apremilast → adalimumab → etanercept → BSC
- **Apremilast sequence 2**: apremilast → etanercept → adalimumab → BSC
- **Apremilast sequence 3**: adalimumab → etanercept → apremilast → BSC
- **Apremilast sequence 4**: etanercept → adalimumab → apremilast → BSC
- **Comparator sequence 1**: adalimumab → etanercept → BSC
- **Comparator sequence 2**: etanercept → adalimumab → BSC

Clearly if the alternative TNFs/ustekinumab and/or shorter/longer biologic sequences were to be considered then then the decision problem gets exponentially larger. However, even if the comparator sequence was fixed (i.e. length and order) and apremilast was only considered to add to an existing sequence, then a minimum of 3 sequences would still need to be compared: (i) a sequence with apremilast positioned first, (ii) a sequence with apremilast positioned last and (iii) a sequence without apremilast included. Even with a more restricted set of comparison based on apremilast and the 2 TNF inhibitors included in the base-case, it is evident that a more formal comparison of a broader range of sequences is needed to more formally assess any potential uncertainties surrounding the extent to which the cost-effectiveness of apremilast may be driven by uncertainties surrounding the cost-effectiveness of the comparator sequence.

The approach outlined by the ERG is also consistent with other STAs where sequential therapy has been a consideration. In 2010 the NICE technology appraisal committee assessing the use of tocilizumab for the treatment of rheumatoid arthritis requested that the NICE decision support unit (DSU) undertake additional analyses to understand the cost-effective sequence of biologic use. The DSU stated that:

"To establish the most cost-effective of the four strategies it is necessary to undertake a fully incremental analysis comparing all the sequences simultaneously. This is a central tenet of cost-effectiveness analysis and involves assessing the incremental cost of generating additional health effects when moving from one option to a more effective one, and assessing this against a relevant measure of opportunity cost (e.g. the NICE threshold). Calculating a series of pair-wise ratios between the alternative tocilizumab-based sequences and the standard of care is not appropriate when considering the optimal position of tocilizumab and, in particular circumstances can be misleading…" p.6 [28]

In the points for clarification the ERG requested an updated model that would allow these issues to be explored further. The manufacture provided an updated model that enabled apremilast to be positioned at any point in the pathway. However, the manufacturer declined the ERG's request to incorporate additional functionality to allow the simultaneous comparison of more than two strategies. In justifying their response the manufacturer stated:

"It is not clear to Celgene how the presentation of analyses comparing three or more mutually exclusive strategies simultaneously would provide any additional, useful information to the NICE technical team or the ERG on addressing the current decision problem as part of this STA". p.37

In addition to providing a more appropriate assessment of cost-effectiveness and ensuring that the cost-effectiveness of apremilast is not driven by the comparator sequence, the additional functionality would also increase the efficiency of undertaking the analyses (i.e. running one set of analyses as opposed to having to run multiple analyses for different treatment sequences), it would avoids error in transcription from combining different analyses and finally and most importantly allows probabilistic sensitivity analysis to be run using the same parameter simulations between comparators. While the ERG has subsequently undertaken a more thorough exploration of the sequence issue using the manufacturer's revised model, the restriction to only being able to include 2 strategies simultaneously means that the majority of ERG analyses presented in Section 6 are also limited to 2 simultaneous sequences, where >2 sequences are compared the results are based on deterministic results.

The ERG considers that due to the restricted NICE guidance on infliximab to psoriasis patients with very severe disease, as defined by a PASI ≥20 and DLQ I>18, it was appropriate to exclude it from the primary analysis. However, the ERG feel it would have been beneficial for the manufacturer to have presented an additional analysis of patients in this severe disease sub-group given its inclusion in the NICE Scope as well as the repeated reference to infliximab in the MS presented.

DLQI ≤ 10 model differences

In the additional base-case analysis the manufacturer argues that the NICE guidance's stipulation that patients are only eligible to receive biologics if they have both PASI ≥ 10 and DLQI > 10, means there exists a population with PASI ≥ 10 but DLQI ≤ 10 who are unserved by existing treatments post conventional systemic therapies.[10] The DLQI≤ 10 analysis considers apremilast followed by BSC against BSC alone, with no additional scenarios considering alternative therapies.

The ERG considers the manufacture's interpretation of the NICE guideline justifiable.

5.2.5 Perspective, time horizon and discounting

The perspective of the manufacturer's analysis was the NHS and Personal Social Services. An annual discount rate of 3.5% on both costs and health effects was applied, in line with NICE guidance. The time horizon of the model was 10 years, which was used to ensure consistency with previous evaluations.

The ERG notes that a 10 year time horizon implies that, by the end of the analysis, 75% of the apremilast arm and 83% of the comparator arm were in the BSC or dead states. Additional scenarios saw the time horizon change to 1, 5 and 40 years.

Additional scenario analyses are presented in which the discount rate on costs and outcomes are varied.

DLQI ≤ 10 model differences

The DLQI ≤ 10 base-case takes the same approach as the DLQI > 10 population with regards to perspective, time horizon and discounting. In this model at the end of 10 years 96% of patients in the apremilast arm are in BSC or dead. No scenarios analyses are presented for this population around these variables.

5.2.6 Treatment effectiveness and extrapolation

The main factor concerning treatment effectiveness in the MS represents the probability of improvement in psoriasis, by PASI response, by the end of each trial period of treatment. At the end of each trial period patients are considered to be able to achieve one of four health states, with a fifth of no PASI improvement (PASI0) applied to BSC alone:

- An improvement in their psoriasis of less than 50% using the PASI, i.e. PASI < 50;
- An improvement in their psoriasis of between 50% and 75% using the PASI, i.e. PASI50;
- An improvement in their psoriasis of between 75% and 90% using the PASI, i.e. PASI75;
- An improvement in their psoriasis of between 90% and 100% using the PASI, i.e. PASI90.

These parameters are informed by the NMA presented in Section 6.7 of the MS. The results of this NMA are reported in Table 19 below and are as presented in Table 20 of the MS. The ERG notes that the values presented in this table were not the same as those used to inform the original cost-effectiveness model presented and this was raised as a point for clarification. The manufacturer acknowledged this mistake and updated these values in the model resubmitted to the ERG with the values from the table below, these values are from the original NMA presented in the MS. The corrected values did not affect the manufacturer's conclusion.

Please note that the probability of PASI<50 is not reported as it simply represents those not achieving a PASI50, i.e. 1 – PASI50.

Table 19: Absolute probability of response for each treatment

	Mean	SD	Median	95% CrI
Probability of PASI-50				
Placebo	0.17	0.03	0.17	(0.12, 0.22)
Adalimumab 40 mg EOW w/ 80 mg loading	0.83	0.04	0.83	(0.75, 0.89)
Apremilast 30 mg bid	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25 mg biw/ 50 mg QW	0.70	0.05	0.70	(0.59, 0.8)
Infliximab 5 mg/kg at Week 0, 2, 6	0.95	0.02	0.96	(0.92, 0.98)
Ustekinumab 45 mg at Week 0, 4 and q12w	0.91	0.02	0.91	(0.87, 0.95)
Ustekinumab 90 mg at Week 0, 4 and q12w	0.93	0.02	0.93	(0.89, 0.96)
Probability of PASI-75				
Placebo	0.06	0.01	0.05	(0.04, 0.08)
Adalimumab 40 mg EOW w/ 80 mg loading	0.62	0.06	0.62	(0.51, 0.73)
Apremilast 30 mg bid	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25 mg biw/ 50 mg QW	0.45	0.06	0.45	(0.34, 0.57)
Infliximab 5 mg/kg at Week 0, 2, 6	0.85	0.04	0.85	(0.77, 0.91)
Ustekinumab 45 mg at Week 0, 4 and q12w	0.76	0.04	0.77	(0.68, 0.83)
Ustekinumab 90 mg at Week 0, 4 and q12w	0.80	0.04	0.81	(0.72, 0.87)
Probability of PASI-90				
Placebo	0.01	0.00	0.01	(0.01, 0.02)
Adalimumab 40 mg EOW w/ 80 mg loading	0.35	0.05	0.35	(0.25, 0.46)
Apremilast 30 mg bid	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 25 mg biw/ 50 mg QW	0.21	0.04	0.21	(0.13, 0.3)
Infliximab 5 mg/kg at Week 0, 2, 6	0.64	0.06	0.64	(0.52, 0.75)
Ustekinumab 45 mg at Week 0, 4 and q12w	0.51	0.05	0.51	(0.41, 0.61)
Ustekinumab 90 mg at Week 0, 4 and q12w	0.56	0.05	0.57	(0.46, 0.66)

As discussed in Section 4.4.1, the ERG requested an updated NMA including two trials that had not been included in the original MS. The manufacturer provided this updated NMA in the points for clarification which demonstrated only very small differences in the responses, but the manufacturer did not incorporate the results of the updated NMA in their base-case economic analysis.

The ERG notes that while probabilities associated with a placebo response are reported, no placebo response is included in BSC in the base-case model submitted, which assumed patients had no PASI improvement (discussed further in Section 5.2.7.1 below), nor is the placebo response deducted from the probability of response associated with other treatments. The manufacturer justified this approach saying that it was consistent with previous TAs (NICE TA's 103, 134, 146 and 180).[26] However, as discussed further in Section 5.2.7.1 this approach is inconsistent with the CG153 approach.[10] In addition, it is not clear to the ERG that the approach taken is consistent with previous TAs, as the

available documentation in the TAs gives no definitive indication that patients on BSC are assumed to have a PASI0 response. Previous TAs typically refer to the use of response rates from reported NMAs with no clear indication that placebo responses are not incorporated into the efficacy of BSC.

In the base-case model the probability of achieving the different PASI levels of response was assumed to be independent of the point in the sequence it was used, i.e. all treatments were assumed to be equally effective at inducing a response whether they were used first line or fifth line. This assumption is not supported by CG153[10] which found that a meta-analysis of ustekinumab and infliximab resulted in lower results when used as second line. The manufacturer also assumed that the types of previous treatments did not influence the effectiveness of subsequent lines of therapy. No justification for these assumptions was offered by the manufacturer.

A patient who achieves a PASI75 improvement or greater during the trial period of the treatment is assumed to have achieved an adequate response to the treatment and moves to continued use of that drug. This definition of adequate response is consistent with previous studies and the NICE Guideline.[10]

If patients are judged to have had an adequate response to the treatment and move to its continued use they face a probability of withdrawal from that treatment of 1.70% per 28 days (the cycle length used). This withdrawal rate is based on a 20.0% annual dropout rate as applied in the York Model and a number of recent studies.[6] However, an important assumption in the model is that all treatments are assumed to have the same withdrawal rate, including apremilast. The ERG considers that this is an area of uncertainty which has not been fully justified or explored.

The manufacturer has undertaken additional scenario analysis using an alternative withdrawal rates (i.e. based on a higher annual estimate of [redacted]% from the second year of the PSOR-008 trial). In this scenario analysis the same estimate is applied to apremilast and all other biological therapies. While this approach allows investigation of the robustness to the absolute withdrawal rate, it does not address uncertainties concerning whether it reasonable to assume the same withdrawal rate for the existing biologics (TNF inhibitors and ustekinumab) and apremilast. Given the different forms of administration, their separate mechanisms of action and the difference in their efficacy, the ERG considers that there are additional uncertainties regarding this assumption that need to be explored further. During clarifications the manufacturer identified the estimate of [redacted]% annual withdrawal was incorrect and should have been [redacted]%. Additional results were presented by the manufacturer showing that the use of this updated result did not change the conclusion of the base-case cost-effectiveness analysis when all treatments were assumed to have the same withdrawal rate.

A background probability of mortality conditional on age is applied using life tables for England and Wales (ONS).[29] This represents the only mortality effect included in the model and is independent of treatment.

DLQI ≤ 10 model differences

As with the DLQI > 10 population analysis, efficacy of treatment is defined by PASI response category. Table 20 below provides the estimated efficacy rates for patients with baseline DLQI ≤ 10 used in this model. The results are reported in the MS as being drawn from the PSOR-008 and PSOR-009 trial sub-populations with a DLQI ≤ 10.

Table 20: Efficacy rates for patients with baseline DLQI ≤ 10

Parameter	Estimate
PASI-90	[redacted]
PASI-75	[redacted]
PASI-50	[redacted]

The only difference in the effectiveness of apremilast between the DLQI>10 analysis and the DLQI≤ 10 analysis are the response rates used in the model. Withdrawal and mortality rates were assumed to be the same between the two populations. The manufacturer also assumed no BSC response for this population.

5.2.7 Health related quality of life

Health related quality of life (HRQoL) outcomes are attributed to the different PASI response categories used within the cost-effectiveness model. As discussed in Section 5.2.1 and 5.2.6 the model considers patients to be in one of five health states at all times (excluding death) based on the change in their PASI score from baseline:

- No improvement in PASI from baseline, i.e. PASI0;
- An improvement in their psoriasis of less than 50% using the PASI, i.e. PASI < 50;
- An improvement in their psoriasis of between 50% and 75% using the PASI, i.e. PASI50;
- An improvement in their psoriasis of between 75% and 90% using the PASI, i.e. PASI75;
- An improvement in their psoriasis of between 90% and 100% using the PASI, i.e. PASI90.

To quantify the HRQoL associated with each of these health states the manufacturer applies the utility gains associated with each of the PASI improvement categories published in the York model[6] and applies them to a baseline score from published literature.[30] Table 21 below provides the baseline HRQoL score used and the respective increments.

Table 21: Utility scores by PASI response used in model

Variable		HRQoL score/increment	Source
Baseline HRQoL, PASI0		0.7	Revicki [30]
Increments	PASI < 50	0.05	Woolacott[6]
	PASI50	0.17	
	PASI75	0.19	
	PASI90	0.21	

As each treatment is associated with a different proportion of patients achieving the different levels of PASI response, each treatment is associated with a different HRQoL. In the base-case the manufacturer assumes that BSC is associated with no improvement in PASI and patients on BSC have the same HRQoL they had at baseline, i.e. 0.7.

This approach is justified through a number of arguments. Firstly, while EQ-5D was directly collected in the apremilast trials PSOR-008, 009 and 010, for all arms (i.e. covering apremilast, placebo and etanercept across the three trials) as the trials did not include all biologics compared in the MS (i.e. adalimumab, ustekinumab and infliximab) the use of this data was excluded from the base-case analysis. A scenario analysis is presented in which EQ-5D data from the pooled PSOR-008 and 009 trials are used (see Section 5.3 for further details on sensitivity analyses).

Secondly, data from the PSOR-010 trial was used to justify the use of the same estimates for apremilast as for biologics. The manufacturer argued that the mean change from baseline EQ-5D scores appeared similar in the apremilast and etanercept arms of the trial for different PASI response categories, as shown in Table 22 below, and therefore apremilast could be assumed to have the same HRQoL for a given change in PASI score.

Table 22: Mean change from baseline in EQ-5D scores at week 16 of PSOR-010, ± SD

Endpoint	APR 30 mg bid	ETN 30 mg bid
PASI50	[redacted]	[redacted]
PASI75	[redacted]	[redacted]
PASI90	[redacted]	[redacted]

Finally, the justification for using the baseline estimate of HRQoL from Revicki[30] and utility increments from Woolacott[6] was to maintain consistency with previous HTA submissions for biologic agents in this disease.

As noted by the manufacturer in Section 7.4.4 of the MS, the utility values used in Woolacott were obtained through the mapping of DLQI to EQ-5D through the use of an ordinary least squared (OLS) regression model. This mapping was conducted using data from the Health Outcomes Data

Repository (HODaR) which collects both DLQI and EQ-5D. The completed mapping could then be used to consider how, given treatment, patients' improvements in PASI score coincided with improvements in DLQI score, and through the mapping algorithm, EQ-5D. The manufacturer's use of the HRQoL increments reported by Woolacott is equivalent to assuming the same change in DLQI within each PASI category as reported in the etanercept trials. Furthermore, as this set of values is applied to all treatments the assumption is that all treatments are associated with the same change in DLQI within each PASI category. A more appropriate approach might have been for the manufacturer to use the same mapping function reported by Woolacott[6] but to apply the function to the change in DLQI data within each PASI category reported in the apremilast trials.

Since Woolacott[6] several other studies have reported mapping algorithms linking change in DLQI to change in EQ-5D. The original Woolacott estimation contained 86 patients' responses from HODaR. The original algorithm was deemed to be confidential, however, in their submission to NICE for the consideration of ustekinumab in this population, Janssen and Cilag Ltd. re-estimated the Woolacott algorithm.[26] The mapping algorithms presented in these studies (including the Woolacott re-estimation) are presented in Table 24.

The ERG requested additional data in the points for clarification on the change in DLQI by PASI response category from the trials. The manufacturer provided DLQI by PASI response for all patients and for each of the populations considered in the model (DLQI>10 and DLQI≤10). The ERG used these DLQI scores to estimate HRQoL from the Woolacott mapping, and compared them to the HRQoL estimated by Woolacott from the etanercept DLQI change scores. The ERG additionally requested the direct EQ-5D observations from the combined trials. Additional exploratory analyses using these alternative approaches are reported in Section 6 using the different HRQoL estimates presented in Table 23 below.

Table 23: HRQoL by PASI score scenarios

Scenario	PASI<50	PASI50-75	PASI75-90	PASI>90
DLQI>10 estimates				
Manufacturer's base-case	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D observed from combined PSOR-008/009/010 trials	[redacted]	[redacted]	[redacted]	[redacted]
DLQI mapped from the combined PSOR-008/009/010 trials using the Woolacott mapping function	[redacted]	[redacted]	[redacted]	[redacted]
DLQI≤10 estimates				
Manufacturer's base-case: rounded EQ-5D observed from combined PSOR-008/009	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D observed from combined PSOR-008/009/010 trials	[redacted]	[redacted]	[redacted]	[redacted]
DLQI mapped from the combined PSOR-008/009/010 trials using the Woolacott mapping function	[redacted]	[redacted]	[redacted]	[redacted]

The ERG are unable, given the lack of available data, to determine the impact of using all of the different mapping algorithms presented in Table 24 on the cost-effectiveness estimates. In addition, it should be noted that the mapping algorithm used in the MS, Woolacott,[6] reported the lowest R^2 value of any of those presented in Table 24. The manufacturer made no attempt to implement other mapping algorithms available in the literature. Algorithms such as Heredi's[31] multivariate algorithm which was associated with an R^2 of 0.488 in 200 patients might be considered more appropriate. The need to undertake this analysis is also tempered by the opportunity to use direct EQ-5D estimates. The use of such mapping functions to estimate HRQoL is discussed by Norlin, who concludes that:

'When assessing psoriasis treatments and making decisions about treatment guidelines and resource allocation, EQ-5D, DLQI and PASI provide a useful set of complementary tools, answering to different needs. If EQ-5D is not included in the original trial the second-best option in cost-effectiveness studies is to use mapping between DLQI and EQ-5D' abstract[32]

This is also supported by the NICE methods guide which states:

"When EQ-5D data are not available, these data can be estimated by mapping other health-related quality of life measures or health-related benefits observed in the relevant clinical trial(s) to EQ-5D. The mapping function chosen should be based on data sets containing both health-related quality of life measures and its statistical properties should be fully described, its choice justified, and it should be adequately demonstrated how well the function fits the data. Sensitivity analyses to explore variation in the use of the mapping algorithms on the outputs should be presented."[19]

The ERG further notes that the Woolacott algorithm used in the MS was associated with the lowest correlation between utility and DLQI of the simple algorithms reported. As such the use of Woolacott is likely to favour apremilast which would be expected to have a worse improvement in DLQI by PASI response category than other biologics given its lesser efficacy.

There are three main problems with the manufacturer's chosen HRQoL. Firstly and most importantly, the HRQoL estimates used are based on mapping, when EQ-5D data are available from the trial. Secondly, the mapping algorithm chosen has not been appropriately justified (aside from an argument of consistency with previous NICE TAs) considering that there are other published algorithms with better predictive statistics. Finally, the DLQI scores used to inform the algorithm are from etanercept. The manufacturer has demonstrated that EQ-5D scores in their trial PSOR-010 are similar at different PASI levels for etanercept and apremilast, however to justify using an algorithm based on DLQI, comparisons of DLQI between treatments would be more relevant.

The ERG therefore conclude that the manufacturer's approach to HRQoL is subject to several assumptions and uncertainties. The ERG considers the most appropriate approach would have been to present a base-case that used direct EQ-5D estimates, an approach presented in Section 6.

<u>DLQI ≤ 10 model differences</u>

The approach taken by the manufacturer in the DLQI ≤ 10 is structurally identical to the main base-case presented, with a range of HRQoL increments based on PASI response category applied to a baseline score. The same baseline score is used, that of Revicki,[30] a score of 0.7. However, rather than utilising the HRQoL increments from Woolacott the manufacturer uses utility scores collected directly from the PSOR-008 and 009 trials, collected from patients in the trial with DLQI ≤ 10. As noted above, both of these trials (as well as PSOR-010 which is not included in this analysis) directly collected EQ-5D from patients. The values used are reported in Table 23. The ERG notes the apparent inconsistency in the EQ-5D observed from the combined PSOR-008/009/010 trials for the DLQI ≤ 10 reported in Table 23, whereby utility scores are higher for PASI50-75 improvement than PASI75-90. As such in the additional analyses conducted in Section 6 the ERG uses the manufacturer's base-case utilities for this population rather than these inconsistent values.

No justification was provided by the manufacturer for the different approach taken in the DLQI ≤ 10 population. As this analysis only considers apremilast and BSC as available treatments no assumptions about the applicability of this data to other treatments is required.

The ERG considers the use of direct EQ-5D from the trial is appropriate. However, it is not clear why the manufacturer did not also include the HRQoL scores for this population from the PSOR-010 trial,

especially as HRQoL scores are used from this trial to justify the similarity of apremilast to etanercept (see Table 38, p151 of the MS). In addition, the ERG feels it is not appropriate to apply the same baseline utility to these values as in doing so the manufacturer is implicitly assuming that starting DLQI score has no impact on HRQoL, which seems to contradict the relationship between DLQI and EQ-5D as well as the use of Woolacott to inform the DLQI ≥ 10 population analysis.

Table 24: Change in DLQI to EQ-5D mapping algorithms in the literature

Variable	Norlin PASI<10 [32]	Norlin PASI≥10 [32]	Blome EQ-5D VAS [33]	Blome EQ-5D VAS [33]	Heredi [31]	Heredi [31]	Currie [34]	Ustekinumab MS, re-estimation of Woolacott [26]	Ustekinumab MS [26]
R^2	Not reported, 0.2799 for combined PASIs		0.242	0.313	0.169	0.488	0.27	0.1315	Not reported
Constant	0.8781	0.8789	77.367	93.002	0.8	1.026	0.956	0.8554	0.908
DLQI	-0.0197	-0.0201	-1.493	-1.418	-0.02	-0.080	-0.2548	-0.0162	-0.016
PASI				-0.153					
active arthritis				-4.728		-0.134			
concomitant disease				-3.563					
light/laser therapy				2.252					
age				-0.256					
#psoriasis hospitalisations, year				-1.104		-0.104			
Gender (female)						-0.090			
Psoriasis duration						-0.004			
Chronic plaque psoriasis						-0.089			
Palmoplantar psoriasis						-0.347			
Scalp psoriasis						0.152			
#psoriasis GP visits, month						-0.160			
Use of home help						-0.139			

5.2.7.1 HRQoL and health improvements in BSC

In the MS patients receiving BSC are assumed to have a constant HRQoL score, modelled at the baseline value. This baseline level, as discussed in Section 5.2.7, is 0.7 and is based on published literature.[30] No justification is given for the use of an external baseline estimate rather than from the clinical trials. However, the ERG notes as it is the difference from baseline that drives cost-effectiveness this would not impact the incremental result.

It is important to consider this approach against previous cost-effectiveness models. The NICE guideline development group took the following approach.

'In the base-case, effectiveness of best supportive care was assumed to be based on the placebo response data from the clinical review. This was tested in a series of one-way sensitivity analyses in which the effectiveness of best supportive care was varied first to assume that best supportive care was not at all effective (0% response), and then to match response data measured in a UK observational study by Woods and colleagues' p671[10]

Woods et al.[35] reports the results from a multi-centre service review conducted in four dermatology departments in the UK. Over a nine month period data was collected for 183 patients to determine which factors predicted length of stay for patients with psoriasis. The aim was to propose a standard for the length of stay required for patients admitted with different severities of psoriasis, as measured by PASI score. The study inclusion criteria did not stipulate the stage of treatment patients had to be at. Woods finds a significant correlation between PASI score at admission and length of stay and reports the proportion of patients achieving PASI50 at the time of discharge. These estimates were used to inform the CG153 scenarios on the effectiveness of BSC.

As noted in Section 5.2.6 this differs to the approach taken in the MS, which assumed no placebo effect associated with BSC. This comparison is important as it seems inconsistent for the manufacturer not to use the guideline development group's approach to BSC effectiveness but to use their approach to the cost of BSC, as discussed in Section 5.2.8.3. Table 25 provides the treatment effects associated with BSC in the guideline development group's approach. These are compared to the treatment effects associated with the second line biologic treatment effectiveness, as modelled in CG153, to give the BSC treatment effects context.

Table 25: Treatment effects used in CG153 analysis, probability of response

	Median	2.5% CI	97.5% CI
Response = PASI50			
Best supportive care	3.8%	3.3%	4.4%
Biologic therapy	79.4%	70.4%	86.7%
Response = PASI75			
Best supportive care	0.8%	0.6%	1.1%
Biologic therapy	57.3%	46.1%	68.2%
Response = PASI90			
Best supportive care	0.1%	0.1%	0.2%
Biologic therapy	31.9%	22.6%	43.0%

In addition CG153 presented three scenarios around the effectiveness of BSC:

Scenario 1: effectiveness assumed to be zero, i.e. no one receiving best supportive care achieved a PASI50 or higher;

Scenario 2: effectiveness based on observations from Woods[35] wherein 65% of people admitted for inpatient treatment with baseline PASI10 to 20 achieved PASI50;

Scenario 3: effectiveness based on observations from Woods[35] wherein 83% of people admitted for inpatient treatment with baseline >PASI20 achieved PASI50.

Similarly, the original York model constructed by Woolacott et al.[6] assumed a probability of beneficial treatment effects associated with BSC, these are presented in Table 26.

Table 26: Treatment effects used in Woolacott analysis, probability of response

	Mean	2.5% CI	97.5% CI
Response = PASI50			
Best supportive care	14%	12%	16%
Etanercept (50mg)	76%	54%	92%
Infliximab	93%	81%	99%
Cyclosporine	80%	66%	92%
Methotrexate	82%	50%	98%
Response = PASI75			
Best supportive care	3%	2%	4%
Etanercept (50mg)	50%	25%	74%
Infliximab	79%	55%	95%
Cyclosporine	55%	37%	75%
Methotrexate	59%	23%	89%
Response = PASI90			
Best supportive care	0%	0%	1%
Etanercept (50mg)	22%	7%	43%
Infliximab	52%	24%	79%
Cyclosporine	25%	12%	45%
Methotrexate	31%	6%	66%

These results can be directly compared to the manufacturer's NMA results (Table 19) which showed a mean (median) estimated placebo response for PASI50, PASI75 and PASI90 of 17% (17%), 6% (5%) and 1% (1%) respectively, showing a similar scale of response in the manufacturer's NMA as the original Woolacott analysis but much greater than used in the base-case CG153 analysis.[10] However, as noted these was not used in the base-case model, instead the manufacturer assumed all patients on BSC would have a PASI0 improvement (i.e. no improvement from baseline).

The ERG sought clarification as to why the manufacturer made this assumption and requested additional analysis using the approaches proposed in CG153[10], using the data from Woods.[35]

The manufacturer responded to the ERG request stating that BSC having no effect is consistent with previous submissions to NICE.[26] However, as the ERG has noted this approach is not consistent with the original York model or the model used in CG153.[10]

In response to the ERG's request for additional analyses the manufacturer stated that a scenario was presented in the original submission which used the CG153 base-case placebo response and that their clinical advisors had expressed a belief that it was unlikely that after failing multiple lines of therapy patients would experience any significant benefit in skin clearance from BSC alone. The

manufacturer additionally argued that the use of the placebo response estimates from the NMA were not a fair representation of the modelled position of BSC given that the placebo populations in the trials had not failed multiple lines of biologics. Similarly the additional scenario presented using the results from the Woods[35] study was argued to be an improbable one, no additional reason was given as to why this study was not thought to be representative of the decision problem modelled.

DLQI ≤ 10 model differences

The manufacturer took the same approach to modelling the HRQoL and health of patients in the DLQI≤10 population analysis. It is not clear to the ERG that those patients who have failed biologics in the DLQI>10 analysis, will have the same BSC or response to BSC as patients who are biologic naïve, i.e. those in the DLQI≤ 10 population. The ERG considered that the position of BSC in the DLQI≤ 10 model was similar to placebo in the manufacturer's trials. The ERG considered the placebo effect from the manufacturer's trials as an appropriate estimate of the effect of BSC in DLQI≤ 10 population.

5.2.8 Resources and costs

The resource use and costs detailed in the MS include the costs of the intervention and comparators (i.e. drug acquisition and administrative costs, monitoring and laboratory costs) and other healthcare costs related to the separate health states of the model (e.g. additional costs incurred due to non-response and the costs of BSC).

The general approach to estimating resource use by the MS is argued to be consistent in several key aspects with the approach and estimates applied within the previous CEA undertaken to support NICE CG153.[10] In particular, the manufacturer uses resource use and cost estimates reported in CG153 for two key input parameters: (i) the costs of non-responders during the trial period of a subsequent line of therapy and (ii) the costs of BSC. The ERG considers that these input parameters are critical to the robustness and validity of the manufacturer's cost-effectiveness results. The appropriateness of using estimates from CG153 and specifically their generalisability to the manufacturer's stated decision problem (and separate populations) is a key consideration in the following sections.

5.2.8.1 Treatment and administration costs

All treatments, except infliximab, were assumed to be self-administered and were therefore not associated with any treatment cost beyond the acquisition price of the drug, this includes both subcutaneous and oral treatments. The model includes an administrative cost of infliximab which is assumed to require an inpatient hospitalisation. These assumptions are in line with the base-case analysis presented in the CG153 cost-effectiveness analysis.[10]

Pharmacological costs for the biologic therapies included in the MS were obtained from the British National Formulary,[21] with the cost of apremilast provided by Celgene. Ustekinumab is the only biologic with a patients access schemes (PAS) in the treatment of this population. According to the PAS the 90mg dose is the same price as the 45mg dose. All costs are based on usage from EMA guidelines.[1]

The treatment costs per cycle are reported in Table 27 below. The ERG considers the application of these costs within the manufacturer's model to be appropriate.

Table 27: Treatment and administration costs per cycle

Items	Apremilast	Adalimumab	Etanercept	Ustekinumab
Treatment unit cost	£9.82	£352.14	£89.38	£2,147.00
Source for treatment cost	Celgene	BNF[21]	BNF	BNF
Dosage description	30mg twice daily	80mg initial dose followed by 40mg every other week starting one week after initial dose	25mg twice weekly	45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks (all patients assumed <90kg)
Treatment cost per cycle	Cycle 1: £540.18 Cycle 2: £550.00 Cycle 3: £550.00 Continued use: £550.00	Cycle 1: £1,408.56 Cycle 2: £704.28 Cycle 3: £704.28 Continued use: £704.28	Cycle 1: £715.04 Cycle 2: £715.04 Cycle 3: £715.04 Continued use: £715.04	Cycle 1: £2,147.00 Cycle 2: £2,147.00 Cycle 3: £0.00 Continued use: £715.67

5.2.8.2 Monitoring and laboratory costs

A range of monitoring and laboratory costs are considered which include regular physician visits, as presented in Table 28.

Table 28: Monitoring and laboratory resource use

Items	Apremilast	Adalimumab	Etanercept	Ustekinumab
Physician visits	[redacted]	**Two** outpatient visits during the trial period, and **four** times a year thereafter during continued use. GDG (2012)		
Laboratory tests	[redacted]	Cycle 1: FBC, LFT, U&E Cycle 2: no tests Cycle 3: FBC, LFT, U&E Continued use: **4 FBCs, 4 LFTs, 4 U&Es**		

FBC-Full blood count, LFT-liver function test, U&E-urea and electrolytes

Application of unit costs from the NHS reference costs 2012-13[20] and the Woolacott study[6] to all monitoring and laboratory costs results in the costs per cycle reported in Table 29.

Table 29: Cost per cycle (28 days) of monitoring and laboratory tests

Cycle	Apremilast	Adalimumab	Etanercept	Ustekinumab
Cycle 1	£117.24	£117.24		
Cycle 2	£0.00	£0.00		
Cycle 3	£103.63	£103.63		
Continued use	£7.60	£31.89		

As shown in Table 28 and Table 29 the only difference in the monitoring and laboratory tests across the evaluated treatments (not including cyclosporine and methotrexate which form part of BSC and infliximab which is not presented in any sequence in the MS) is around continued use. The manufacturer assumes that patients on apremilast require three less physician visits per year than its comparators and no laboratory test. The ERG considers that the assumptions leading to this difference in resource use associated with continued use of apremilast versus other treatments is not adequately justified , and while associated with a small cost per cycle difference (£24.29) over an extended period of time it represents an important potential driver of the cost-effectiveness of apremilast. Discussions with our clinical advisor suggested that the monitoring was likely to be similar in practice given that many patients will continue to receive other therapies and also concerns expressed regarding whether clinicians would prescribe a drug at this cost for such an extended period of time. The length of the prescription will be important as the more medication prescribed at one time could result in the potential for more wasted medication when the patient withdraws, conversely the more frequently the medication is prescribed may result in additional physician costs. The prescription and wastage of apremilast is not discussed in the MS. The ERG consider further scenarios in Section 6 around these potential costs.

5.2.8.1 Adverse event costs

No adverse event costs associated with treatment are explicitly considered in the MS. The manufacturer argues this is likely to represent a conservative approach for apremilast since it is likely to be associated with fewer serious adverse events compared to other biologic therapies. However, while the logic of this argument would appear reasonable if apremilast were to replace an existing therapy within an existing sequence, this clearly doesn't hold when apremilast is being assumed to be added to an existing sequence. Consequently, the ERG considers that the exclusion of adverse events is optimistic rather than conservative towards apremilast.

5.2.8.2 Health-state costs - Hospitalisations

For all subsequent lines of treatment in the model, additional healthcare costs are assumed for non-responders during subsequent trial periods. The manufacturer stated that in the absence of published data on the rate of hospitalisation in patients with psoriasis, all non-responders are assumed to require hospitalisation. The hospitalisation costs assigned to non-responders is summarised in Table 30. The duration of the hospitalisation is based on the average number of annual impatient days as reported in the cost-effectiveness analysis from the NICE CG153,[10] an estimate of 20.8 days. The manufacturer subsequently adjusts this estimate by the cycle length of the model to estimate an average number of inpatient days per cycle for those who withdraw from first line treatment of 1.60 days (20.8/13). The cost of this hospitalisation is also based on the estimated cost of a 20.8 day hospitalisation from the Psoriasis Costing Report,[22] which estimated a cost of £5,876. This estimate of £5,876 is inflated to 2012-13 prices and adjusted by the number of cycles per year by the manufacturer to give an estimate of the hospitalisation cost per cycle. The manufacturer makes an important assumption that the same hospitalisation costs for non-responders would be incurred in both the DLQI>10 and DLQI≤10 populations.

Table 30: Hospitalisation costs

Parameter	Estimate	Source
Average inpatient days per year	20.80	NCGC – Appendix P[10]
Average inpatient days per cycle	1.60	NCGC – Appendix P
Hospitalisation cost per 20.8 days	£5,876.00	Psoriasis costing report[22]
Implied hospitalisation cost per cycle	£462.56	Psoriasis costing report

NCGC, National clinical guidelines centre

The ERG considers that using resource estimates from the NICE CG153 is an important assumption that is not fully justified or explored by the manufacturer. Since the same source is also used to estimate the costs of BSC, a more detailed critique is undertaken in the next section.

5.2.8.3 Health-state costs - BSC

The most significant parameter input which underpins the validity and robustness of the cost-effectiveness results is the cost assigned to patients who receive BSC. Based on the manufacturer's view that apremilast would extend an existing treatment sequence (as opposed to displacing an existing therapy within the existing sequence), the main drivers of cost-effectiveness are inevitably the different HRQoL and cost assumptions applied to patients receiving apremilast compared to those receiving BSC. That is, the inclusion of apremilast as an additional line of therapy in existing treatment pathways extends the time taken for the average patient to reach the BSC state. Consequently, since the addition of apremilast is not assumed to affect either the number, order or effectiveness of subsequent biologic therapies, the value of apremilast is ultimately driven by the difference in costs and outcomes while they receive apremilast versus those that they would otherwise incur (i.e. BSC costs).

As shown in Table 31 the manufacturer assumes a cost of £887.90 per cycle for BSC (approx. £11,543. per year). Importantly, the cost per cycle applied to BSC is greater than the costs assigned to the continuous use (i.e. for responding patients) of any of the active treatments presented in the MS (including their respective monitoring requirements). Since the manufacturer assumes that the costs of active treatment are not additive to the costs of BSC, it logically follows that the period of time a patient is receiving continuous use of an active therapy, it will dominate BSC (i.e. assuming the active therapy is not less effective than BSC). This is a critical assumption and the differences in the costs assumed for active therapies vs BSC is the main factor which drives the subsequent cost-effectiveness results and subsequent conclusions from the manufacturer (i.e. that a sequence adding apremilast as an extra therapy dominates a sequence without it).

Table 31: Total cost per cycle of treatments and BSC

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

Although the manufacturer undertook a separate review of relevant resource data for the UK (Section 7.5.3 p155-157) no formal justification for using the costs of BSC from the NICE CG153[10] were provided and only limited sensitivity analyses were presented. The ERG consider that this is an important limitation of the submission and this aspect is further explored in this section and in the exploratory analyses reported in Section 6.

Table 32 and Table 33 summarise the annual resource use assumed for BSC from the MS (Table 32) and other sources including NICE CG153 (Table 33). As shown in Table 32 all of the cost estimates used in the MS to estimate the annual cost of BSC are drawn from CG153, the ERG believes the total annual cost difference between the two (£10,730.00 in CG153 versus £11,542.73 in the MS) is the result of both inflating of the unit costs to 2012-13 prices as well as the use of a more expensive form of cyclosporine (discussed further in Section 6). The ERG also notes the CG153 incorporated a maximum of 2 years of cyclosporine, which was not incorporated into the MS model.

The costs from CG153 were reported to be based on discussions with the guideline development group, evidence from two retrospective cohort studies and assumptions made in previous NICE technology appraisals. Accordingly, the results from CG153, given in Table 33, were reported in CG153 to provide a working definition of BSC, in the context of patients with moderate to very severe plaque psoriasis who are being considered for further biologic therapy. The ERG has three specific concerns regarding the use of these estimates by the manufacturer. Firstly, it is not clear whether the context in which the working definition of BSC were provided can be generalised to the manufacturer's proposed positioning of apremilast (i.e. at the point at which patients are being considered for their first biologic therapy). Secondly, it is not clear whether the working definition can be generalised to the DLQI≤10 population since this group of patients is not currently eligible for biological therapies. Finally, the guideline development group recognised there were substantial uncertainties in these model parameters which were then subject to extensive sensitivity analysis. CG153 stated that each of these were considered when making the guideline recommendations.

Table 32: BSC costs in MS

Treatment	**Percentage of patients receiving treatment**	**Annual resource use**	**Unit (annual) cost** *(calculated by ERG)*	**Total annual cost**	**Source**
Non-biologic + monitoring cost					
Methotrexate	45%	N/A	£38.48 + £150.67	£85.12	CG153 (inflated)[10]
Cyclosporine	45%	N/A	£3,058.64 + £150.80	£1,527.20	CG153 (inflated)
Other treatments					
Day centre care	100%	5 visits	£371.07	£1,855.35	CG153 (inflated)
NBUVB	16%	24 sessions	£87.15	£334.66	CG153 (inflated)
High need	82%	20.8 days in hospital	£289.10	£4,930.89	CG153 (inflated)
Very high need	18%	53.04 days in hospital	£289.10	£2,760.10	CG153 (inflated)
Physician visits	10%	5 visits	£98.85	£49.43	CG153 (updated reference cost)
Average annual cost				**£11,542.73**	

Table 33: Comparison of different annual cost of BSC approaches

Study	Population considered	Base-case resource use assumption, per year if not otherwise stated				Total cost per year as reported	Additional cost scenarios considered
		Treatments included	Outpatient visits	Day centre care	Hospitalisations		
Apremilast for psoriasis	Post biologic moderate to severe psoriasis (same approach for DLQI > and ≤10 models)	45% of patients receive methotrexate, 45% cyclosporine continuously , 16% have 24 sessions of NBUVB a year	10% of patients have 5 visits	All patients have 5 visits	82% of patients (high need) have 20.8 days hospitalised, 18% (very high need) have 53.04 days hospitalised	£11,542.73	None
CG153[10]	Post biologic moderate to severe psoriasis	45% of patients receive methotrexate, 45% cyclosporine continuously **(maximum 2 years)**, 16% have 24 sessions of NBUVB a year	10% of patients have 5 visits	All patients have 5 visits	82% of patients (high need) have 20.8 days hospitalised, 18% (very high need) have 53.04 days hospitalised	£10,730.00	Extensive sensitivity analysis conducted, see table 178 p673 of GDG 153
Ustekinumab TA[26]			2		One 21 day hospital stay per year	£6,209.54	Length of stay adjusted to 17.5 and 27.5 days
Woolacott[6]			2			£113.20	Replacement of assumption around PASI75 hospitalisation with 21 day stay for all BSC patients

Table 33 further shows how the NICE CG153 estimates and those assumed by the manufacturer compare to those used in the previous MTA Woolacott and the most recent STA for ustekinumab. The initial model, that of Woolacott et al.,[6] only assumed an additional cost per year of BSC of £113.20, associated with two additional outpatient visits. A scenario was also presented in Woolacott considering an additional 21 day hospitalisation per year for all non-responders (on treatment and on BSC), based on data on mean length of stay for psoriasis and two local audits.

The ustekinumab TA base-case analysis assumed an annual cost of £6,209.54 for all non-responders (as the TA, similar to Woolacott, only considered one line of treatment non-responders were always those on BSC, in contrast to the MS approach). The approach taken in the ustekinumab TA was, as such, based on the Woolacott scenario in which all non-responders had an addition 21 day hospitalisation per year.

It is reported in NICE CG153 (Appendix P),[10] that the guideline development group discussed using a similar definition of BSC as that assumed by Woolacott et al (i.e. 2 outpatient visits in a base-case and 21 inpatient days per year in a scenario analysis), but they argued that these estimates of resource use are likely to be an underestimate of what currently happens in clinical practice for patients that would require a second line biologic. The guideline development group reported that the patients meeting the eligibility criteria for biologic therapy are generally high-need patients and utilise a lot of health care resources through inpatient admissions, lengthy hospital stays, frequent visits to day clinics for specialist-applied topical treatments and UVB and monitoring toxicity related to systemic treatments. Importantly the guideline development group further stated that:

"When translating this information to build the NCGC model, which focuses on patients who are being considered for treatment with a second biologic, the GDG is certain that these resource use estimates are inadequate. In their opinion, the group of patients requiring a second biologic are likely to be even more high-need and resource intensive; therefore it would be inappropriate to assume the same assumptions about what comprises BSC" Appendix P, p.3[10]

The guideline development group assumed a base-case cost per year of £10,731. However, it was noted that, there is substantial variability in the long-term costs of psoriasis patients so the guideline development group undertook extensive sensitivity analyses with respect to the cost of BSC, with 12 separate scenarios presented in the final guideline.

As Table 33 shows the approach taken by the manufacturer to estimate the cost of BSC is largely consistent with the base-case approach taken in by the guideline development group in CG153. While

the base-case approach to the cost of BSC is consistent with CG153, the wide range of scenarios considered by the guideline development group are not sufficiently represented in the MS.

The guideline development group implemented the following scenarios around the resource use inputs for BSC:

1. No drugs in BSC
2. Longer length of hospital stay (23.7 days)
3. 30% very high need
4. 5% very high need
5. 0.25 hospitalisations for high need and 2.55 hospitalisations for very high need (match Driessen)[36]
6. 0.5 hospitalisations for high need and 2 hospitalisations for very high need
7. 1 hospitalisation for all
8. 0.312 hospitalisations for all (match Fonia)[7]
9. No hospitalisations
10. 1 hospitalisation for all and no drugs
11. 1 hospitalisation and 5 outpatient visits per year
12. 1 hospitalisation and 5 outpatient visits per year and 4th Quartile DLQI

CG153 particularly highlighted the scenarios relating to the Driessen and Fonia studies (5 and 8 above),[36] noting that both studies estimated mean inpatient days in the year preceding initial treatment with biologic therapy and thus the values may underestimate the likely resource use in the patients represented in this model, who have already failed one line of biologic treatment.

The manufacturer failed to present any scenario analyses considering the cost of BSC in the original MS, with only a deterministic sensitivity analysis (DSA) considering an arbitrary 25% change being applied. No original justification was provided by the manufacturer as to why a more robust approach consistent with the GDG was not presented.

The ERG considers the base-case analysis implemented by the manufacturer with regards to the cost of BSC to be subject to important uncertainties and questions regarding the generalisability of the CG153 estimates to the specific decision problem being considered by the manufacturer. The ERG therefore requested additional analyses during the clarification stage in line with the key scenarios presented in CG153 as well as clarification as to why the resource use inputs related to the cost of BSC were not included in the deterministic sensitivity analysis (DSA) or probabilistic sensitivity analysis (PSA) uncertainty analyses.

In their response the manufacturer acknowledged the failure to include parameter uncertainty around the cost (or HRQoL) of BSC in the PSA. In response to the point for clarification the manufacturer reported additional results incorporating a triangular distribution with a variation of 20% around the base-case values of both the costs and HRQoL associated with BSC. The incorporation of these uncertainties does not change the 100% probability of the apremilast sequence dominating the comparator sequence under this revised PSA.

Given that cost difference between patients is more a question of variability than uncertainty the ERG requested additional analyses implementing the following specific scenarios concerning the costs associated with BSC (note that these scenarios only considered changes to the costs associated with BSC, no changes to the base-case HRQoL were implemented despite changes in the required rate of hospitalisation):

i) 0.25 hospitalisations for high need and 2.55 hospitalisations for very high need (as per Driessen)[36];
ii) 0.312 hospitalisations for all (as per Fonia)[7];
iii) No hospitalisations.

The results of these additional scenarios are presented later in Section 5.

The manufacturer in their response argued that the Driessen and Fonia studies used to inform scenarios one and two are not representative of BSC as modelled. The Driessen and Fonia studies collected costs in patients prior to biologic use; the manufacturer argued that the modelled BSC population represents sicker patients because they have failed two lines of biologic therapy. The ERG considers this rationale to be inconsistent with the manufacturer's approach to modelling psoriasis as a chronic but non-progressive disease. The arguments cited by the manufacturer and their justification for using the BSC costs from NICE CG153 appear to be potentially conflating issues that relate to the natural history of psoriasis (i.e. whether it is a chronic progressive or non-progressive disease) and to issues of patient heterogeneity (or selection). That is, the argument that patients who have failed one or more prior lines of biologic therapy are potentially 'sicker' than those who have not may be more closely related to a selection effect (i.e. patients who fail on a biologic therapy or multiple biologic therapy may be systematically different from those who do not) than to supporting the assumption that, at a group level, psoriasis is a progressive disease. This is a central consideration in establishing whether it is reasonable to generalise the costs from the guideline development group to the manufacturer's decision problem and model. The guideline development group modelled a select population that were severe enough to consider use of a second line biologic. This select population is likely to have higher future costs than the total group of patients that would be considered for first line biologics.

In the model all patients who start a first line biologic will eventually receive BSC. This includes all patients eligible for biologic treatment, some of whom will eventually be eligible for a second line biologic and have the high costs assumed in CG153 and others who will not require a second line biologic and have lower costs. Hence the argument that patients who fail are sicker is unlikely to hold at the group level over the time horizon of the model. It may well be that the patients who progress to BSC quickest are the most severe patients (i.e. higher costs than average) but correspondingly those progressing later are the less severe (i.e. lower costs than average). Without additional data it would seem more appropriate to use the best 'average' cost of BSC for the entire population.

The ERG have previously discussed different estimates of BSC costs, considering the costs estimated in Fonia[7] to be the most appropriate for this analysis for four reasons:

1. Evidence based;
2. UK costs and practice;
3. Average patient similar to apremilast studies;
4. All patients went on to have a biologic; representative of treatment in the absence of apremilast or biologics.

The Fonia et al. costs come from a UK study incorporating UK practice and costs. As demonstrated in Table 34 below, the baseline patient characteristics cover a broad range of patient severity and the average patient characteristics are similar to those reported in the apremilast trials. Given that this is being modelled as a non-progressive disease it is reasonable to assume that pre-biologic costs would be similar to post-biologic costs. An assumption of progressive disease would have important implications for treatment benefits, however the model is not sufficiently flexible to test this assumption.

Table 34: Baseline patient characteristics comparing Fonia[7] to the three apremilast studies

Study	% Male	Mean Age (years)	Psoriasis Duration (years)	PASI score
Fonia 2010	71%	47.3 (range 23-74)	24.7 (range 5.3-45.5)	18.7 (range 2.7-42.1)
Apremilast	56.8%-73.0%	range 43.3-47.0	range 16.6-19.8	range 18.1-20.3

The costs reported in Fonia include £1249.40 per annum of non-biologic systemic treatments, £1.14 of other supportive drugs, and £2956.70 of inpatient visits, outpatient visits, ICU and HDU admissions (of which there were none), AE visits, day ward admissions and phototherapy. The total cost of non-biologic treatment was reported to be £4207, £4581 inflated to 2012/13 prices. The effect of this cost on the cost-effectiveness of apremilast is considered further in Section 6.

There may be subgroups of 'sicker' patients which are observable at the point of considering the 1st biologic or apremilast (i.e. based on higher PASI and/or DLQI). However, the issue is that the manufacturer has not formally considered any subgroups outside of the 2 DLQI categories. It also raises the issue about whether a less effective (but oral) therapy would be considered before a more effective biologic in these more severe subgroups.

DLQI ≤ 10 model differences

The manufacturer took the same approach to the analysis of the cost of BSC in the DLQI≤10 population. The MS implicitly assumes that a population with lower DLQI scores and therefore less severely affected by psoriasis, is deemed to have the same level of psoriasis related care need. In particular the ERG disagree with the assumption that patients with a DLQI≤10 would have at least 21 days in hospital a year.

The ERG requested further justification as to why the manufacturer assumed the same costs associated with BSC in the DLQI≤10 population as the DLQI>10 population, despite the lower level of severity in the former population. The manufacturer responded that there was limited data available in the use of BSC in the DLQI≤10 population. They highlighted that a threshold analysis was presented in the original submission, the updated results of which show that at a cost-effectiveness threshold of £30k/QALY a reduction in the cost of BSC of 45% (to £492 per cycle) would be required to make the apremilast arm not cost-effective in this population.

In addition, the manufacturer argued clinical advice suggests hospitalisation is likely to be driven by skin involvement rather than HRQoL. Thus the manufacturer argued that the main driver of costs associated with BSC (the high rate of hospitalisation) was unlikely to be strongly correlated with DLQI status. The ERG notes however, that such an argument is based purely on clinical suggestions and not data.

The manufacturer also presented additional scenario analyses considering the rate of hospitalisation associated with BSC for this population, in line with the three scenarios presented for the DLQI≥10 population.

5.2.10 Uncertainty analysis

The manufacturer presented the uncertainty in the model in three ways: a series of one way deterministic sensitivity analyses (DSA), a probabilistic sensitivity analysis (PSA) and a series of scenarios. In all cases the presentation of uncertainty analyses are limited to the DLQI ≥ 10 population; the ERG are unable to comment on the impact of uncertainty in the DLQI < 10 population model presented in the MS.

Deterministic Sensitivity Analyses

The presented series of one-way DSA consider uncertainty in the model by changing each variable, deemed to be uncertain. Table 35 gives the full range of variables subjected to DSA and the source of the selected range over which to vary it.

Table 35: Variables subject to DSA

Input parameter	Base-case	Lower value	Upper value	Source
PASI-50				
Apremilast	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Adalimumab	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Etanercept	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Infliximab	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Ustekinumab	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
PASI-75				
Apremilast	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Adalimumab	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Etanercept	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Infliximab	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Ustekinumab	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
PASI-90				
Apremilast	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Adalimumab	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Etanercept	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Infliximab	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Ustekinumab	[redacted]	[redacted]	[redacted]	95% CrI, Celgene, NMA results
Long-term drop-out rate				
Apremilast	1.70%	1.28%	2.13%	+/-25%, clinical expert opinion
Adalimumab	1.70%	1.28%	2.13%	+/-25%, Turner *et al.* [37]
Etanercept	1.70%	1.28%	2.13%	+/-25%, Pan *et al.*[38]
Infliximab	1.70%	1.28%	2.13%	+/-25%, Woolacott *et al.*[6]
Ustekinumab	1.70%	1.28%	2.13%	+/-25%, Pan *et al.*
Utility gain by PASI response				
≥ PASI-90	0.21	0.11	0.31	95% CI, Woolacott *et al.*
≥ PASI-75 - < PASI 90	0.19	0.11	0.27	95% CI, Woolacott *et al.*
≥ PASI-50 - < PASI 75	0.17	0.09	0.25	95% CI, Woolacott *et al.*
< PASI-50	0.05	0.03	0.07	95% CI, Woolacott *et al.*
Costs				
Hospitalisation	£462.56	£416.30	£508.82	+/-10%, Psoriasis costing report[22]
BSC	£887.90	£799.11	£976.69	+/-25%, assumption
Probability of hospitalisation				
Probability	1.00	0.00	1.00	Assumption (no hospitalisation)
Hospitalisation - Length of stay (LOS)				
LOS	1.6	1.44	1.76	+/-10%, CG153[10]
Discount rate				
Costs	0.03	0.00	0.06	NICE [19]
Utilities	0.03	0.00	0.06	NICE

The ERG considers the approach taken to DSA to be appropriate and the range of variables included to be reasonable. However, the ERG feels the use of one-way DSA is limited in its consideration of the extent of uncertainty since the range of values appears arbitrary for several key inputs.

Probabilistic Sensitivity Analysis

The manufacturer also conducted a PSA which allows for a better understanding of the cumulative effect of the uncertainty of all variables on the conclusions of the cost-effectiveness analysis. The

PSA is conducted by running a large number of Monte Carlo simulations of the model (5,000 in the analysis presented), varying each of the variables deemed to be uncertain in each of the runs. The variables subjected to PSA uncertainty are presented in Table 36. In addition to the variables presented in Table 36 the manufacturer incorporated uncertainty around the efficacy of treatments and the correlation between the efficacy inputs (PASI50, PASI75 and PASI90 response rates) by sampling from the posterior distributions obtained from the NMA.

Table 36: Variables subject to PSA

Input parameter	Mean	SE	Distribution	Alpha	Beta
Long-term drop-out rate					
Apremilast	1.70%	0.001	Beta	377.59	21809.63
Adalimumab	1.70%	0.001	Beta	377.59	21809.63
Etanercept	1.70%	0.001	Beta	377.59	21809.63
Infliximab	1.70%	0.001	Beta	377.59	21809.63
Ustekinumab	1.70%	0.001	Beta	377.59	21809.63
Methotrexate	1.70%	0.001	Beta	377.59	21809.63
Utility gain by PASI response					
≥ PASI-90	0.21	0.05	Normal	0.21	0.05
≥ PASI-75 - < PASI-90	0.19	0.04	Normal	0.19	0.04
≥ PASI-50 - < PASI-75	0.17	0.04	Normal	0.17	0.04
< PASI-50	0.05	0.01	Normal	0.05	0.01
Costs					
Hospitalisation	£462.56	£23.60	Gamma	384.15	1.27
Probability of hospitalisation					
Probability of hospitalisation	1.00		Uniform	1.00	1.00
Hospitalisation - Length of stay					
LOS	1.60	0.10	Uniform	1.44	1.76

The ERG has several concerns regarding the PSA approach taken. Firstly, the manufacturer has excluded any uncertainty around BSC in health outcomes, HRQoL and costs. The approach taken to the health outcomes and HRQoL of BSC (see Section 5.2.9.1) in assuming patients always find themselves in the baseline PASI level (and thus HRQoL) means that the manufacturer implicitly excludes the health of BSC patients from the PSA. The ERG sought clarification from the manufacturer as to why the costs associated with BSC were excluded from the PSA. In response to the points for clarification the manufacturer submitted a re-evaluation of the PSA incorporating uncertainty around the costs and quality of life of patients on BSC. For the both the costs and utilities of BSC the manufacturer assumed a triangular distribution with a variation of 20% around the base-case value. The ERG were not satisfied that the manufacturer's chosen distribution or the variation chosen captured the variation of the different cost estimates available for BSC, particularly considering the wide range of scenarios undertaken in CG153.

In addition, while the manufacturer lists the probability of hospitalisation (at treatment discontinuation) and the associated length of stay as included in the PSA, on further inspection of the model the ERG conclude that these are not incorporated properly. The manufacturer gives the probability of hospitalisation (see Table 36) as a uniform distribution with mean=1, alpha=1 and beta=1. As such the probability of hospitalisation is always 1 in all Monte Carlo simulations. While the distribution attributed to length of stay is not a single value it is not connected to the model, and does not impact the cost-effectiveness results.

Scenario analyses

The manufacturer also presents a range of scenario analyses to take account of the structural assumptions made by the base-case model. It should be noted that these scenarios only apply to the DLQI > 10 population, no uncertainty is considered with regards the DLQI ≤ 10 population model.

Table 37: Scenario analyses presented in the MS

Scenario	Scenario approach	Base-case approach
Treatment sequence scenario 1	The replacement of etanercept in the sequence with ustekinumab: **Apremilast sequence:** Apremilast → Adalimumab → Ustekinumab → BSC **Comparator sequence:** Adalimumab → Ustekinumab → BSC	**Apremilast sequence:** Apremilast → Adalimumab → Etanercept → BSC **Comparator sequence**: Adalimumab → Etanercept → BSC
Treatment sequence scenario 2	The use of only one biologic: **Apremilast sequence**: Apremilast → Adalimumab → BSC **Comparator sequence:** Adalimumab → BSC	
Treatment sequence scenario 3	The addition of Ustekinumab as a third biologic: **Apremilast sequence:** Apremilast → Adalimumab → Etanercept → Ustekinumab →BSC **Comparator sequence:** Adalimumab → Etanercept → Ustekinumab →BSC	
Apremilast positioning scenario	Position apremilast as a post-biologic versus as a pre-biologic: **Pre-biologic sequence:** Apremilast → Adalimumab → Etanercept → BSC versus **Post-biologic sequence:** Adalimumab → Etanercept →Apremilast→ BSC Uses post-biologic efficacy rates for apremilast from an updated NMA.	
Decline in efficacy of biologics following first-line therapy scenario 1	Efficacy decrement of PASI response rate of 13.7% and an 82% increase in drop-outs after first-line biologic failure.	Treatment efficacy is assumed to not vary with response to previous therapy.
Decline in efficacy of biologics following first-line therapy scenario 2	Scenario 1 as well as a 5% decrement in treatment efficacy of first-line biologic following apremilast.	
Time horizon scenario 1	Time horizon considered adjusted to 1 year	A time horizon of 10 years is modelled
Time horizon scenario 2	Time horizon considered adjusted to 5 year	
Time horizon scenario 3	Time horizon considered adjusted to 40 year	
Alternative BSC health effects/HRQoL estimates	Application of limited PASI response of patients while on BSC based on CG153 estimates. Probability of response are modelled as PASI50-3.80%, PASI75-0.80% and PASI90 0.10%.	No PASI response is assumed for all patients on BSC such that baseline HRQoL is assumed for all
Alternative HRQoL estimates	HRQoL increments and baseline associated with PASI response estimates from PSOR-008 and 009 are used. Estimates are: PASI<50-0.01; PASI50-75-0.04; PASI75-90-0.07; PASI>90-0.10	HRQoL baseline from Revicki used (0.70).[30] Increments from Woolacott are used.[6] Estimates are: PASI<50-0.05; PASI50-75-0.17; PASI75-90-0.19; PASI>90-0.21
Trial period of apremilast	The trial period is assumed to be 24 weeks for apremilast	The trial period for apremilast is assumed to be 16 weeks for apremilast
Long term drop-out scenario 1	An annual long term drop-out rate of [redacted]% is assumed	An annual long term drop-out rate of 20% is assumed
Long term drop-out scenario 2	An annual long term drop-out rate of 10% is assumed	

The ERG feels the scenarios presented to be appropriate. However, as noted in previous sections, many of these scenarios are considered by the ERG to be representative of a more appropriate base-case analysis (see primarily Sections 5.2.6 and 5.2.7).

5.2.11 Cost effectiveness results

5.2.11.1 Base-case

The manufacturer presented results for the base-case analysis for both the DLQI>10 and DLQI≤10 populations. The manufacturer presents pair-wise comparisons of a sequence including apremilast versus the same sequence without apremilast for the DLQI>10, and a comparison of apremilast versus BSC alone in the DLQI≤10 population. The results are given in Table 38 and Table 39 respectively.

In both populations the apremilast sequence is found to dominate the comparator sequences (i.e. greater QALYs but at a lower total cost). The incremental QALY gains are relatively modest in both cases, representing 2% and 0.8% of the total QALYs associated with the apremilast sequence respectively. This small gain in total QALYs is largely attributable to the short period of time for which patients are on apremilast in the model and the lack of mortality impact of psoriasis resulting in all gains being limited to HRQoL associated with treatment.

Table 38: Cost-effectiveness results for DLQI>10 population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
Apremilast sequence	£89,374	6.83	–£3,2226	0.14	Dominant
Comparator sequence	£92,589	6.69			

Table 39: Cost-effectiveness results for DLQI≤10 population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
Apremilast sequence	£92,354	6.01	–£5,911	0.05	Dominant
Comparator sequence	£98,265	5.96			

Comparing the two populations in Table 38 and Table 39 demonstrates the limitations of the approach taken by the manufacturer. First, the total costs in both sequences in the DLQI≤10 population are

greater than in the DLQI>10 population. These results suggest that it is more expensive to provide treatment to a population who by definition suffers less from psoriasis. As presented in Section 5.2.9.2 the manufacturer assumes the same costs per cycle of BSC in both populations, and as the DLQI≤10 population only has, at most, one line of treatment they are considered to spend longer in this high cost BSC state. This result illustrates the importance of the BSC costs and calls into question the generalizability of these costs across the populations.

Secondly, the manufacturer's results suggest that the total QALYs for patients in the DLQI≤10 population is less than that of the DLQI>10 population. In contrast to the cost approach, as show in Section 5.2.9.1, the manufacturer used different values of HRQoL in the two population models. This is likely due to using the same baseline health related quality of life.

5.2.11.2 Sensitivity analyses in MS

As presented in Section 5.2.10 a range of sensitivity analyses were conducted by the manufacturer. The manufacturer only conducted sensitivity analysis in the DLQI>10 population, as such the ERG is unable to comment on the impact of uncertainty on the conclusions drawn from the cost-effectiveness analysis of the DLQI≤10 population.

Deterministic sensitivity analysis (DSA)

For the full range of one-way DSA analyses performed (see Table 35), the manufacturer reported that the apremilast sequence always dominated the comparator sequence. Details were not provided as to what extent the associated costs and QALYs changed and as such the ERG is unable to comment further.

Probabilistic sensitivity analysis (PSA)

The manufacturer conducted a PSA, the results of which are presented in Figure 5 Each small blue dot in the figure represents a single iteration of the Monte Carlo simulation, the large orange dot represents the result of the deterministic analysis (see Table 38), and the ellipse the area within which 95% of the iterations are included. An accompanying CEAC is presented in the MS, which due to all iterations of the PSA finding the apremilast sequence dominant results in a probability of being cost-effective of 1 for all cost-effectiveness thresholds.

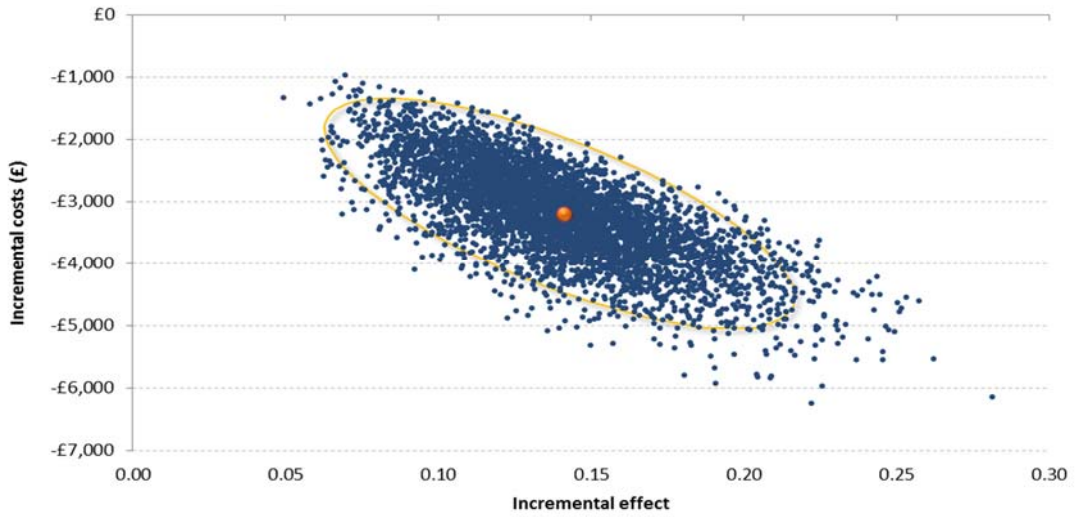


Figure 5: PSA cost-effectiveness results

While the PSA presented finds apremilast to be dominant in all perceived simulations, as discussed in Section 5.2.10 (putting aside all other criticisms of the model structure) the ERG does not feel that the manufacturer accurately represented the full extent of uncertainty in the model presented. As such, the ERG does not consider the uncertainty results presented by the PSA is an accurate characterisation of decision uncertainty surrounding the cost-effectiveness of apremilast.

Scenario analyses

The MS also included a series of scenario analyses as discussed in section 5.2.10. The results of these analyses are reproduced in Table 40 below. The MS found that apremilast maintained its dominance of the comparator in all scenarios except for the apremilast positioning scenario and the scenario reducing the time horizon to 1 year.

The apremilast positioning scenario compares the base-case sequence (Apremilast → Adalimumab → Etanercept → BSC) to the same sequence but with apremilast post-biologic. The scenario finds apremilast to be slightly less effective as a pre-biologic agent (an incremental QALY of -0.01) but also less expensive (an incremental cost of –£1381). The MS highlights that this equates to a cost per QALY saved (if using apremilast as a post-biologic rather than a pre-biologic) of £104,286/QALY. As such they conclude that at conventional cost-effectiveness thresholds the reduced effectiveness of apremilast as a pre-biologic is worth the savings and thus the use of the pre-biologic base-case is appropriate.

The scenario in which the time horizon is reduced to 1 year results in the apremilast sequence being cost saving but lest effective and resulting in a cost per QALY saved of £22,117. While this would suggest the comparator sequence to be potentially more cost-effective the ERG does not believe the use of such a short time horizon to be appropriate.

Table 40: Results of the scenario analyses presented

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Treatment sequence scenario 1					
Apremilast sequence	£89,978	6.98	-£3,189	0.11	Dominant
Comparator sequence	£93,167	6.87			
Treatment sequence scenario 2					
Apremilast sequence	£90,379	6.61	–£3,447	0.18	Dominant
Comparator sequence	£93,826	6.44			
Treatment sequence scenario 3					
Apremilast sequence	£89,227	7.12	-£3,030	0.08	Dominant
Comparator sequence	£92,257	7.04			
Apremilast positioning scenario					
Pre-biologic sequence	£89,048	6.83	–£1381	-0.01	Cost-saving but less effective £104 286 saved per QALY lost
Post-biologic sequence	£90,430	6.84			
Time horizon scenario 1: One-year time horizon					
Apremilast sequence	£11,020	0.80	–£221	–0.01	Cost-saving but less effective £22 117 saved per QALY lost
Comparator sequence	£11,241	0.81			
Time horizon scenario 2: 5-year time horizon					
Apremilast sequence	£47,765	3.84	–£2,089	0.07	Dominant
Comparator sequence	£49,854	3.77			
Time horizon scenario 3: 40-year time horizon					
Apremilast sequence	£218,727	14.95	–£3,966	0.21	Dominant
Comparator sequence	£222,693	14.74			
Decline in efficacy of biologics following first-line therapy scenario 1					
Apremilast sequence	£90,150	6.74	–£3,376	0.16	Dominant
Comparator sequence	£93,526	6.59			
Decline in efficacy of biologics following first-line therapy scenario 2					
Apremilast sequence	£90,349	6.72	–£3,177	0.14	Dominant
Comparator sequence	£93,526	6.59			
Alternative BSC health effects/HRQoL estimates					
Apremilast sequence	£89,374	7.02	–£3,215	0.09	Dominant
Comparator sequence	£92,589	6.93			

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Alternative HRQoL estimates					
Apremilast sequence	£89,374	7.09	-£3,215	0.05	Dominant
Comparator sequence	£92,589	7.03			
Trial period of apremilast					
Apremilast sequence	£88,822	6.82	–£3,767	0.13	Dominant
Comparator sequence	£92,589	6.69			
Long term drop-out scenario 1					
Apremilast sequence	£90,693	6.79	–£1,896	0.10	Dominant
Comparator sequence	£92,589	6.69			
Long term drop-out scenario 2					
Apremilast sequence	£87,542	6.88	-£5,047	0.19	Dominant
Comparator sequence	£92,589	6.69			

5.2.11.3 Additional sensitivity analyses undertaken in response to clarifications

The ERG requested a range of additional sensitivity analyses be conducted by the manufacturer during clarifications, the results of which are detailed in this section.

Apremilast as replacement to existing therapy

As a result of the concerns raised in Section 5.2.1 regarding the appropriate positioning of apremilast the ERG requested additional analyses be conducted by the manufacturer where apremilast replaced an existing biologic therapy in the sequence (clarification B1). The manufacturer re-iterated their position and clinical advice regarding the use of apremilast as an additional line of therapy rather than displacing a current therapy in a sequence. However, additional analyses were reported which considered three displacement strategies, as detailed in Table 41 below. All results presented are in the DLQI>10 population. In all scenarios considered the apremilast arm is less effective due to its poor efficacy compared to other biologics but also less expensive.

Table 41: Results of apremilast as replacement scenarios

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Base-case					
Apremilast sequence	£89,479	6.82	–£3,226	0.14	Dominant
Comparator sequence	£92,705	6.68			
Apremilast→Adalimumab→Ustekinumab→BSC versus Etanercept→Adalimumab→Ustekinumab→BSC					
Apremilast sequence	£90,111	6.97	–£2,659	-0.07	Cost-saving but less effective. £39,121 saved per QALY lost
Comparator sequence	£92,770	7.04			
Apremilast→Adalimumab→BSC versus Etanercept→Adalimumab→BSC					
Apremilast sequence	£90,599	6.59	–£2,570	-0.09	Cost-saving but less effective. £27,634 saved per QALY lost
Comparator sequence	£93,170	6.68			
Apremilast →BSC versus Etanercept→BSC					
Apremilast sequence	£92,545	6.17	–£2,425	-0.11	Cost-saving but less effective. £21,098 saved per QALY lost
Comparator sequence	£94,970	6.29			

The rate of hospitalisation in BSC

The ERG requested additional analyses implementing the following specific scenarios concerning the costs associated with BSC (clarification B5), note that these scenarios only considered changes to the costs associated with BSC, no changes to the base-case HRQoL were implemented despite changes in the required rate of hospitalisation:

i) 0.25 hospitalisations for high need and 2.55 hospitalisations for very high need (as per Driessen)[36];

ii) 0.312 hospitalisations for all (as per Fonia)[7];

iii) No hospitalisations.

The manufacturer presented additional results for all three requested scenarios for both the DLQI > 10 and DLQI ≤ 10 population models. The impact of these scenarios on the cost-effectiveness results are reported in Table 42 below. In the population with DLQI > 10, the ICER for the apremilast sequence ranged from £281 to £25,097 per QALY. In the population with DLQI ≤ 10, the ICER for the apremilast sequence ranged from dominant to £107,890 per QALY.

Table 42: Cost-effectiveness results, scenario analysis on hospitalisations in BSC, by DLQI population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
DLQI > 10 (Apremilast>adalimumab>etanercept>BSC vs Adalimumab>etanercept >BSC)					
Base-case (1 admission in high need, 2.55 in very high need, each of 20.8 days)					
Apremilast sequence	£89,479	6.82	–£3,226	0.14	Dominant
Comparator sequence	£92,705	6.68			
Scenario 1 (0.25 admission in high need, 2.55 in very high need, each of 20.8 days)					
Apremilast sequence	£76,085	6.82	£40	0.14	£281
Comparator sequence	£76,045	6.68			
Scenario 2 (0.312 admissions for all, of 20.8 days)					
Apremilast sequence	£68,419	6.82	£1,910	0.14	£13,436
Comparator sequence	£66,509	6.68			
Scenario 3 (no hospitalisations)					
Apremilast sequence	£61,624	6.82	£3,567	0.14	£25,097
Comparator sequence	£58,057	6.68			
DLQI ≤10 (Apremilast->BSC vs BSC)					
Base-case (1 admission in high need, 2.55 in very high need, each of 20.8 days)					
Apremilast sequence	£91,965	6.01	–£6,300	0.05	Dominant
Comparator sequence	£98,265	5.96			
Scenario 1 (0.25 admission in high need, 2.55 in very high need, each of 20.8 days)					
Apremilast sequence	£66,070	6.01	–£712	0.05	Dominant
Comparator sequence	£66,782	5.96			
Scenario 2 (0.312 admissions for all, of 20.8 days)					
Apremilast sequence	£51,249	6.01	£2,386	0.05	£50,412
Comparator sequence	£48,762	5.96			
Base-case (1 admission in high need, 2.55 in very high need, each of 20.8 days)					
Apremilast sequence	£38,112	6.01	£5,321	0.05	£107,890
Comparator sequence	£32,790	5.96			

Efficacy of BSC

The ERG requested additional analysis be conducted to consider more scenarios around the efficacy of BSC (as presented previously the MS presented a scenario considering the application of the placebo response from CG153). Additional analyses were requested using the placebo response values from the MS NMA alongside those from the CG153 (clarification B8) and the use of the Woods[35] study (clarification B9) consistently with the scenario analyses in CG153.[10]

As shown in Table 43 the additional scenarios requested by the ERG, when applied in isolation to the base-case, did not change the dominance of the apremilast sequence over the comparator sequence. However, in the scenario in which the results from Woods[35] were used to estimate the BSC placebo response, the incremental QALYs fell from 0.14 to 0.03 in favour of the apremilast sequence.

Table 43: Cost-effectiveness results, scenario analysis on placebo response, by DLQI population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
DLQI > 10 (Apremilast>adalimumab>etanercept>BSC vs Adalimumab>etanercept >BSC)					
Base-case (no placebo response)					
Apremilast sequence	£89,479	6.82	–£3,226	0.14	Dominant
Comparator sequence	£92,705	6.68			
Scenario 1 (NCGC, 3.8% PASI-50 0.8% PASI-75, 0.1% PASI-90)					
Apremilast sequence	£89,479	7.02	–£3,226	0.10	Dominant
Comparator sequence	£92,705	6.92			
Scenario 2 (Celgene meta-analysis 17.01% PASI-50, 5.52% PASI-75, 1.09% PASI-90)					
Apremilast sequence	£89,479	7.08	–£3,226	0.08	Dominant
Comparator sequence	£92,705	7.00			
Scenario 3 (Woods 65% of BSC experience PASI response)					
Apremilast sequence	£89,479	7.28	–£3,226	0.03	Dominant
Comparator sequence	£92,705	7.25			
DLQI ≤10 (Apremilast->BSC vs BSC)					
Base-case (no placebo response)					
Apremilast sequence	£91,965	6.01	–£6,300	0.05	Dominant
Comparator sequence	£98,265	5.96			
Scenario 1 (NCGC, 3.8% PASI-50 0.8% PASI-75, 0.1% PASI-90)					
Apremilast sequence	£91,965	6.01	–£6,300	0.05	Dominant
Comparator sequence	£98,265	5.97			
Scenario 2 (Celgene meta-analysis 17.01% PASI-50, 5.52% PASI-75, 1.09% PASI-90)					
Apremilast sequence	£91,965	6.04	–£6,300	0.04	Dominant
Comparator sequence	£98,265	6.00			
Scenario 3 (Woods 65% of BSC experience PASI response)					
Apremilast sequence	£91,965	6.10	–£6,300	0.03	Dominant
Comparator sequence	£98,265	6.07			

Network Meta-Analysis

In addition to the error identified by the ERG in the discrepancy between the NMA produced in the MS and that used in the submitted model (which has been incorporated into the base-case results presented in Section 5.2.11 the ERG requested an additional analysis in which the results from the NMA including the PSOR-010 trial were incorporated into the economic model. The results are presented in Table 44 and show only a small change in the costs and QALYs with no change in the overall conclusion of dominance. The manufacturer only provided an additional analysis for the DLQI > 10 population.

Table 44: Base-case results for DLQI > 10 (revised using NMA results including PSOR-010 data)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Apremilast sequence	£89,682	6.80	–£3,142	0.14	Dominant
Comparator sequence	£92,824	6.66			

Withdrawal rates

The ERG additionally requested an additional scenario which incorporated the withdrawal rate from the PSOR-008 trial reported in the MS (a revised value of [redacted]% per annum). The manufacturer only provided an additional analysis for the DLQI > 10 population, shown in Table 45. The analysis found the higher withdrawal rate decreased the relative effectiveness of the apremilast sequence but the sequence remained dominant.

Table 45: Base-case results for DLQI > 10 (using apremilast trial based withdrawal rate of [redacted]% per year)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Apremilast sequence	£90,861	6.78	–£1,844	0.10	Dominant
Comparator sequence	£92,705	6.68			

5.2.9 Model validation and face validity check

The approach used by the manufacturer was primarily validated by one clinical expert with regards to current clinical practice, Professor Eugene Healy, Southampton, UK. The manufacturer reports that Professor Healy completed a questionnaire with questions on the definition of psoriasis, model

structure, treatment pathways, treatment efficacy, withdrawal rates and adverse events. Professor Healy also validated the model structure and key inputs. The manufacturer notes that he also suggested the treatment sequences to be included in the model.

Additional validation was provided by three unnamed UK practicing clinicians, who were presented with all the key inputs and assumptions included in the economic model. It is not clear what comments were received from this panel.

The manufacturer further notes that a number of advisory boards sought to clarify key assumptions in the economic model, no details are given as to the response or specific questions.

The manufacturer did not provide details of the specific validation conducted and if in any cases the experts consulted failed to validate the model. Specific examples are given of assumptions by the manufacturer being validated by the clinical expert (i.e. the HRQoL of patients on BSC (p151 of the MS), the use of adalimumab and etanercept as the most commonly used biologics (p146), the resource use associated with monitoring and laboratory tests (p154), the lack of PASI improvement on BSC (p163). A health economist was not involved in the validation of the model.

Internal validation was conducted to quality assess the economic model presented. This included the reprogramming on the model solely using Visual Basic Application (VBA) language.

The ERG identified an error in the efficacy values used to inform the DLQI > 10 population model, which were not consistent with what was reported in the MS. During clarification the manufacturer identified the NMA results used in the model were incorrect and included the correct results in the re-submitted model.

The ERG was unable to validate much of the re-submitted model due to its increased reliance on VBA language compared to the originally submitted model.

As noted in Section 5.1.4 the ERG considered that the manufacturer could have done more to cross-validate their model with existing models. The ERG conducted a limited range of such cross-validation which are reported in Section 6.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG identified a number of parameters and structural issues of the model that required further consideration. As discussed, only one sequence was considered in the base-case. Further analyses were undertaken by the ERG to understand the cost-effective use and position of apremilast. In

Section 5 the ERG identified the modelling of BSC to be important, particularly the costs of BSC but also the treatment effect.

5.4 Conclusions of the cost effectiveness section

No previous cost-effectiveness studies of apremilast for moderate to severe psoriasis were identified by the manufacturer. Therefore, a de novo analysis was submitted to estimate the cost-effectiveness of a sequence including apremilast in two separate populations. These populations met the scope of the decision problem. The manufacturer's de novo model was made available to the ERG and was well described in the MS.

The justification for parameters was often weak and the manufacturer was over reliant on previous technology appraisals despite having trial based apremilast specific evidence, i.e. withdrawal rates and HRQoL. This was also a concern for the assumptions used for BSC, where the manufacturer dismissed observational evidence of the costs and effectiveness of BSC that the ERG considered more representative of the average patient that would receive apremilast or biologic treatment.

Of further concern is the limited number of comparator sequences presented by the manufacturer. While the model was limited to pairwise comparisons a fully incremental analysis is required in the NICE methods guide.

The model is based on the assumption that apremilast will have no adverse effect on the subsequent use or effectiveness of biologics. No evidence was available to inform this assumption. The manufacture did not consider the potential costs of wastage or non-compliance of apremilast, nor did they consider the costs of adverse events.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the manufacturer's cost-effectiveness analysis presented in Section 5. In this Section the ERG's exploratory analyses are presented, followed by the ERG's preferred analysis. The ERG's exploratory analyses are focussed on the following four areas:

1. Approaches to sequencing in the model
2. The cost associated with BSC
3. The effectiveness of BSC
4. HRQoL

Other issues explored include; withdrawal rates, drug wastage and the use of the updated NMA (i.e. with PSOR-010 data).

6.2 Additional ERG analyses

6.2.1 Issues and approaches to sequencing

As discussed in Section 5 the manufacturer used only one comparator sequence. This was chosen following the opinion of their clinicians and a publication suggesting adalimumab and etanercept are the most commonly used biologics for plaque psoriasis in the UK.[27] The ERG considered the base-case sequence proposed by the manufacturer represented a limited set of potentially relevant sequences and that the manufacturer's base-case cost-effectiveness results were not a sufficient basis to inform the most efficient use and position of apremilast.

The ERG requested (clarification points B1 and B2), and was provided with an additional model able to consider the position and combination of any treatment at any point in the sequence. This section presents an exploration of additional sequences and comparisons from this updated model. While the ERG does not believe that any single additional sequence presented represents a more clinically likely scenario than the base-case presented by the manufacturer, the consideration of such additional sequences is a vital part of understanding the economic model submitted by the manufacturer, and the evaluation of apremilast within its licenced indication as required by the NICE scope.

6.2.1.1 A comparison of all treatments as a single line of therapy

A comparison of all treatments as a single line of therapy provides a valuable insight into the analysis presented in the MS and allows for important comparisons to be made to previous economic

evaluations in this disease area. Table 46 below presents the cost-effectiveness results associated with the full range of single line treatment options, including a direct comparison to BSC and to ustekinumab and infliximab which were not presented in the manufacturer's base-case sequence.

Table 46: A comparison of treatments as a single line of therapy

Strategy	Costs	QALYs	Compared to BSC	Compared to apremilast	ICER
BSC->BSC	£98,265	5.96	-	Dominated	Dominated
Apr->BSC	£92,545	6.17	Dominates BSC	-	-
Eta->BSC	£94,970	6.29	Dominates BSC	£20,208	Dominated
Ada->BSC	£94,076	6.41	Dominates BSC	£6,379	£6,379
Ust->BSC	£94,975	6.52	Dominates BSC	£6,943	£8,173
Inf->BSC	£115,798	6.59	£27,830	£55,364	£297,471

The table shows that all single line treatments, except infliximab, dominate BSC; that is they are more effective but less expensive. An important validation exercise is to compare these single line treatment strategies (in Table 47) with previous economic evaluations. Table 47 below reports some of the key findings of previous TAs, the Table presents the results presented by the manufacturers in their original submissions as well as the results reported by the NICE committees, where available, or ERGs. For simplicity and due to the lack of full reporting of results only the ICERs are presented in each case.

Table 47: Single line treatment cost-effectiveness results versus BSC/placebo in previous TAs

Source	Manufacturer, NICE committee or ERG results	Comparators	ICER
TA103- etanercept[23]	Manufacturer	Placebo vs intermittent etanercept	£37,200
	ERG	BSC vs intermittent etanercept	£65,320
TA134- infliximab[24]	Manufacturer	BSC vs infliximab	£22,240
	NICE committee	BSC/etanercept/efalizumab vs infliximab	>£35,000
TA146- adalimumab[25]	Manufacturer	BSC vs adalimumab	£30,500
		BSC vs infliximab	£42,500
		BSC vs etanercept	£37,700
	NICE committee	BSC vs adalimumab	£30,500
TA180- ustekinumab[26]	Manufacturer	BSC vs ustekinumab	£29,587 (£41,000 without PAS)
		BSC vs etancercept	£34,281
		BSC vs adalimumab	£31,022
		BSC vs infliximab	£39,153
	ERG	BSC vs ustekinumab	£40,952

A comparison of the results from the manufacturer's submitted model (Table 46) and those from previous TAs (Table 47) demonstrates that under the manufacturer's model assumptions all treatments dominate BSC alone (except infliximab with an ICER of £27,830), whereas in none of the previous TAs is BSC dominated by any single line of treatment. Furthermore, not only do single lines of treatment not dominate but they rarely result in an ICER under £30,000. This result shows that the economic model presented by the manufacturer and the assumptions made are not consistent with those of previous TAs.

As seen in Table 46 a comparison of treatments as a single line of therapy demonstrates the cost-effectiveness of apremilast versus each treatment option in the model. At a threshold of £20,000/QALY adalimumab and ustekinumab are cost-effective compared to apremilast, while etanercept is estimated to have an ICER of £20,208 per QALY and infliximab an ICER of £55,364 per QALY. In a fully incremental analysis the cost-effective treatment in the manufacturer's model, when a single line of therapy is considered, at a threshold of £20,000 per QALY is ustekinumab.

6.2.1.2 The use of apremilast at different positions within a sequence

The manufacturer's base-case analysis only considers the use of apremilast as a pre-biologic therapy based on clinical expert opinion. However, the licence granted for apremilast, as outlined in the NICE scope, does not specify the positioning of apremilast. As such the ERG in this section compares the positioning of apremilast at each of the treatment points in a sequence.

Table 48 below presents the results of this range of strategies and their ICERs. The table shows that apremilast is more effective (i.e. the highest QALYs) the later it is used in a sequence, however it is also more expensive and as such not cost-effective under the base-case assumptions made by the manufacturer.

Table 48: Comparison of apremilast as pre- and post-sequence treatment

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Ada->Eta->BSC	£92,705	6.667	-	-	Dominated
Eta->Ada->BSC	£93,170	6.667	£465	0.000	Dominated
Apr-> Eta->Ada->BSC	£89,471	6.819	-£3234	0.152	-
Apr->Ada->Eta->BSC	£89,479	6.819	£8	0.000	Dominated
Ada-> **Apr**->Eta->BSC	£90,041	6.822	£562	0.003	£190,000
Ada->Eta->**Apr**->BSC	£90,431	6.825	£390	0.003	Dominated
Eta-> **Apr**->Ada->BSC	£90,345	6.827	-£86	0.002	£60,800
Eta->Ada->**Apr**->BSC	£90,895	6.831	£550	0.004	£137,500

Table 48 also demonstrates that adding a third line of treatment dominates two lines of treatment. As discussed previously this is because all biologic treatments are assumed to be less expensive and more effective than the BSC they displace.

6.2.2 The cost associated with BSC

In Section 5.2.8.3 the ERG have previously identified that the manufacturer uses the most expensive cyclosporine as part of BSC. Table 49 reports all cyclosporine prices currently accessible on the BNF. In the model the manufacturer uses the cost of cyclosporine of £72.57 per pack although three other less expensive alternatives exist.

Table 49: Drug costs of different cyclosporine, BNF 2015 as accessed 27/02/2015

Cyclosporine brand	Pack and dose details	Pack cost	Cost per mg
Neoral	30-cap pack 100mg	£72.57	2.4p
Capimune	30-cap pack 100mg	£48.50	1.6p
Capsorin	30-cap pack 100mg	£48.89	1.6p
Deximune	30-cap pack 100mg	£48.90	1.6p
Sandimmun	N/A as intravenous treatment		

The results of replacing Neoral with Capimune, the cheapest cyclosporine, are shown in Table 50 and Table 51 below. The table shows that all sequences are cheaper, with the cost saving nature of the apremilast first sequence being reduced by £403.

Table 50: Implications of using Capimune rather than Neoral in DLQI>10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Manufacturer's base-case, using Neoral					
Comparator sequence	£92,705	6.68			
Apremilast first sequence	£89,479	6.82	–£3,226	0.14	Dominant
Scenario using Capimune as cyclosporine treatment					
Comparator sequence	£90,649	6.68			
Apremilast first sequence	£87,826	6.82	-£2,823	0.14	Dominant

Table 51: Implications of using Capimune rather than Neoral in DLQI≤10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Manufacturer's base-case, using Neoral					
Comparator sequence	£98,265	5.96			
Apremilast first sequence	£91,965	6.01	-£6,300	0.05	Dominant
Scenario using Capimune as cyclosporine treatment					
Comparator sequence	£94,379	5.96			
Apremilast first sequence	£88,768	6.01	-£5,610	0.05	Dominant

In addition, the manufacturer assumes the 45% of patients who receive cyclosporine when on BSC do so indefinitely; this is not consistent with the approach used in CG153,[10] which assumed that patients

could only be on cyclosporine for a maximum of two years. Due to the structure of the model presented by the manufacturer (lack of 'memory' to record how long patients have been on BSC), the ERG has been unable to accurately estimate the impact of this assumption. However the direction of effect of the manufacturer's assumption is expected to be optimistic in favour of apremilast.

In the points for clarification the ERG requested that the manufacturer implement three BSC cost scenarios undertaken in CG153. In Table 52 below the ERG have updated added a fourth scenario using the observed costs from Fonia inflated to 2012/13 prices.[7] Previously a wide range of costs have been used for BSC. In Woolacott an annual cost of £113.20 representing 2 additional outpatient visits was used.[6] The most recent TA, for ustekinumab used an annual cost of £6,209.54 and CG153 assumed £10,730.00.

Table 52: BSC costs using low cost cyclosporine for previously reported scenarios

Scenario	Cost per cycle of BSC	Cost per year of BSC
Manufacturer's base-case	£887.90	£11,542.73
Low cost cyclosporine	£852.79	£11,086.27
Scenario 1 (0.25 admission in high need, 2.55 in very high need, each of 20.8 days)	£568.31	£7,388.03
Scenario 2 (0.312 admissions for all, of 20.8 days)	£405.49	£5,271.37
Scenario 3 (no hospitalisations)	£261.17	£3,3395.21
Scenario 4 (direct cost observed from Fonia, uprated to 2012/13 prices consistent with manufacturer's approach)	£352.41	£4,581.34

In some of the scenarios described above the cycle cost of BSC was lower than the £462.56 cost the manufacturer applied to patients that did not respond. The ERG did not consider it reasonable that a cycle of BSC would be less expensive than the additional cost of non-response. To ensure consistency with the approach taken by the manufacturer in the modelling of costs associated with treatment non-response in Scenario 4 the ERG assumed the cost per cycle of non-respondents was the same as for BSC (i.e. £352.41 in this scenario rather than £462.56 as in the MS). For Scenario 4 no additional assumption was necessary about the cost of cyclosporine because the estimate from Fonia is a direct estimate of the annual BSC cost and already incorporates the use of other treatments such as cyclosporine and methotrexate.

As shown in Table 53 when the Fonia scenario is compared to the no hospitalisation scenario in the DLQI>10 population the incremental costs are higher in the no hospitalisation scenario. In contrast,

Table 54 shows that when the Fonia scenario is compared to the no hospitalisation scenario in the DLQI≤10 population the incremental costs are lower in the no hospitalisation scenario. This difference in the direction of effect appeared to be due to the DLQI≤10 model having no additional cost of non-responders.

Table 53: Results of additional BSC cost scenario DLQI>10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's base-case (1 admission in high need, 2.55 in very high need, each of 20.8 days)					
Comparator sequence	£92,705	6.68			
Apremilast sequence	£89,479	6.82	–£3,226	0.14	Dominant
Scenario 1 (0.25 admission in high need, 2.55 in very high need, each of 20.8 days)					
Comparator sequence	£73,988	6.68			
Apremilast first sequence	£74,431	6.82	£443	0.14	£3,118
Scenario 2 (0.312 admissions for all, of 20.8 days)					
Comparator sequence	£64,453	6.68			
Apremilast first sequence	£66,765	6.82	£2,313	0.14	£16,273
Scenario 3 (no hospitalisations)					
Comparator sequence	£56,001	6.68			
Apremilast first sequence	£59,970	6.82	£3,970	0.14	£27,934
Scenario 4 (Fonia uprated cost of £352.41 applied to BSC and non-responders)					
Comparator sequence	£61,057	6.68			
Apremilast first sequence	£63,595	6.82	£2,538	0.14	£17,859

Table 54: Results of additional BSC cost scenario DLQI≤10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's base-case (1 admission in high need, 2.55 in very high need, each of 20.8 days)					
Comparator sequence	£98,265	5.96			
Apremilast sequence	£91,965	6.01	-£6,300	0.05	Dominant
Scenario 1 (0.25 admission in high need, 2.55 in very high need, each of 20.8 days)					
Comparator sequence	£62,896	5.96			
Apremilast first sequence	£62,873	6.01	-£22	0.05	Dominant
Scenario 2 (0.312 admissions for all, of 20.8 days)					
Comparator sequence	£44,876	5.96			
Apremilast first sequence	£48,052	6.01	£3,176	0.05	£64,398
Scenario 3 (no hospitalisations)					
Comparator sequence	£28,904	5.96			
Apremilast first sequence	£34,915	6.01	£6,011	0.05	£121,875
Scenario 4 (Fonia uprated cost of £352.41 applied to BSC and non-responders)					
Comparator sequence	£39,001	5.96			
Apremilast first sequence	£43,221	6.01	£4,219	0.05	£85,538

6.2.3 The effectiveness of BSC

In addition to assuming a high cost of BSC the manufacturer assumes, in the base-case analysis, that patients treated with BSC never have an improvement in their PASI score from baseline, i.e. a PASI0, despite receiving treatment. Limited additional analyses were conducted by the manufacture to test this assumption.

The manufacturer's base-case is inconsistent with CG153 and previous cost-effectiveness analysis which assumed a level of BSC response. In addition previous analyses have assumed that patients who do not achieve a response rate of PASI50 or more on BSC are assumed to achieve a PASI improvement of between 0 and 50, in contrast to the PASI0 that is always assumed in the manufacturer's base-case.

In CG153 96.2% of patients on BSC do not achieve PASI50; however it is not the same as saying patients have no improvement, as not all patients who have a PASI<50 response will have PASI=0 response. In CG153 the guideline development group assumed a HRQoL improvement of 0.05 for those patients that did not have a PASI50 or greater response. In the Woolacott model patients

receiving BSC who do not achieve PASI50 are also assumed to have an improvement in HRQoL of 0.05.

The ERG has constructed four alternative scenarios based on CG153 and Woods[35] study:

Scenario 1: CG153 base-case approach;

Scenario 2: effectiveness based on observations from Woods 2008 wherein **65%** of people admitted for inpatient treatment with baseline PASI10 to 20 achieved PASI50;

Scenario 3: effectiveness based on observations from Woods 2008 wherein **83%** of people admitted for inpatient treatment with baseline >PASI20 achieved PASI50.

Scenario 4: effectiveness based on observations from Woods 2008, scenario 2 (**65%** of patients admitted achieving PASI50) with an additional **30%** of these achieving PASI75.

Scenarios 2 and 3 are consistent with those applied in the CG153 sensitivity analysis. The fourth scenario incorporates additional evidence from Woods, the authors noted:

'Two thirds (65%) of our patients achieved PASI 50 during their hospital stay. However, only 30% of our patients achieved PASI 75.' p269[35]

In the clarifications provided by the manufacturer (clarification B9) they noted that they felt the use of the Woods results represented an improbable scenario in clinical practice. The ERG notes, however, that no reason was given for this position, nor any alternative data provided to discredit its use. The ERG acknowledges the Woods study does not represent the same population as considered in this submission, representing all psoriatic patients admitted to hospital rather than only those with moderate to severe plaque psoriasis. However, in the view of the ERG there is likely to be significant similarities across types of psoriasis. The ERG also notes that the data informing Woods is from 2004 and as such there is likely to have been improvements in the standard of care provided during a period of hospitalisation.

In the implementation of these scenarios the ERG has taken the same approach as that taken by the manufacturer in their clarification response B9, that is, unless otherwise stated, the stated improvement in PASI score is in addition to the placebo response presented in the CG153 report. For clarity the implications of the three scenarios are presented in Table 55 below compared to the original MS base-case and the CG153 approach. As the efficacy of BSC is modelled by the manufacturer by the proportion of patients achieving the different HRQoL levels these are included in the table.

Table 55: Effectiveness of BSC scenarios

	Associated HRQoL score	**MS base-case**	**Scenario 1**	**Scenario 2**	**Scenario 3**	**Scenario 4**
PASI0	**0**	100%	0%	0%	0%	0%
PASI<50	**0.05**	0%	96.2%	35.0%	17.0%	35%
PASI 50-75	**0.17**	0%	3.0%	64.2% *(65%-0.7%-0.1%)*	82.2% *(83%-0.7%-0.1%)*	35% *(65%-30%)*
PASI75-90	**0.19**	0%	0.7%	0.7%	0.7%	29.9% *(30%-0.01%)*
PASI>90	**0.21**	0%	0.1%	0.1%	0.1%	0.1%

Table 56: Results of additional BSC efficacy scenarios DLQI>10 model

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£/QALY)**
Manufacturer's base-case					
Comparator sequence	£92,705	6.68			
Apremilast sequence	£89,479	6.82	–£3,226	0.14	Dominant
Scenario 1					
Comparator sequence	£92,705	6.92			
Apremilast first sequence	£89,479	7.02	-£3,226	0.09	Dominant
Scenario 2					
Comparator sequence	£92,705	7.25			
Apremilast first sequence	£89,479	7.28	-£3,226	0.03	Dominant
Scenario 3					
Comparator sequence	£92,705	7.35			
Apremilast first sequence	£89,479	7.36	-£3,226	0.01	Dominant
Scenario 4					
Comparator sequence	£92,705	7.28			
Apremilast first sequence	£89,479	7.30	-£3,226	0.02	Dominant

Table 57: Results of additional BSC efficacy scenarios DLQI≤10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's base-case					
Comparator sequence	£98,265	5.96			
Apremilast sequence	£91,965	6.01	-£6,300	0.05	Dominant
Scenario 1					
Comparator sequence	£98,265	5.97			
Apremilast first sequence	£91,965	6.01	-£6,300	0.05	Dominant
Scenario 2					
Comparator sequence	£98,265	6.07			
Apremilast first sequence	£91,965	6.10	-£6,300	0.03	Dominant
Scenario 3					
Comparator sequence	£98,265	6.10			
Apremilast first sequence	£91,965	6.13	-£6,300	0.02	Dominant
Scenario 4					
Comparator sequence	£98,265	6.10			
Apremilast first sequence	£91,965	6.12	-£6,300	0.03	Dominant

As Table 56 and Table 57 show in all scenarios the apremilast sequence remains dominant (higher QALYs and lower costs), but the magnitude of improvement decreases as low as 0.01 in the DLQI>10 population and 0.02 in the DLQI≤10 population.

6.2.4 HRQoL

6.2.4.1 Different HRQoL values by PASI state

As raised in Section 5.2.7 the ERG believes the approach taken to modelling HRQoL presented by the manufacturer to be inappropriate. To take account of the vast level of available data on the HRQoL of this patient population (both DLQI>10 and ≤10) the ERG has constructed four additional scenarios using trial data and mapping algorithms from the literature, two for the DLQI>10 population (Table 58) and two for the ≤10 population (Table 59). These scenarios capture the variation in HRQoL values from using EQ-5D data directly observed in the trial or by mapping the DLQI from the trial using the algorithm from previous appraisals.

Table 58: DLQI>10 HRQoL by PASI score scenarios

Scenario	PASI<50	PASI50-75	PASI75-90	PASI>90
Manufacturer's base-case	0.0500	0.1700	0.1900	0.2100
Scenario 1: EQ-5D observed from combined PSOR-008/009/010 trials	0.0134	0.0537	0.1150	0.1333
Scenario 2: DLQI mapped from the combined PSOR-008/009/010 trials using the Woolacott mapping function	0.08748	0.17496	0.20736	0.26244

The same two scenarios were investigated by the ERG in the DLQI≤10 population model, using the DLQI≤10 specific data. The scenarios are presented in Table 59 below. As discussed previously the difference between the manufacturer's base-case and scenario 1 is the addition of data from trial PSOR-010. The HRQoL scores used in scenario 1 are very similar to those used in the manufacturer's base-case however, there is an inconsistency in the values used in scenario 1 as the PASI50-75 HRQoL is larger than the PASI75-90 HRQoL. This small difference only has a small effect on the ICER (Table 61).

Table 59: DLQI≤10 HRQoL by PASI score scenarios

Scenario	PASI<50	PASI50-75	PASI75-90	PASI>90
Manufacturer's base-case: rounded EQ-5D observed from combined PSOR-008/009	0	0.02	0.03	0.07
Scenario 1: EQ-5D observed from combined PSOR-008/009/010 trials	-0.0024	0.0275	0.0256	0.0704
Scenario 2: DLQI mapped from the combined PSOR-008/009/010 trials using the Woolacott mapping function	0.02414	0.05524	0.06529	0.08343

The results of these scenarios are presented in Table 60 and Table 61 below. As expected these scenarios do not affect the incremental costs, but do affect the QALYs. These scenarios demonstrate that lower HRQoL values decrease the incremental QALY benefit, but apremilast continues to be dominant in all scenarios.

Table 60: Results of additional HRQoL scenarios DLQI>10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's base-case					
Comparator sequence	£92,705	6.68			
Apremilast first sequence	£89,479	6.82	–£3,226	0.14	Dominant
Scenario 1: EQ-5D observed from combined PSOR-008/009/010 trials					
Comparator sequence	£92,705	6.40			
Apremilast first sequence	£89,479	6.48	-£3,226	0.08	Dominant
Scenario 2: DLQI mapped from the combined PSOR-008/009/010 trials using the Woolacott mapping function					
Comparator sequence	£92,705	6.81			
Apremilast first sequence	£89,479	6.97	-£3,226	0.17	Dominant

Table 61: Results of additional HRQoL scenarios DLQI≤10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's base-case					
Comparator sequence	£98,265	5.96			
Apremilast first sequence	£91,965	6.01	-£6,300	0.049	Dominant
Scenario 1: EQ-5D observed from combined PSOR-008/009/010 trials					
Comparator sequence	£98,265	5.96			
Apremilast first sequence	£91,965	6.01	-£6,300	0.046	Dominant
Scenario 2: DLQI mapped from the combined PSOR-008/009/010 trials using the Woolacott mapping function					
Comparator sequence	£98,265	5.96			
Apremilast first sequence	£91,965	6.04	-£6,300	0.08	Dominant

6.2.5 The ERG preferred analysis

The ERG preferred analysis incorporates the manufacturer's updated NMA results for the DLQI>10 population, BSC costs from UK observational data, HRQoL from the trial and BSC effectiveness data from the placebo arm of a meta-analysis of second line biologic trials.

The following scenarios are combined one at a time to understand the individual impact of each assumption.

1. Manufacturer's NMA results including PSOR-010 trial for the DLQI>10 population; no updated NMA results were provided for the DLQI≤10 population.

2. BSC costs from Fonia as well as cost of non-responders per cycle
3. HRQoL from EQ-5D observed from the combined three trials (to account for inconsistency in HRQoL from combining the 3 trials in DLQI≤10 population the ERG analysis for this population uses the manufacturer's base-case HRQoL results)
4. BSC efficacy data from base-case CG153 analysis

Results of this analysis are presented for the DLQI>10 population in Table 62 and Table 63 for the DLQI≤10 population. As demonstrated previously, the updated NMA has only a small effect on the manufacturer's base-case ICER. The results of the updated NMA are slightly different from those presented by the manufacturer. It is not clear what the difference is because the manufacturer did not provide their model with these inputs, but the difference may be from the manufacturer rounding the NMA results provided to the ERG.

Table 62: Results of ERG base-case analysis scenarios DLQI>10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's base-case					
Comparator sequence	£92,705	6.68			
Apremilast first sequence	£89,479	6.82	–£3,226	0.14	Dominant
Incorporating NMA results including PSOR-010 (1)					
Comparator sequence	£92,840	6.66			
Apremilast first sequence	£89,696	6.80	-£2,144	0.14	Dominant
Addition of BSC cost from Fonia (1+2)					
Comparator sequence	£60,687	6.66			
Apremilast first sequence	£63,265	6.80	£2,578	0.14	£18,342
Addition of HRQoL observed from trials (1+2+3)					
Comparator sequence	£60,687	6.39			
Apremilast first sequence	£63,265	6.47	£2,578	0.08	£32,636
Addition of BSC effectiveness data (1+2+3+4), ERG base-case					
Comparator sequence	£60,687	6.46			
Apremilast first sequence	£63,265	6.53	£2,578	0.07	£39,391

Scenarios 1 and 3 from above were not considered in the DLQI≤10 population because:

i) the manufacturer did not provide an updated NMA incorporating PSOR-010 in the DLQI≤10 population;

ii) the ERG used the manufacturer's HRQoL estimates due to the inconsistency across health states discussed in Section 5.

The results below demonstrate that using the BSC costs in Fonia result in and ICER of £85,538 per QALY. The ICER increases to £87,908 per QALY when it is also assumed that BSC also has a treatment effect.

Table 63: Results of ERG base-case analysis scenarios DLQI≤10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's base-case					
Comparator sequence	£98,265	5.96			
Apremilast first sequence	£91,965	6.01	-£6,300	0.049	Dominant
Incorporating BSC cost from Fonia (2)					
Comparator sequence	£39,001	5.96			
Apremilast first sequence	£43,221	6.01	£4,219	0.049	£85,538
Addition of BSC effectiveness data (2+4), ERG base-case					
Comparator sequence	£39,001	5.97			
Apremilast first sequence	£43,221	6.01	£4,219	0.048	£87,908

6.2.5.1 Additional scenario analyses using the ERG's preferred analysis

In Section 5.2.6 the ERG discusses the importance of withdrawal rates in the model. In the base-case analysis the manufacturer assumes that all treatments are withdrawn from at the same annual rate of 20%. The ERG considers this assumption to be unsupported by evidence and in need of further exploration because of the differences in administration, the separate mechanisms of action and the differences in efficacy. The manufacturer presents evidence from the second year of the PSOR-008 trial that the withdrawal rate of apremilast is [redacted]%. The ERG undertake further analyses applying the withdrawal rate of apremilast to the ERG's preferred analysis. In scenario 1 the ERG assume that all treatments have the same withdrawal rate as apremilast, i.e. [redacted]%. In the second scenario the ERG assume only apremilast has a withdrawal rate of [redacted]% and that all other treatments have the same withdrawal rate of 20% (Table 64). In the DLQI≤10 population no other treatments were included in the treatment sequence so the annual withdrawal rate of [redacted]% was only applied to apremilast (Table 65). These analyses demonstrate that the ERG's preferred analysis is sensitive to differences in the withdrawal rate. A higher withdrawal rate results in a higher ICER for the apremilast sequence. When it is assumed that apremilast has a different and higher withdrawal rate the ICER increases to £58,789 per QALY in the DLQI>10 population.

Table 64: Results of ERG base-case withdrawal analyses DLQI>10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base-case (20% annual withdrawal)					
Comparator sequence	£60,687	6.46			
Apremilast first sequence	£63,265	6.53	£2,578	0.07	£39,391
Scenario 1 ([redacted]% annual withdrawal)					
Comparator sequence	£55,542	6.35			
Apremilast first sequence	£58,770	6.40	£3,229	0.06	£55,857
Scenario 2 ([redacted]% annual withdrawal apremilast, 20% other treatments)					
Comparator sequence	£60,687	6.46			
Apremilast first sequence	£63,249	6.50	£2,561	0.04	£58,789

Table 65: Results of ERG base-case withdrawal analyses DLQI≤10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base-case (20% annual withdrawal)					
Comparator sequence	£39,001	5.97			
Apremilast first sequence	£43,221	6.01	£4,219	0.048	£87,908
Scenario 1 ([redacted]% annual withdrawal)					
Comparator sequence	£39,001	5.97			
Apremilast first sequence	£42,120	6.00	£3,118	0.03	£99,169

In Section 5.2.8.2 the ERG discussed the monitoring costs of apremilast. The ERG noted the manufacturer's assumption that apremilast would have fewer follow-up physician visits than the other biologics. They assume that patients on apremilast will have the same number of outpatient visits as other treatments during the trial period but will only have one a year during continuous use, compared to four annual visits for all other biologic treatments. Discussions with our clinical advisor suggested that the monitoring was likely to be similar in practice given that many patients will continue to receive other therapies and also concerns whether clinicians would prescribe a drug at this cost for such an extended period of time. The frequency of monitoring will be important for apremilast as this may influence the amount of medication prescribed at one time. The more medication prescribed could result in more wasted medication when the patient withdraws, conversely the more frequently the medication is prescribed, and therefore the less potential for wasted medication, the higher the physician costs. The ERG undertook further analyses to understand the effect of this assumption on

the ERG's preferred analysis. In the first scenario the ERG assumed that patients on apremilast would have the same number of physician visits as other biologics. This assumption increased the ICER to £44,459 per QALY (Table 66) in the DLQI>10 population and to £95,820 per QALY in the DLQI≤10 population (Table 67). In scenario 2 the ERG assumed that patients who withdraw from apremilast will have 3 months of wasted medication at a onetime cost of £1,787; in scenario 3 the ERG assumed 6 months of wasted medication at a onetime cost of £3,575. These assumptions increased the ICER up to £90,681 per QALY and £159,276 per QALY in the DLQI>10 population and the DLQI≤10 population respectively. Although 6 months of wasted medication seems very high, this might be the average amount of wasted medication in a population that is prescribed medication only once a year.

Table 66: Results of ERG base-case monitoring and wastage costs analyses DLQI>10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG preferred analysis					
Comparator sequence	£60,687	6.46			
Apremilast first sequence	£63,265	6.53	£2,578	0.07	£39,391
Scenario 1 (apremilast 4 visits per year)					
Comparator sequence	£60,687	6.46			
Apremilast first sequence	£63,597	6.53	£2,910	0.07	£44,459
Scenario 2 (3 months of apremilast wasted at non-response)					
Comparator sequence	£60,687	6.46			
Apremilast first sequence	£64,944	6.53	£4,257	0.07	£65,036
Scenario 3 (6 months of apremilast wasted at non-response)					
Comparator sequence	£60,687	6.46			
Apremilast first sequence	£66,623	6.53	£5,935	0.07	£90,681

Table 67: Results of ERG base-case monitoring and wastage costs analyses DLQI≤10 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG preferred analysis					
Comparator sequence	£39,001	5.97			
Apremilast first sequence	£43,221	6.01	£4,219	0.048	£87,908
Scenario 1 (apremilast 4 visits per year)					
Comparator sequence	£39,001	5.97			
Apremilast first sequence	£43,600	6.01	£4,599	0.05	£95,820
Scenario 2 (3 months of apremilast wasted at non-response)					
Comparator sequence	£39,001	5.97			
Apremilast first sequence	£44,933	6.01	£5,932	0.05	£123,592
Scenario 3 (6 months of apremilast wasted at non-response)					
Comparator sequence	£39,001	5.97			
Apremilast first sequence	£46,646	6.01	£7,644	0.05	£159,276

6.3 Conclusions from ERG analyses

The ERG considered that the manufacturer's base-case cost-effectiveness results were not necessarily a sufficient basis to inform the most efficient use and position of apremilast. The ERG was also concerned that uncertainties surrounding the cost-effectiveness of the comparator sequence and any implications for the cost-effectiveness of apremilast had not been robustly demonstrated by the manufacturer, since only partial comparisons were made.

The ERG conducted a range of exploratory analyses to assess the uncertainties raised in the review and critique of the manufacturer's clinical and cost-effectiveness evidence. The ERG's exploratory analyses focussed on: the issues and potential approaches to sequencing, the costs associated with BSC, the effectiveness of BSC in improving PASI score, and different approaches to HRQoL. Where appropriate all exploratory analyses were conducted on both the DLQI>10 and DLQI⩽10 populations.

The additional analyses undertaken by the ERG suggest that the addition of apremilast to a treatment sequence does not decrease costs. The ICERs of the ERG's preferred analyses ranged from £39,391 to £90,681 per QALY in the DLQI>10 population and from £87,908 to £159,276 per QALY in the DLQI⩽10 population.

7 End of life

This intervention does not meet the end of life criteria published by NICE.

8 Overall conclusions

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

The cost-effectiveness of apremilast is dependent on questionable assumptions about the costs and effectiveness of BSC. The ERG did not consider that the cost approach taken by the manufacturer represented the appropriate BSC for the average patient who would otherwise be taking apremilast. Using evidence from UK clinical practice the ICER of apremilast increased above £20,000 per QALY in both patient populations of interest. Trial data on the withdrawal rate of apremilast increased the ICER further. Treatment adherence was not considered in the model, but drug wastage was explored by the ERG.

8.1 Implications for research

There is still uncertainty about the long term safety of apremilast and longer term response. Longer-term data from the ongoing extension phase of the PSOR-008, PSOR-009 and PSOR-010 trials should provide additional information about loss of response to treatment, as it is unclear why [redacted] patients who continued apremilast treatment during the randomised treatment withdrawal phase of PSOR-008 lost PASI-75 response before Week 52. In addition, longer term safety data from these trials will be informative, as currently the safety data only extends to one year.

The manufacturer suggests positioning apremilast before biological therapy in the treatment pathway. However, no data were presented on patients' response to biological therapies after having received apremilast; therefore, it is unclear whether subsequent treatment effectiveness is affected by prior use of apremilast.

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10 Appendices

10.1 ERG appraisal of the network meta-analysis

Appraisal criteria	Item satisfactory?
A. DEFINITION OF THE DECISION PROBLEM	
A1. Target population for decision	
A1.1. Has the target patient population for decision been clearly defined?	Yes
A2. Comparators	
A2.1. Decision Comparator Set: Have all the appropriate treatments in the decision been identified?	Yes in terms of those treatments approved by NICE
A2.2. Synthesis Comparator Set: Are there additional treatments in the Synthesis Comparator Set, which are not in the Decision Comparator Set? If so, is this adequately justified?	Yes (no additional treatments included). It could be argued that licenced or near-licence new treatments not yet approved by NICE such as secukinumab should have been included in the NMA as these are, from a scientific perspective valid comparators and their inclusion would strengthen the network and also make the analysis durable if/when new treatments are approved
A3. Trial inclusion/exclusion	
A3.1 Is the search strategy technically adequate and appropriately reported?	Yes
A3.2 Have all trials involving at least two of the treatments in the Synthesis Comparator Set been included?	Yes
A3.3 Have all trials reporting relevant outcomes been included?	Yes
A3.4 Have additional trials been included? If so, was this adequately justified?	Yes (no additional trials included)
A4. Treatment definition	
A4.1 Are all the treatment options restricted to specific doses and co-treatments, or have different doses and co-treatments been 'lumped' together? If the latter, is it adequately justified?	Yes (different doses have not been 'lumped' together)
A4.2 Are there any additional modelling assumptions?	The model assumes that PASI cut offs are drawn from an underlying continuous distribution using a multinomial model. This assumption is not tested but is reasonable given the nature of the data
A5. Trial outcomes and scale of measurement chosen for the synthesis	
A5.1 Where alternative outcomes are available, has the choice of outcome measure used in the synthesis been justified?	Yes – PASI cutoffs are the outcomes in the economic model
A5.2 Have the assumptions behind the choice of scale been justified?	Yes
A6. Patient population: trials with patients outside the target population	
A6.1 Do some trials include patients outside the target population? If so, is this adequately justified?	N/A (trials only include target population – either whole trial population or biologic naïve for the subgroup NMA)
A6.2 What assumptions are made about the impact, or lack of impact this may have on the relative treatment effects? Are they adequately justified?	No exploration of factors that would have made the population more relevant to the exact licenced population have been explored
A6.3 Has an adjustment been made to account for these differences?	N/A
A7. Patient population: heterogeneity within the target population	
A7.1 Has there been a review of the literature concerning potential modifiers of treatment effect?	N/A
A7.2 Are there apparent or potential differences between trials in their patient populations albeit within the target population? If so, has this been adequately taken into account?	N/A (patient characteristics were broadly similar between trials)
A8. Risk of bias	
A8.1 Is there a discussion of the biases to which these trials, or this ensemble of trials, are vulnerable?	N/A (most trials were rated good or excellent quality)
A8.2 If a bias risk was identified, was any adjustment made to the analysis and was this adequately justified?	N/A
A9. Presentation of the data	
A9.1 Is there a clear table or diagram showing which data have been included in the base-case analysis?	Yes (Table 19 of MS)
A9.2 Is there a clear table or diagram showing which data have been excluded and why?	N/A (relevant outcomes data were

	included)
B. METHODS OF ANALYSIS AND PRESENTATION OF RESULTS	
B1. Meta-analytic methods	
B1.1 Is the statistical model clearly described?	Yes (adequately described)
B1.2 Has the software implementation been documented?	Details of software used have been provided, but the actual code was not presented
B2. Heterogeneity in the relative treatment effects	
B2.1 Have numerical estimates been provided of the degree of heterogeneity in the relative treatment effects?	No (the MS states that heterogeneity was assessed using the Q-statistic and was present for PASI-50 estimates for adalimumab ($p<0.05$). Numerical estimates were not presented for other results)
B2.3 Has there been adequate response to heterogeneity?	Yes (the authors removed one trial from the heterogeneity assessment to investigate heterogeneity and presented a hypothesis as to why it may have been significant)
B2.4 Does the extent of unexplained variation in relative treatment effects threaten the robustness of conclusions?	Unlikely to threaten the robustness of the conclusions
B2.5 Has the statistical heterogeneity between baseline arms been discussed?	The manufacturer acknowledges that there is some heterogeneity between trials and that the relatively small number of trials and limited ability to adjust for heterogeneity reduces the degree of certainty associated with the results of the analysis
B3. Baseline model for trial outcomes	
B3.1 Are baseline effects and relative effects estimated in the same model? If so, has this been justified?	N/A
B3.2 Has the choice of studies to inform the baseline model been explained?	N/A
B4. Presentation of results of analyses of trial data	
B4.1 Are the relative treatment effects (relative to a placebo or 'standard' comparator) tabulated, alongside measures of between-study heterogeneity if a RE model is used?	Relative treatment effects were tabulated, but not alongside heterogeneity
B4.2 Are the absolute effects on each treatment, as they are used in the CEA, reported?	Yes
B5. Synthesis in other parts of the natural history model	
B5.1 Is the choice of data sources to inform the other parameters in the natural history model adequately described and justified?	N/A
B5.2 In the natural history model, can the longer-term differences between treatments be explained by their differences on randomised trial outcomes?	N/A
C. ISSUES SPECIFIC TO NETWORK SYNTHESIS	
C1. Adequacy of information on model specification and software implementation	
C2. Multi-arm trials	
C2.1 If there are multi-arm trials, have the correlations between the relative treatment effects been taken into account?	As WinBUGS code was not provided this could not be checked, but as a standard NMA model appeared to be used it is probable that this was done
C3. Connected and disconnected networks	
C3.1 Is the network of evidence based on randomised trials connected?	Yes
C4. Inconsistency	
C4.1 How many inconsistencies could there be in the network?	Most trials were comparisons with placebo, so there was limited trial evidence to investigate inconsistencies between treatments
C4.2 Are there any *a priori* reasons for concern that inconsistency might exist, due to systematic clinical differences between the patients in trials comparing treatments A and B, and the patients in trials comparing treatments A and C, etc?	No
C4.3 Have adequate checks for inconsistency been made?	These were not reported in the MS. However, the ERG has checked the results of the NMA

	against the data input into the analysis and also against the results of similar NMA and found the results to be reasonably consistent with these
C4.4 If inconsistency was detected, what adjustments were made to the analysis, and how was this justified?	This was not reported in the MS nor in the clarification response
D. EMBEDDING THE SYNTHESIS IN A PROBABILISTIC COST EFFECTIVENESS ANALYSIS	
D1. Uncertainty propagation	
D1.1 Has the uncertainty in parameter estimates been propagated through the CEA model?	Yes
D2. Correlations	
D2.1 Are there correlations between parameters? If so, have the correlations been propagated through the CEA model?	Yes