NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Apremilast for treating active psoriatic arthritis (rapid review TA372) [ID1017]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

NICE National Institute for Health and Care Excellence

NICE guidance

Apremilast for treating active psoriatic arthritis

Technology appraisal guidance
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1 Guidance

1.1 Apremilast alone or in combination with disease-modifying antirheumatic drug (DMARD) therapy is not recommended within its marketing authorisation for treating adults with active psoriatic arthritis that has not responded to prior DMARD therapy, or such therapy is not tolerated.

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

2 The technology

2.1 Apremilast (Otezla, Celgene) is a small-molecule inhibitor of phosphodiesterase 4 (PDE4). Apremilast down-regulates the inflammatory response by modulating the expression of inflammatory and anti-inflammatory cytokines and mediators associated with psoriatic arthritis (including tumour necrosis factor [TNF]-alpha and interleukin [IL]-23). Its UK marketing authorisation states that apremilast 'alone or in combination with disease-modifying antirheumatic drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy'.

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

2.3 Apremilast is an oral tablet. The recommended dosage is 30 mg twice daily after an initial titration schedule. A single 10 mg dose is given on the first day of treatment; this is titrated to 30 mg twice daily over 5 days (see the summary of product characteristics for the dose titration schedule). The price of apremilast is £265.18 for a 14-day treatment initiation pack (4×10 mg tablet; 4×20 mg tablet; 19×30 mg tablet) and £550.00 for a 28-day-treatment standard pack (56×30 mg; excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] online, accessed March 2015). The cost of 12 months of treatment with apremilast is estimated at £7140.18 (company submission). Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

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

Clinical effectiveness

3.1 The company's submission included 3 international, multicentre, randomised, double-blind, placebo-controlled trials, that were almost identical in design (n=1493): PSA-002 (also known as PALACE 1), PSA-003 (PALACE 2) and PSA-004 (PALACE 3). The trials included adults with active psoriatic arthritis (3 or more swollen and tender joints for at least 6 months) who previously had treatment with conventional disease-modifying antirheumatic drugs (DMARDs) or tumour necrosis factor (TNF) alpha inhibitors (PSA-004 also included patients with at least 1 psoriasis lesion, of at least 2 cm, which had not responded adequately to conventional DMARDs). The baseline characteristics were very similar across the randomised groups in the 3 trials. An analysis of pooled data from the 3 trials was included in the company submission.

3.2 Each trial had a planned duration of 5 years and consisted of 2 treatment phases: an initial 24-week double-blinded, placebo-controlled phase and a 236-week (4.5 years) active treatment/long-term safety phase. At week 16, all people in the placebo group whose disease had not shown improvement (that is, whose swollen joint count and tender joint count had not improved by at least 20% from baseline) crossed over to blinded active treatment (randomised to either 20 mg or 30 mg apremilast). Those already having apremilast whose disease did not improve, remained on the same dose of apremilast. At week 24, people having placebo were re-randomised to have apremilast.

3.3 The 3 trials collected measures of health-related quality of life using: the Health Assessment Questionnaire Disability Index (HAQ-DI); the SF-36v2 survey; EQ-5D; the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Medical Outcomes Study (MOS) sleep scale; and the work limitations questionnaire (WLQ).

3.4 The primary outcome in all 3 trials was the American College of Rheumatology response criteria (ACR20 response) at week 16. The major secondary outcome was the change from baseline to week 16 in the HAQ-DI score and the modified

Psoriasis Arthritis Response Criteria (PsARC) response, and a 75% reduction in the Psoriasis Area Severity Index (PASI-75 response). Other outcomes included: Maastricht Ankylosing Spondylitis Enthesitis Score (MASES); dactylitis severity scores; ACR50; and ACR70. Data were collected at weeks 16, 24 and 52. Follow-up data were included for up to 104 weeks for PSA-002 and up to 52 weeks for PSA-003 and PSA-004.

3.5 The company presented pooled analyses of the 3 trials which showed that, compared with placebo, apremilast was associated with statistically significant improvements in the proportion of people who had an ACR20 response. An ACR20 response was experienced by 37% of people having apremilast compared with 19% having placebo ($p \leq 0.0001$). Apremilast, compared with placebo, was also associated with statistically significant improvements in the proportion of people experiencing an ACR50 response (13.9% and 6.5% respectively; $p \leq 0.0001$), PsARC response (49% and 30% respectively; $p \leq 0.0001$) and minimal clinically important difference (MCID) of equal to, or more than, 0.30 in the HAQ-DI score (36.4% and 26%, respectively; $p \leq 0.001$). No statistically significant difference was shown for ACR70 response or enthesitis score.

3.6 In the 30 mg apremilast group and the placebo group, 221 and 205 people, respectively, had dactylitis. The dactylitis count at baseline was 3.3 (standard deviation [SD] 3.26) in the 30 mg apremilast group and 3.2 (SD 3.29) in the placebo group. The reduction in dactylitis at both week 16 and 24 was greater in the 30 mg apremilast group than in the placebo group (−1.7, standard error [SE] 0.17] compared with −1.3, SE 0.18, $p=0.0485$; and 1.8, SE 0.16, compared with −1.2, SE 0.17, $p=0.0097$ respectively). At week 52, 65.9% of people with pre-existing dactylitis no longer had the condition on their hands or feet compared with 43.1% at week 16.

3.7 In the pooled analysis, 249 people in the 30 mg apremilast group and 231 people in the placebo group had at least 3% of their body surface area affected by psoriasis at week 16 and were therefore evaluated for a PASI-75 response. A greater proportion of people in the apremilast group than in the placebo group achieved a PASI-75 response at week 16 (22.1% compared with 5.2%, $p<0.0001$). At week 52, 38.3% of people had a PASI-75 response. The company noted that the pooled population had low baseline PASI scores making

the PASI scale less sensitive to change and possibly underestimating the magnitude of improvement.

3.8 As there were no head-to-head trials comparing apremilast with all of the relevant comparators, the company carried out a systematic review and a network meta-analysis using a Bayesian analysis framework for the outcomes PsARC, ACR 20/50/70, PASI, and HAQ-DI. The company considered the treatments of interest in the network meta-analysis to be apremilast, adalimumab, etanercept, golimumab and infliximab. However, following a clarification request from NICE and the Evidence Review Group (ERG) for a more comprehensive set of analyses, updated network meta-analyses were presented. These included 19 studies that compared apremilast with adalimumab, etanercept, golimumab, infliximab, certolizumab pegol and ustekinumab. The deviance information criterion (DIC) slightly favoured the fixed-effect model so that was selected for all outcomes, except HAQ-DI for which a random-effects model was selected. The efficacy outcome endpoints in the included trials ranged from 12–16 weeks. These analyses were carried out for the whole population and also for people who have not had TNF-alpha inhibitor treatment. The apremilast results were provided as academic in confidence and therefore cannot be reported.

3.9 The highest probabilities of PsARC response for the whole population were seen with golimumab 50 mg followed by golimumab 100 mg and infliximab 5 mg/kg. Probability of PsARC response with apremilast was lower than all of the other active treatments. The company validated the PsARC result using data from Rodgers et al., 2011.

3.10 The highest probability of response for ACR20, 50 and 70 for the whole population was seen with infliximab 5 mg/kg. Apremilast had a lower probability of response than all of the other active treatments. The highest probability of response for all of the PASI outcomes was also seen with infliximab 5 mg/kg. Apremilast had a higher probability of response compared with placebo.

3.11 When comparing active treatments with placebo, large reductions in HAQ-DI were seen after treatment with infliximab and etanercept. The smallest reduction was seen after treatment with apremilast. Reductions in HAQ-DI were larger in people who had a PsARC response than in those who did not.

3.12 The company did a subgroup analysis for people who had not had TNF-alpha inhibitor treatment. This was not a predefined subgroup in the trials. Outcomes for ACR20, 50 and 70, PASI, PsARC and HAQ-DI were calculated during the network meta-analyses. The data showed the effect of apremilast to be consistent with the treatment benefit observed for the whole population.

3.13 Adverse events were not a primary outcome in any of the trials, however, the trials did record serious adverse events, severe adverse events and adverse events leading to discontinuation from treatment. The company presented data from the pooled analysis of all 3 trials which showed that treatment-related adverse events were almost double in the apremilast 30 mg group compared with the placebo group; 189 (38.0%) and 92 (18.6%) respectively. Adverse events did not lead to deaths in either group but did lead to discontinuation of treatment; 36 people (7.2%) in the apremilast group and 21 people (4.2%) in the placebo group. The adverse events decreased between weeks 0, 24 and 52.

Cost effectiveness

Company's original submission

3.14 The company developed a Markov model with a 28-day cycle length (to account for the 12- and 16-week treatment trial periods) and 40-year time horizon. The company did not apply a half-cycle correction to the model because it considered the cycle to be sufficiently short. The model compared treatment sequences including and excluding apremilast. If a person's disease did not respond they were counted as a 'non-responder' and moved to the next treatment option in the pathway. 'Responders' continued treatment until they experienced lack of efficacy or adverse events. A discount rate of 3.5% was applied for costs and outcomes, and the analysis was from the NHS and personal social services perspective.

3.15 Each treatment in the company's model consisted of 2 possible health states: trial period (that is, response period) and continued use (that is, maintenance). The response to treatment (with apremilast or TNF-alpha inhibitors) was evaluated at the end of each treatment-specific trial period according to PsARC criteria (at 16 weeks for apremilast, in line with the trials, and at 12 weeks for the TNF-alpha inhibitors, in line with previous other NICE psoriatic arthritis appraisals). At the end of the trial period people whose disease responded to

treatment were assumed to continue treatment until they stopped because of lack of efficacy ('secondary non-responders') or other causes, based on an annual all-inclusive long-term withdrawal rate. People whose disease did not respond to treatment moved to the next treatment option in the sequence.

3.16 The transition probabilities for both the response and maintenance periods were determined by the PsARC response criteria, calculated from the company's network meta-analysis. In the base case analysis, the short- and long-term efficacy (PsARC rates and long-term withdrawal rates) for the TNF-alpha inhibitors were reduced for primary non-responders (that is, people whose disease did not show a response to treatment in the 16-week trial period). This was because of a likely reduction in the efficacy of TNF-alpha inhibitors if used again at subsequent lines of treatment. No efficacy reduction was applied to secondary non-responders to TNF-alpha inhibitors. For people whose condition did not respond to an initial therapy, but that did respond to a subsequent TNF-alpha inhibitor therapy, the loss of efficacy was applied for the proportion of people who stopped treatment due to loss of efficacy (a hazard ratio [HR] of 2.7). The company assumed that apremilast would not affect the efficacy of subsequent TNF-alpha inhibitor treatments and therefore no change in efficacy was necessary. It was assumed that the withdrawal rate was constant over time for all treatments (16.5%), taking into account loss of initial response and withdrawal due to adverse events and that the rate was the same for all the TNF-alpha inhibitors and apremilast.

3.17 Trials PSA-002, PSA-003 and PSA-004 collected EQ-5D data at baseline and at week 16, but the company noted that these data were not available for all of the TNF-alpha inhibitors included in its analysis. Utility values for the health states were therefore modelled using the correlation coefficient between the PsARC scores and PASI scores (measuring skin disease response) using a previously published regression equation (Rodgers et al. 2011) based on data from the ADEPT trial (correlation coefficient 0.436). The values were assumed to be unchanged until the person's condition no longer responded to treatment (non-responder). A key assumption in the model was that people whose condition continued to respond to treatment at the end of the trial period remained with the same HAQ-DI score. PASI was included in the health states to account for the impact of psoriasis on the quality of life of people with psoriatic arthritis. When the person's psoriatic arthritis stopped responding to treatment they were assumed to become non-responders and were assigned a greater

HAQ-DI score. Changes in HAQ-DI scores for PsARC responders and non-responders were treatment specific. People who reached best supportive care were assumed to experience subsequent natural progression of their disease, resulting in an increase (worsening) in HAQ-DI score of 0.006 per 28 days over time, up to a maximum score of 3, based on Rodgers et al. 2011. The death health state captured age-related mortality.

3.18 In the model, adverse events were only considered in terms of the effects on initial response (responders could stop treatment because of adverse events) and on the long-term discontinuation and withdrawal rates from each treatment option.

3.19 The company provided results for their original base case. However, in response to uncertainties raised about the model in the appraisal consultation document, the company submitted a revised base case. The Committee accepted these revisions and therefore all original analyses have now been superseded.

ERG's critique and exploratory analyses

ERG comments on the company's original submission

3.20 The ERG considered that all 3 randomised placebo-controlled trials (PSA-002, PSA-003 and PSA-004) were of a very similar design and all were well conducted, but noted that the longer term phases of the trials, after 24 weeks, had limited clinical value because of factors including a lack of control groups, lack of adequate blinding (particularly important because many outcomes were patient-reported), and lack criteria for stopping treatment. NICE and the ERG requested clarification from the company on the imputation methods used and the proportion of people with data missing. The company stated that non-responder imputation and last observation carried forward were used for the primary outcome of ACR20 and that very similar results were seen. The ERG considered this an appropriate method.

3.21 The ERG noted that radiographic evidence of joint damage can be used to monitor disease progression. The company clarified that no radiographic assessments were done in the apremilast trials. The ERG considered this lack of assessment to be important because the only measure of disease progression in the trials was calculated through functional capacity using the HAQ-DI

assessment (taking a mean score of the 8 categories included in the questionnaire).

3.22 The ERG noted that the pooled trial results presented by the company were calculated by adding together the individual trial data rather than using meta-analysis methods to calculate a pooled weighted average of the trials. The ERG stated that although this approach is generally not recommended, all 3 trials were very similar in terms of patient characteristics and study methods, therefore the results are likely to be reliable.

3.23 The ERG considered the pooled efficacy results at week 16 and noted that ACR50 response is a more clinically important outcome than ACR20. The proportion of people having apremilast who experienced an ACR50 response was quite low and there was uncertainty about whether the improvement in function provided by apremilast reached clinically-relevant levels. The ERG also noted that outcomes such as PsARC, MCID and HAQ-DI are prone to high response rates in the placebo group, therefore these outcomes may not provide the most informative estimates of relative efficacy.

3.24 The ERG stated that HAQ-DI is an important outcome in terms of a person's physical functioning and in assessing disease progression. It noted that the European Medicines Agency's assessment report commented on the HAQ-DI results for apremilast, noting that the minimum clinically important difference (MCID) for HAQ-DI in psoriatic arthritis has not been clearly established. The European Medicines Agency stated that improvements in the HAQ-DI score observed in the pooled apremilast 30 mg treatment groups exceeded the estimated MCID of −0.13 provided by 1 study (Kwok 2010), but not the estimated MCIDs of −0.3 and −0.35 provided in 2 other studies (Mease 2004 and Mease 2011). When observing the HAQ-DI data for the whole population, the ERG noted that the HAQ-DI results in the updated network meta-analysis results did not appear plausible. The ERG asked for revised results but they were not provided before the ERG report deadline. The ERG also noted that the company had not used the updated data in the model. The ERG tried to identify the magnitude of the differences between the model inputs and the updated network meta-analysis and commented that the differences were small, moving in the same direction and the order of treatments remained the same, and therefore the impact should not be significant.

3.25 During clarification NICE and the ERG requested updated sensitivity analyses using data only from people who had not had TNF-alpha inhibitor treatment for the ACR, PASI, PsARC and HAQ-DI outcomes. The company's updated analyses showed that the results were very similar to those for the overall population, because a large majority of the overall population had not had TNF-alpha inhibitor treatment.

3.26 The ERG noted that the company considered that apremilast, compared with TNF-alpha inhibitors, was likely to be associated with fewer serious adverse events over time such as serious infections and malignancies. However, the ERG could not find any clear evidence to show that apremilast had a more favourable safety profile. It also considered this argument to be inconsequential given that the company proposed apremilast in addition to a TNF-alpha inhibitor, as part of a sequence of treatments, and higher adverse events for TNF-alpha inhibitors would not be reduced by adding a therapy to the sequence.

ERG's critique of company's cost effectiveness in the original submission

3.27 The ERG noted that the decision problem addressed by the company compared treatment sequences, including and excluding apremilast, and did not provide a cost-effectiveness analysis of apremilast compared with a single comparator. It noted that the positioning of apremilast in the treatment pathway by the company was based on clinical expert opinion. The ERG considered that the company's approach to the decision problem represented a limited set of potentially relevant sequences and possible positions of apremilast in the treatment sequence.

3.28 The ERG noted that the company carried out a systematic review of cost-effectiveness evidence that identified studies of biological therapies for psoriatic arthritis, and stated that these were not directly relevant to the decision problem. However, the ERG considered that the studies could have provided a basis for the development of the economic model for apremilast; informing the model inputs and assumptions, and assisting in its validation.

3.29 The ERG stated that the original company model was not flexible and only allowed the ERG to examine the use of apremilast as an additional line of therapy before TNF-alpha inhibitors. During clarification NICE and the ERG asked the company to provide a revised version of the model:

- allowing apremilast to replace an existing TNF-alpha inhibitor in the sequence
- allowing apremilast to be positioned in any of the 5 possible lines of sequence
- including certolizumab pegol and ustekinumab as treatment options and allowing them to be positioned in any of the possible lines of treatment
- allowing comparison of at least 3 mutually exclusive strategies, simultaneously. Each of the strategies should allow apremilast to be included in any of the 5 possible lines of sequence.

3.30 In response the company provided an updated network meta-analysis to include ustekinumab and the ERG stated that the format of the economic model did not allow it to include ustekinumab as a treatment option The company further stated that although ustekinumab was included in the final scope (as a possible comparator subject to a NICE technology appraisal of ustekinumab), it would not form part of routine established clinical practice in the management of psoriatic arthritis in England at the time of this appraisal. Similarly, the company stated that certolizumab pegol would not form part of routine established clinical practice in the management of psoriatic arthritis in England at the time of this appraisal, and for this reason it had not included these comparisons in its analyses. Finally, the company did not provide a revised economic model that allowed comparison of at least 3 mutually exclusive strategies simultaneously, because it considered that the base case incremental cost-effectiveness ratio (ICER) and cost-effectiveness acceptability curve (CEAC) provide sufficient information to adequately address the decision problem and inform the decision-making process.

3.31 The ERG was unable to fully validate the re-submitted model because of its increased reliance on Visual Basic for Applications (VBA) language compared with the originally submitted model.

3.32 The ERG had concerns regarding a number of other approaches, assumptions and data used in the company's submission and economic model. The ERG noted that the baseline patient characteristics in the model were taken from the pooled data from PSA-002, PSA-003 AND PSA-004, but it would have been more appropriate to use characteristics from the studies included in the network meta-analysis because these were used to generate the treatment efficacy parameters.

3.33 The ERG's main concern was the key model assumption that apremilast halts HAQ-DI progression for PsARC responders while people remain on treatment, because there is no long-term clinical evidence on radiographic disease progression to support this. The ERG was also concerned about the company's assumptions of a reduction in efficacy for subsequent lines of TNF-alpha inhibitors after previous TNF-alpha inhibitors or apremilast, the monitoring costs of apremilast and disease-related costs applied for HAQ-DI and PASI, the placebo response in the model being different from that seen in the trials, the application of the same withdrawal data for TNF-alpha inhibitors and apremilast, and the utility algorithm used. In addition, the ERG identified a number of data inconsistencies between the company submission and the economic model. The ERG also noted that the network meta-analyses updated after clarification, which excluded phase II trial data and unlicensed arms of apremilast, were not included in the re-submitted model.

3.34 The ERG was concerned about the price of infliximab used by the company in its base-case analysis because the average weight of a patient was presumed to be 85.65 kg, in line with the apremilast trials. The ERG stated that the company should have used the average weight of a person as reported in the Rodgers et al. study (70 kg) because the company had utilised many of the other assumptions from this study. This would have reduced the number of vials needed for each patient. The ERG also noted that the company assumed that people would have 2 visits per year to a rheumatologist for any of the TNF-alpha inhibitor treatments, but only 1 visit for apremilast. The clinical expert advisers to the ERG stated that because apremilast is a new treatment more regular check-ups and monitoring are likely.

3.35 The ERG had concerns about the use of different trial periods for apremilast (16 weeks) and the TNF-alpha inhibitors (12 weeks) and the effect of this on clinical efficacy and the subsequent cost-effectiveness results. The ERG commented that it is not possible to know if the number of non-responders to TNF-alpha inhibitor treatment would stay the same, if the response period was extended from 12 to 16 weeks. An additional 4 weeks of treatment would be likely to increase the number of people who respond, producing a greater PsARC response rate for that treatment group (apremilast).

3.36 The ERG was concerned that although the placebo PsARC response and HAQ-DI score were reported in the company's network meta-analysis, these

results were not incorporated in the model or base-case analyses. The ERG was also concerned about the trajectory of HAQ-DI over time, which assumed that people whose disease responded to treatment had no (zero) progression in HAQ-DI. The ERG was unsure what evidence this assumption was based on.

3.37 The ERG did not agree with the company's assumption that patients did not progress (experienced full disease modification) while on apremilast. The disease modifying elements of the TNF-alpha inhibitors have been demonstrated previously using radiographic evidence, but this evidence is not available for apremilast at this time.

New evidence submitted by the Company in response to the appraisal consultation document

3.38 The company was granted permission to provide new evidence and new cost-effectiveness analyses (see sections 3.39 to 3.44) to respond to some areas of uncertainty raised by the Committee and documented in the appraisal consultation document.

3.39 The company provided additional clinical evidence on the following:

- Radiographic progression of disease: the company stated that the association between joint damage and functional decline is not well defined, and that evidence suggests that structural joint damage is slow and sub-clinical, therefore a significant decline is needed before there is a meaningful impact on function. It also stated that a study of the comparator drug golimumab by Kavanaugh et al. (2015) showed that control of disease symptoms was associated with less radiographic progression and better functional outcomes. It further stated that apremilast has demonstrated long-term control of disease symptoms. The company stated that its interpretation of, and conclusions about, this evidence was supported by a number of leading rheumatologists.
- The long-term safety of apremilast: the company provided 3 year pooled data about adverse events for apremilast from trials PSA-002, PSA-003, and PSA-004.
- Uncertainty in HAQ-DI scores because of the unblinded period of the apremilast trials: the company explained that the design of their pivotal trials were standard, with the placebo period minimised for ethical reasons, and that patients and investigators remained blinded to initial treatment and current dosage, even in the unblinded

period. The company also provided analyses to show that the HAQ-DI score was unlikely to be subject to bias:

- The company tested different imputation strategies to derive missing values for long-term outcomes for week 16 PsARC responders. It found that the week 52 HAQ-DI score was consistent with week 16, and concluded that the outcome was robust to different imputation strategies.
- The company compared the correlation coefficients in the blinded (week 16) and unblinded (week 52) trial periods between patient reported outcomes (HAQ-DI) and objective physician-assessed outcomes (swollen/tender joint count). It found no significant differences.

3.40 The company's new cost-effectiveness analysis included the following amendments to its original base-case analysis:

- Including updated network meta-analysis results supplied as part of clarification (excluding the Schett et al. study, which included unlicensed doses of apremilast).
- A revised utility function based on apremilast trial data using UK tariff sets for EQ-5D utility values applied to all treatments (and not US tariffs, as had been incorrectly used by the company in a scenario analysis in the original base case). The company stated that a comparison of the revised utility function with the Rodgers et al. function used in its original base case indicated that the 2 functions were similar.
- Inclusion of a placebo response in the best supportive care health state, in line with the trial outcome data (see section 3.5).
- Physician visits and monitoring frequency assumed to be the same for apremilast and TNF-alpha inhibitor therapies (the Committee's preferred scenario in the appraisal consultation document). The company accepted that initially there would be higher than usual levels of monitoring (as with any active treatment), and stated that in the longer term the frequency would reduce. It further stated that the original assumption of less monitoring, used in the original model, was based on clinical opinion and the summary of product characteristics.

3.41 The company presented new base-case analyses, sensitivity analyses and scenario analyses. The revised base case was based on the same treatment sequence as in the original base case (that is, apremilast, adalimumab, etanercept and best supportive care compared with adalimumab, etanercept and best supportive care). The company noted that, in the appraisal consultation

document, the Committee had expressed a preference for scenarios in which treatments were substituted. The company emphasised its original position that the sequencing modelling approach accurately reflected how apremilast would be used in clinical practice, and that this was supported by a number of rheumatologists. However, it did present a treatment substitution scenario (see section 3.44).

3.42 The results from the company's new cost-effectiveness analyses are presented in table 1. The revised base case ICER was £19,510 per quality-adjusted life year (QALY) gained (incremental costs £12,046, incremental QALYs 0.62).

Table Company's revised base case and other scenarios

Technologies	Cost (£)	QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
1: Original base case sequences using updated NMA results					
Comparator	106,820	7.35	–	–	–
Apremilast	117,685	8.09	10,865	0.74	14,684
2: Scenario 1 plus apremilast trial data used for utility function for all treatments					
Comparator	106,820	7.47	–	–	–
Apremilast	117,685	8.12	10,865	0.65	16,704
3: Scenario 2 plus addition of placebo response to BSC health state					
Comparator	102,007	7.68	–	–	–
Apremilast	113,717	8.30	11,710	0.62	18,966
4: Scenario 3 plus monitoring frequency assumed equal (company revised base case)					
Comparator	102,007	7.68	–	–	–
Apremilast	114,053	8.30	12,046	0.62	19,510
5: Scenario 4 plus no decline in efficacy assumed for TNF-alpha inhibitors					
Comparator	108,051	7.98	–	–	–
Apremilast	119,379	8.56	11,328	0.58	19,699

Comparator arm: adalimumab, etanercept, best supportive care.

Apremilast arm: apremilast, adalimumab, etanercept, best supportive care.

Abbreviations: BSC, best supportive care; Inc., incremental; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality adjusted life year; TNF, tumour necrosis factor.

3.43 The company's deterministic results showed the ICER was most sensitive to the slope of HAQ-DI. When assuming HAQ-DI progression of 0.001 per cycle when not on treatment (and not 0.006 as in the base case), the ICER was £54,629 per QALY gained. The company's probabilistic results showed that the probability of cost effectiveness at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained were less than 50%, and 86%, respectively.

3.44 The company did a number of scenario analyses:

- HAQ-DI progression: the company varied the HAQ-DI progression rate for apremilast in relation to best supportive care (assuming best supportive care progression rate of 0.006 per cycle). The lowest ICER was £22,667 per QALY gained (HAQ-DI progression for 100% of apremilast patients at a rate equal to best supportive care, with dropout at HAQ-DI score of 1.18) and the highest ICER was £29,117 per QALY gained (as previous ICER, but with dropout at HAQ-DI score of 2). However, the company stated that it was unreasonable to assume that the HAQ-DI for all patients declined over time, because there is evidence that HAQ-DI response is maintained for at least 2 years, and that approximately 10% of people having apremilast who show an initial clinical response may experience some degree of worsening of HAQ-DI while having therapy (supported by week 104 trial data). The company also stated that clinical opinion suggests that patients would likely move to another treatment if HAQ-DI score worsened to 2 while having apremilast therapy.

- Apremilast given before TNF-alpha inhibitors, compared with apremilast given after TNF-alpha inhibitors: the company compared apremilast, adalimumab, etanercept and best supportive care with adalimumab, etanercept, apremilast and best supportive care, generating an ICER of £13,716 per QALY gained (that is, apremilast was more cost effective when given before TNF-alpha inhibitors).

- Increasing the length of treatment sequences by adding further TNF-alpha inhibitors: when comparing a sequence of apremilast, adalimumab, etanercept, golimumab, infliximab and best supportive care with a sequence of adalimumab, etanercept,

golimumab, infliximab and best supportive care, the ICER was £16,596 per QALY gained. The ICER was £19,946 per QALY gained when comparing a sequence of apremilast, adalimumab, etanercept, golimumab and best supportive care with a sequence of adalimumab, etanercept, golimumab and best supportive care.

- Treatment substitution: the company did a scenario in which apremilast was used instead of adalimumab in a sequence of adalimumab, etanercept, golimumab and best supportive care. The ICER generated was £1437 per QALY gained (incremental costs £239, incremental QALYs 0.17). The company considered this scenario to be of limited relevance, stating that the revised base case (apremilast as an addition to a treatment sequence) was the most accurate representation of the expected use of apremilast in clinical practice, and that this opinion was supported by rheumatologists.

- Comparison of apremilast against best supportive care only: the ICER was £25,220 per QALY gained (assuming HAQ-DI progression for apremilast is equal to rate of best supportive care, and dropout at HAQ-DI score of 3) or £21,706 (assuming that HAQ-DI progression is equal to half the rate of that for best supportive care). However, the company stated that best supportive care was not an appropriate comparator given the proposed positioning of apremilast.

ERG's critique of additional analyses presented by the company during consultation

3.45 The ERG provided the following critique about the responses from the company:

- Radiographic progression: the ERG agreed that control of disease symptoms improves long-term functional and joint damage outcomes. However, it stated that apremilast is less effective than other active treatments for outcomes including HAQ-DI, PASI, and PsARC. It also stated that the comparator TNF-alpha inhibitors have radiographic evidence of effectiveness for peripheral arthritis and radiographic progression, unlike apremilast.

- Utility values: the ERG agreed that UK EQ-5D data is more appropriate than US data. It noted that when UK values are used, the utility function is very similar to the function derived using Rodgers et al. that was used in the original base case.

- HAQ-DI: the ERG stated that the long-term impact of apremilast is still unknown, and that techniques for estimating missing data are not appropriate when data cannot be assumed to be missing at random.

- Monitoring: clinical advisers to the ERG stated that assuming similar monitoring for apremilast and the comparators is appropriate, because apremilast is a new medication, there is likely to be a high proportion of concomitant DMARD use, and patient adherence needs to be ensured.

- Treatment sequence: the ERG stated that the company had presented a limited set of treatment sequences, which were not sufficient to inform the most efficient place for apremilast in the treatment sequence.

3.46 The ERG provided scenario analyses including apremilast compared with a single therapy, treatment sequences with and without apremilast, treatment sequences with an equal number of active comparators before best supportive care, and varying rates of HAQ-DI progression (all HAQ-DI scenarios assumed patients would stop the treatment being received at a HAQ-DI score of 2). The ERG commented that it was unable to validate how HAQ-DI progression was applied in the company's additional analyses, for patients having apremilast. It noted that HAQ-DI progression on apremilast seemed to have been applied correctly when apremilast was the first treatment in the sequence. However, it was unable to validate whether it had been applied appropriately when apremilast was not the first treatment in the sequence. Apremilast resulted in cost savings but a QALY loss in all of the ERG's exploratory analyses:

- Direct comparisons (1 active treatment followed by best supportive care):
  - Compared with etanercept, the ICER ranged from £17,779 saved per QALY lost (when assuming that HAQ-DI progression for apremilast was equal to the rate for best supportive care) to £22,561 saved per QALY lost (when assuming that apremilast had no HAQ-DI progression).
  - Compared with adalimumab, the ICER ranged from £18,764 saved per QALY lost (when assuming HAQ-DI progression at a rate equal to that for best supportive care) to £29,110 saved per QALY lost (when assuming no HAQ-DI progression for apremilast).

- Treatment sequences with an equal number of active comparators before best supportive care, and before TNF-alphas inhibitors (comparing a sequence of apremilast, adalimumab, etanercept and best supportive care with adalimumab, etanercept, golimumab and best supportive care). The ICERs were:

  - £15,088 saved per QALY lost (assuming HAQ-DI progression at the same rate as that for best supportive care), cost savings of £6924 and a QALY loss of −0.459
  - £18,288 saved per QALY lost (assuming HAQ-DI progression at half the rate of that for best supportive care), cost savings of £6739 and a QALY loss of −0.368
  - £27,134 saved per QALY lost (when using the company base case assumptions), cost savings of £6930 and a QALY loss of −0.255.

- Treatment sequences with an equal number of active comparators before best supportive care, and after TNF-alpha inhibitors (using apremilast instead of golimumab in a sequence of adalimumab, etanercept, golimumab and best supportive care). The ICERs were:
  - £11,518 per QALY lost (HAQ-DI progression at the same rate of best supportive care), cost savings of £5630 and a QALY loss of −0.489
  - £14,781 per QALY lost (HAQ-DI progression at half the rate of best supportive care), cost savings of £5343 and a QALY loss of −0.362
  - £26,573 saved per QALY lost (company base case assumptions) cost savings of £5599 and a QALY loss of −0.211.

3.47 Full details of all the evidence are available.

4 Consideration of the evidence

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

Clinical need and practice

4.1 The Committee heard from patient experts about the nature of psoriatic arthritis and their experiences of treatment. It heard that psoriatic arthritis is a lifelong condition that has a serious impact on people's quality of life. It can develop at a young age and affects all aspects of a person's life including education, work, self-care, and social and family life. The Committee heard from the patient expert that skin symptoms can have a major psychological impact, and that joint symptoms can have an even greater impact on the psychological and functional aspects of living with the condition. The Committee concluded that psoriatic arthritis substantially decreases quality of life.

4.2 The Committee considered the current treatment pathway for people with psoriatic arthritis. It heard from clinical experts that after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, most people with non-responsive disease will be treated with a tumour necrosis factor (TNF)-alpha inhibitor, starting with the lowest-cost drug as recommended in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis. It heard from the clinical experts that use of more than 1 TNF-alpha inhibitor is established practice in the NHS; if the disease fails to respond or loses response to the first TNF-alpha inhibitor, or it causes adverse effects, a second TNF-alpha inhibitor will often be used. The Committee considered where apremilast would fit into this existing treatment pathway. It heard from the patient expert that when treatment with a TNF-alpha inhibitor is contraindicated, or it is stopped because of loss of effectiveness or adverse effects (the clinical experts noted approximately 10% of patients per year stop TNF-alpha inhibitor treatment), there may be no alternative treatments available. Therefore, patients and clinicians value having a range of treatment options available, and there is an unmet need for treatments that offer a

different mechanism of action to the TNF-alpha inhibitors or that are administered orally, as with apremilast (a phosphodiesterase-4 inhibitor).

4.3 The Committee was aware that apremilast had the same marketing authorisation as the currently recommended biological treatments, but that the company had stated that apremilast would be used before these treatments in clinical practice, based on its oral route of administration, safety profile compared with current biological and conventional DMARD treatments, no specific requirements in the marketing authorisation for regular monitoring, and a cheaper cost compared with current biological therapies. The Committee was also aware of a written statement from the clinical expert that apremilast could be considered an alternative first or second line drug, because it was likely more effective than methotrexate. However, the written statement from the clinician had noted that placement in the pathway would also depend on treatment cost. The Committee heard from the clinical experts that it would be useful to have an additional treatment option before TNF-alpha inhibitors, because the psoriatic arthritis population is heterogeneous and some people cannot tolerate DMARD therapy, or their disease does not respond adequately to it. The Committee concluded that it was possible that apremilast could be used as a treatment before TNF-alpha inhibitors, but that any use or positioning of apremilast would need to be supported by clinical and cost-effectiveness evidence, particularly because several effective treatment options are already recommended for psoriatic arthritis.

4.4 The Committee considered the most appropriate comparators for this appraisal. It was aware that during the course of this appraisal (in June 2015), NICE had published guidance on ustekinumab for treating active psoriatic arthritis which, as an IL12/23 inhibitor, offered a different mechanism of action to the TNF-alpha inhibitors. However, it accepted that current usage of this drug was likely to be low, both because it had only recently received a positive recommendation, and also because the recommendation is more restrictive than the currently recommended TNF-alpha inhibitors (ustekinumab is recommended as a treatment option only if treatment with TNF-alpha inhibitors is contraindicated but would otherwise be considered, or if the person has had treatment with 1 or more TNF-alpha inhibitors). The Committee was also aware that certolizumab pegol (another TNF-alpha inhibitor) is another possible treatment option for people with psoriatic arthritis; however, it heard from the clinical experts that it is rarely used in clinical practice. The Committee

concluded that the most appropriate comparators for this appraisal were the TNF-alpha inhibitors adalimumab, etanercept, infliximab and golimumab (because they have a similar marketing authorisation to apremilast, and are the most commonly used treatments in clinical practice after the failure of a DMARD) and that ustekinumab could be considered as a comparator if it became relevant to consider making a recommendation specifically for a population for whom TNF-alpha inhibitors are not appropriate.

4.5 The Committee heard from the clinical and patient experts that although methotrexate works well, some people fear the adverse effects associated with it (such as hair loss, nausea and lethargy) and the need for frequent blood tests. The experts stated that apremilast may be better tolerated, although it is associated with a higher incidence of diarrhoea initially compared with some DMARDS such as leflunomide. The clinical experts stated that there is no evidence on whether apremilast is better tolerated than TNF-alpha inhibitors and that, in general, the TNF-alpha inhibitors are well tolerated; apremilast is no better or worse than the TNF-alpha inhibitors, and the majority of patients do not experience unacceptable problems. The clinical experts also suggested that, as with any new treatment, apremilast would need extra monitoring because its long-term adverse events are unknown. The Committee was aware of new evidence about the adverse effects of apremilast that the company had submitted in response to the appraisal consultation document, which provided further evidence about the adverse event profile for apremilast. The Committee concluded that apremilast has an acceptable adverse event profile in people with active psoriatic arthritis.

Clinical effectiveness

4.6 The Committee considered the evidence presented by the company on the clinical effectiveness of apremilast. It noted that the main sources of evidence were the PSA-002, PSA-003 and PSA-004 trials that compared apremilast (20 mg and 30 mg) with placebo in patients with active psoriatic arthritis (3 or more swollen and tender joints for at least 6 months) that had not responded to treatment with up to 3 DMARDs or 1 TNF-alpha inhibitor. The Committee noted that the trials were well conducted and showed that apremilast is more effective than placebo after 16 weeks of treatment for a number of joint, skin and soft tissue outcomes; the primary outcome was American College of Rheumatology response criteria (ACR20), with a response experienced by 37%

of people having apremilast compared with 19% having placebo ($p \leq 0.0001$). The clinical experts noted that apremilast was associated with a similar ACR20 response to methotrexate. The Committee acknowledged that in response to the appraisal consultation document the company stated that it considered this opinion to be subjective, because little comparative evidence is available in this area. The Committee also noted that apremilast was effective for associated problems such as dactylitis and enthesitis (see section 3.6). The Committee agreed that apremilast was a clinically effective treatment compared with placebo.

4.7 The Committee considered the more stringent ACR outcomes (ACR50 and ACR70) presented in the apremilast trials. It heard from the clinical experts that although ACR20 is an accepted outcome measure for treatments of psoriatic arthritis and was the primary outcome in the apremilast trials, people may still have painful and swollen joints and that people start to notice a benefit at ARC50 or ACR70. The Committee agreed that there was a difference between apremilast and placebo but that the absolute differences were less than those seen for ACR20.

4.8 The Committee considered the evidence from the company's network meta-analysis that compared apremilast with TNF-alpha inhibitors in the total population, and in the population who had not been treated with TNF-alpha inhibitors (see section 3.8 to 3.12). The Committee heard from the Evidence Review Group (ERG) that the methods used to identify both published and unpublished studies for the network meta-analysis were appropriate, and the studies were mostly well reported. The Committee discussed the ERG's concerns that the placebo responses (see section 3.33) for some outcomes were high which made it difficult to compare the relative efficacies of apremilast with the different comparators. The Committee noted that the results showed that apremilast had a clinical benefit compared with placebo. However, apremilast demonstrated less clinical benefit than any of the TNF-alpha inhibitors, in either population (the apremilast results were provided as academic in confidence and therefore cannot be reported). The Committee concluded that apremilast is not as clinically effective as the TNF-alpha inhibitors for treating psoriatic arthritis.

4.9 The Committee considered the Health Assessment Questionnaire Disability Index (HAQ-DI) outcome used by the company to calculate functional capacity and to assess disease progression. It heard from the ERG that there were

uncertainties about the results from the apremilast trials because they were not blinded after 24 weeks and there were no stopping rules, which was likely to have influenced the HAQ-DI results. The Committee noted that the company had provided evidence to argue against this in its response to the appraisal consultation document (see section 3.39); for example, the company stated that participants remained blinded to initial treatment and dose during the unblinded period. However, the Committee remained concerned that, in comparison with more objective measures of disease progression such as radiographic assessments, there was a higher possibility of bias.

4.10 The Committee considered the lack of radiographic assessment in the apremilast trials. It heard from the clinical experts that it would be difficult to justify using apremilast early in the treatment pathway (before TNF-alpha inhibitors) without evidence that it can prevent radiological progression, because there is evidence to show that TNF-alpha inhibitors slow disease progression. The Committee also heard from the patient experts that they want treatments that can stop the disease from progressing. It noted that the company had stated in its response to the appraisal consultation document that the relationship between radiographic progression and functional capacity was unclear, and that other measures such as disease activity were equally, if not more, important when considering the impact of disease on quality of life. The Committee accepted that it may be necessary to interpret radiographic evidence with caution, and that disease activity outcomes play an important role in functional capacity. However, it noted that apremilast not only lacked radiographic evidence about disease progression, but had consistently shown the worst performance of any active comparator for all outcomes presented in the network meta-analyses (see section 3.8 to 3.12). Because it is a new treatment, there is a lack of long-term clinical effectiveness data for apremilast. The Committee concluded that the lack of radiographic evidence and the clinical-effectiveness evidence did not support the use of apremilast before TNF-alpha inhibitors in clinical practice.

Cost effectiveness

4.11 The Committee considered the company's revised model which, as in the original base case, compared treatment sequences with and without apremilast, rather than comparing apremilast with a single comparator. This provided a revised base-case incremental cost-effectiveness ratio (ICER) of approximately

£19,500 per quality-adjusted life year (QALY) gained when adding apremilast to a treatment sequence of adalimumab, etanercept, and best supportive care (see table 1). Apremilast remained cost effective (when assuming a maximum acceptable ICER of £30,000 per QALY gained) in exploratory analyses, including when varying apremilast HAQ-DI progression in relation to best supportive care (£22,700 to £29,100 per QALY gained, see section 3.44). The Committee accepted that the use of treatment sequences was a valid approach to modelling.

4.12 The Committee considered whether the structural and parameter assumptions in the company's treatment sequences in the revised base case reflected clinical practice. It noted that the majority of analyses by the company compared treatment sequences that had a different number of active comparators before progression to best supportive care, with the base case comparing 3 active treatments for the apremilast group with 2 for the comparator group. The Committee agreed that, in clinical practice, patients would likely receive more than the 2 active treatments patients were assumed to receive in the comparator group before they progressed to best supportive care. This was because there are a number of active comparators available for treating psoriatic arthritis, particularly since the positive recommendation for ustekinumab. The Committee also considered that models comparing sequences, rather than more traditional direct comparisons, created additional uncertainty in the model. Treatment sequences of different lengths may exacerbate uncertainties in the model, which may also be less easily identifiable, because they are less likely to affect each arm equally than with direct comparisons or equal length sequences. The Committee further understood from the Assessment Group analyses that, assuming all other things were equal, replacing apremilast in the intervention group of the company revised base case with any of the TNF-alpha inhibitors would result in a QALY gain over the comparator sequence. The Committee concluded that in order to prevent the model being confounded by any QALY gain occurring only because of one group in the model having an additional active treatment, in a selected and unrealistically short sequence, it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence.

4.13 The Committee noted that the company had presented a limited exploratory analysis using treatment sequences of equal length in which apremilast was used instead of adalimumab in a sequence of adalimumab, etanercept,

golimumab and best supportive care. However, the Committee noted that this needed to be seen in the context of the ERG's multiple calculations using sequences with an equal number of active comparators, and also noted that the company considered this scenario to be of limited relevance. The Committee also noted that the analyses should be consistent with the direct clinical and cost differences between the TNF-alpha inhibitors and apremilast.

4.14 The Committee considered the company's assumptions about the improvement and progression of joint symptoms (measured using HAQ-DI). It noted that these were key drivers of the economic model and that people whose disease continued to respond to treatment at the end of the trial period retained the same HAQ-DI score (that is, apremilast was assumed to halt HAQ-DI progression while people remained on treatment, therefore zero HAQ-DI progression was applied). The Committee noted that the company's rationale for assuming that apremilast halts disease progression was based on acceptance in previous NICE appraisals for psoriatic arthritis that TNF-alpha inhibitors halt disease progression. The Committee was aware that the assumption that TNF-alpha inhibitors halt disease progression was supported radiographically and also by clinical practice evidence over a number of years. However, there was uncertainty about whether this assumption was equally relevant for apremilast, which has a different mechanism of action and limited evidence of use in clinical practice because it is a relatively new treatment. The Committee also noted that people who progressed to best supportive care were assumed to experience subsequent natural progression of their disease, resulting in an increase (worsening) in HAQ-DI score over time of 0.006 every 28 days, up to a maximum score of 3. The Committee noted that this score appeared high but heard from the clinical experts that, although it is not possible to know if people would experience a linear progression of disease, the clinical experts considered that the increase in HAQ-DI over time is likely to be within the same range as that used by the company. The Committee heard from the ERG that experience with rheumatoid arthritis shows that HAQ-DI does not have a linear trajectory; the rate of progression of the disease slows down over time. However, the Committee also noted comments from the company in response to the appraisal consultation document that the linearity of HAQ-DI progression was hypothetical and that the previous appraisal for ustekinumab for treating active psoriatic arthritis had assumed linear progression. The Committee also noted that patients with the best HAQ-DI responses would be likely to remain in the trials, making the HAQ-DI appear to improve over time. The Committee

acknowledged that there is a lack of evidence to inform these model assumptions, and this added uncertainty to the model. However, the assumption that apremilast completely halts HAQ-DI progression represented a best-case scenario that was not supported by clinical evidence (see sections 4.8, 4.9 and 4.10).

4.15 The Committee considered the use of HAQ-DI and Psoriasis Area Severity Index (PASI) scores mapped to EQ-5D to produce utility values of health in the company's original base case. The Committee noted that the utility values in the company's revised base case were derived from the apremilast trial. Although this reflected the preferences of the Committee as expressed in the appraisal consultation document, the Committee noted that this had little impact on results compared with the values used in the original base case. The Committee was also surprised at the estimates of utility, which appeared very low and similar to technologies for end of life conditions. However, the Committee agreed that the company had used a legitimate source for utility values by using the available trial data, and accepted the utility values for its decision-making.

4.16 The Committee discussed the costs included in the model, particularly the monitoring costs for apremilast treatment. It noted that in response to the appraisal consultation document the company had stated that monitoring costs for apremilast should not be included because there were no specific requirements for screening or regular monitoring, but that it had updated its revised base case to include an equal level of monitoring for all active treatments. The Committee heard from the clinical experts that, as with any new drug, apremilast would initially require more monitoring compared with the current standard of care. It therefore concluded that the revised model had correctly accounted for monitoring costs for apremilast.

4.17 The Committee considered the assumption of different trial periods for apremilast (16 weeks) and TNF-alpha inhibitors (12 weeks) for PsARC responses. The Committee heard from the ERG that the use of different time points could favour apremilast and that, if the trial period for TNF-alpha inhibitors were also increased to 16 weeks, the PsARC responses may increase. The clinical experts agreed that using different trial periods could influence the results. The Committee acknowledged that the company had carried out a scenario analysis altering the length of the apremilast trial period to 24 weeks but leaving the TNF-alpha inhibitor response at 12 weeks. The Committee

concluded that the longer trial period of apremilast could have given a relatively optimistic case for apremilast compared with other comparators.

4.18 The Committee considered the company's assumptions for placebo responses in the original and revised model. It noted that in the original model, the placebo response rate was discounted from best supportive care, but not from the absolute response rates of apremilast or the TNF-alpha inhibitors used in the model. However, in the revised base case, the company had included a placebo response for best supportive care. The Committee agreed that inclusion of placebo response rates in the model was necessary and accepted this revision to the model.

4.19 The Committee noted that the company's original base case results were based on uncertain assumptions. It appreciated that the company had attempted to address this uncertainty by making several changes in its revised model (including equal levels of monitoring for apremilast and TNF-alpha inhibitors, a placebo response for best supportive care, and utility values derived from the apremilast trial), and also by presenting several exploratory analyses. However, most ICERs presented by the company were based on treatment sequences with an unequal number of treatments, which was not the Committee's preference (see section 4.11 and 4.19). The Committee therefore went on to consider the exploratory analyses presented by the ERG. The Committee noted that the ERG had based its analyses on the revised company base case and, therefore, as in the company revised base case, it accounted for several uncertainties in the original base case. Also, the ERG had used the Committee's preferred treatment sequences, with an equal number of active comparators before progression to best supportive care, for its exploratory analyses. The Committee concluded that the exploratory analyses presented by the ERG were the most appropriate for decision-making.

4.20 The Committee considered the results for apremilast as a treatment before TNF-alpha inhibitor therapy, using its preferred exploratory analyses from the ERG (see sections 4.11 and 4.17). The Committee noted that all the ERG's sequences in which apremilast was the first treatment in a sequence (after DMARDs) resulted in cost savings but also a QALY loss, resulting in ICERs that reflected 'savings per QALY lost'. For example, when comparing a sequence of apremilast, adalimumab, etanercept and best supportive care with adalimumab, etanercept, golimumab, and best supportive care, and when using the

Committees preferred assumption of some HAQ-DI progression for apremilast (at half the rate of that for best supportive care) there was a cost saving of £6739 in the apremilast sequence, but a QALY loss of −0.368 (see section 3.46), resulting in an ICER of £18,300 saved per QALY lost. The Committee considered this to be the most plausible scenario because it used its preferred assumptions, and also because the results were consistent with the clinical and cost data; that is, when compared with TNF-alpha inhibitors, apremilast cost less but was also the least effective active treatment. The Committee noted that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. The Committee was aware that psoriatic arthritis is a chronic and progressive condition, that patients want treatments that stop disease progression (see section 4.10), and that apremilast was the least effective treatment in the company analyses (see sections 3.8 to 3.12). Taking all of the above into account, the Committee agreed that the ICER for apremilast was not high enough to compensate for the clinical effectiveness that would be lost. It therefore concluded that apremilast was not a cost-effective option compared with TNF-alpha inhibitors for people with psoriatic arthritis that has responded inadequately to DMARDs.

4.21 The Committee considered whether there was any evidence to consider apremilast as a treatment after TNF-alpha inhibitor therapy, or for people who could not take TNF-alpha inhibitors. It noted that evidence in this area was limited. The available clinical effectiveness evidence for apremilast was mostly for a population who had not previously had TNF-alpha inhibitors. The cost-effectiveness evidence was limited because the company had rejected this possible positioning of apremilast, even though such comparisons (particularly with ustekinumab) were listed in the final scope issued by NICE. The company had presented 2 direct comparisons of apremilast with best supportive care (see section 3.44), and when assuming apremilast HAQ-DI progression at a rate half that of best supportive care, the ICER for apremilast was £21,700 per QALY gained. The Committee noted, however, that the company had not explored the analyses further because it did not consider best supportive care to be an appropriate comparator. Following the publication of ustekinumab for treating active psoriatic arthritis, and given the range of other treatments available for psoriatic arthritis, there are a number of other possible treatments used after TNF-alpha inhibitors that would be available before best supportive care, and

these had not been explored as comparators. The Committee also considered the ERG's scenarios for apremilast used after TNF-alpha inhibitors, which included the Committee's preferred model assumption of the same number of active treatments in each sequence. The Committee was aware of the ERG's comments regarding the validity of its exploratory analyses (see section 3.46) and agreed that as these were the only scenarios presented for apremilast used after TNF-alpha inhibitors, they should be taken into account in its decision-making. The Committee noted that in all the ERG's exploratory analyses the apremilast treatment sequence resulted in cost savings but a QALY loss, resulting in ICERs that reflected 'savings per QALY lost'. For example, a treatment sequence in which apremilast replaced golimumab in a sequence of adalimumab, etanercept, golimumab and best supportive care, assuming HAQ-DI progression at a rate equal to half of best supportive care, resulted in a cost saving of £5343 and a QALY loss of −0.362, with an ICER of £14,800 saved per QALY lost. The Committee agreed that this was the most plausible scenario that had been presented because it used the Committee's preferred assumptions about treatment sequences with an equal number of treatments and some HAQ-DI progression for apremilast, the results were consistent with the clinical and cost data (that is, when compared with TNF-alpha inhibitors, apremilast cost less but was also the least effective active treatment), and also because of the limited evidence presented by the company. The Committee agreed that the ICER for apremilast was not high enough to compensate for the clinical effectiveness that would be lost. It therefore concluded that apremilast could not be recommended as a treatment after TNF-alpha inhibitors. It was unable to make recommendations for its use when people cannot take TNF-alpha inhibitors, because of a lack of evidence for its use in these circumstances.

4.22 The Committee discussed whether apremilast is considered innovative. It heard from clinical and patient experts that apremilast may provide an additional treatment option for patients, due to its different mode of action and oral formulation. However, given its conclusion on clinical efficacy (see section 4.6 to 4.8) the Committee considered that apremilast was not a step change in treatment. The Committee concluded that there were no additional gains in health-related quality of life over those already included in the QALY calculations, and that there was no need to change its conclusions on that basis.

4.23 The Committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant for its consideration of the cost effectiveness of any of the technologies in this appraisal

Summary of Appraisal Committee's key conclusions

TA372	Appraisal title: Apremilast for treating active psoriatic arthritis	Section
Key conclusion		

Apremilast alone or in combination with disease-modifying antirheumatic drug (DMARD) therapy is not recommended within its marketing authorisation for treating adults with active psoriatic arthritis that has not responded to prior DMARD therapy, or such therapy is not tolerated. The Committee considered the results for apremilast as a treatment before TNF-alpha inhibitor therapy. It noted that its preferred analyses by the Evidence Review Group's (ERG) in which apremilast was the first treatment in a sequence (after DMARDs) resulted in cost savings, but also a QALY (quality adjusted life year) loss, with the most plausible ICER being £18,300 saved per QALY lost. The Committee noted that the ERG's results were consistent with the clinical and cost data; that is, when compared with tumour necrosis factor (TNF)-alpha inhibitors, apremilast cost less and was the least effective active treatment in the meta-analyses. The Committee considered whether there was any evidence to consider apremilast as a treatment after TNF-alpha inhibitor therapy. It noted that evidence in this area was limited. The Committee noted that in all its preferred analyses by the ERG, the apremilast treatment sequence resulted in cost savings but a QALY loss, with the most plausible ICER being £14,800 saved per QALY lost. The Committee noted that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. The Committee agreed that the most plausible ICERs of £18,300 and £14,800 saved per QALY lost for apremilast, given before or after TNF-alpha inhibitors respectively, were not high enough to compensate for the clinical effectiveness that would be lost. It therefore concluded that apremilast could not be recommended as a treatment either before or after TNF-alpha inhibitors. It was unable to make recommendations for its use when people cannot take TNF-alpha inhibitors, because of a lack of evidence for its use in these circumstances.	1.1, 4.20, 4.21
Current practice	

Clinical need of patients, including the availability of alternative treatments	The Committee heard from patient experts that psoriatic arthritis is a lifelong condition that has a serious impact on people's quality of life. It can develop at a young age and affects all aspects of a person's life including education, work, self-care, and social and family life. The Committee heard from the patient expert that skin symptoms can have a major psychological impact, and that joint symptoms can have an even greater impact on the psychological and functional aspects of living with the condition. The Committee concluded that psoriatic arthritis substantially decreases quality of life. The Committee heard from patient and clinical experts that there is an unmet need for treatments that offer a different mechanism of action to the TNF alpha inhibitors or that are administered orally, as with apremilast (a PDE4 inhibitor).	4.1, 4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from clinical and patient experts that apremilast may provide an additional treatment option for patients, due to its different mode of action and oral formulation. However, given its conclusions on clinical efficacy the Committee considered that apremilast was not a step change in treatment.	4.22

What is the position of the treatment in the pathway of care for the condition?	The Committee noted that after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and DMARDs most people with non-responsive disease will be treated with a TNF-alpha inhibitor and treatment will be started with the lowest cost drug. The Committee was aware that apremilast had the same marketing authorisation as the currently recommended biological treatments, but that the company had stated that apremilast would be used before these treatments in clinical practice. The Committee concluded that it was possible that apremilast could be used as a treatment before TNF-alpha inhibitors, but that any use or positioning of apremilast would need to be supported by clinical and cost-effectiveness evidence.	4.2, 4.3
Adverse reactions	The Committee concluded that apremilast has an acceptable adverse event profile in people with active psoriatic arthritis.	4.4
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the main sources of evidence were the PSA-002, PSA-003 and PSA-004 trials that compared apremilast (20 mg and 30 mg) with placebo. It concluded that these trials were well conducted. The Committee considered the evidence from the company's network meta-analysis that compared apremilast with TNF-alpha inhibitors in the total population, and also in people who had not had TNF-alpha inhibitors. The Committee heard from the ERG that the methods used to identify both published and unpublished studies for the network meta-analysis were appropriate and the studies were mostly well reported.	4.6, 4.8
Relevance to general clinical practice in the NHS	The Committee understood that treatment with a DMARD such as methotrexate, followed by TNF-alpha inhibitors in people who can take them, is established practice in the NHS but that there is an unmet need for treatments that have a different mechanism of action to TNF-alpha inhibitors.	4.2

Uncertainties generated by the evidence	The Committee discussed the ERG's concerns that the placebo responses for some outcomes were high which made it difficult to compare the relative efficacies of apremilast with the different comparators. The Committee heard from the ERG that there were uncertainties about the PSA-002, PSA-003 and PSA-004 results because the trials were not blinded after 24 weeks and there were no stopping rules. The Committee was therefore concerned that in comparison with more objective measures of disease progression such as radiographic assessments, there was a higher possibility of bias. The Committee further considered the lack of radiographic assessment in the apremilast trials. It accepted that it may be necessary to interpret radiographic evidence with caution, and that disease activity outcomes play an important role in functional capacity. Because it is a new treatment, there is a lack of long-term clinical-effectiveness data for apremilast.	4.8, 4.9, 4.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No specific Committee consideration.	-

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee heard that apremilast was associated with a similar American College of Rheumatology response criteria (ACR20 response) as methotrexate. It noted that apremilast was more effective than placebo for a number of skin and joint outcomes, and for associated conditions such as dactylitis and enthesitis. The Committee agreed that apremilast was a clinically effective treatment compared with placebo. The Committee considered the evidence from the company's network meta-analysis that compared apremilast with TNF-alpha inhibitors in the total population, and also in people who had not had TNF-alpha inhibitors. The Committee noted that the results showed that apremilast had a clinical benefit compared with placebo. However, apremilast demonstrated less clinical benefit than any of the TNF-alpha inhibitors, in either population. The Committee concluded that apremilast is not as clinically effective as the TNF-alpha inhibitors for treating psoriatic arthritis.	4.6, 4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee noted that the company's revised model compared apremilast with treatment sequences rather than with a single comparator. The Committee accepted that the use of treatment sequences was a valid approach to modelling.	4.11

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the company had compared sequences with a different number of active treatments before best supportive care (3 for apremilast, 2 for the comparator group). The Committee agreed that, in clinical practice, patients would likely receive more than the 2 active treatments that patients were assumed to receive in the comparator group before they progressed to best supportive care. The Committee also understood that, assuming all other things were equal, replacing apremilast in the intervention group of the company's revised base case with any of the TNF-alpha inhibitors would result in a QALY gain over the comparator sequence. The Committee concluded that in order to prevent the model being confounded by any QALY gain occurring only because of one group in the model having an extra active treatment, it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence.	4.12
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that the utility values in the company's revised base case were derived from the apremilast trial. The Committee was surprised at the estimates of utility, which appeared very low and similar to technologies for end of life conditions. However, the Committee agreed that the company had used a legitimate source for utility values by using the available trial data, and accepted the utility values for decision making. The Committee did not hear that there were any additional gains in health-related quality of life over those already included in the QALY calculations.	4.15

Are there specific groups of people for whom the technology is particularly cost effective?	No specific Committee consideration.	-
What are the key drivers of cost effectiveness?	The Committee noted that HAQ-DI was a key driver of the economic model. The Committee concluded that in order to prevent the model being confounded by any QALY gain occurring only because of one group in the model having an extra active treatment, it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence.	4.14, 4.12

Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that all the ERG's sequences in which apremilast was the first treatment in a sequence (after DMARDs) resulted in cost savings, but also a QALY loss. For example, when comparing apremilast, adalimumab, etanercept and best supportive care with adalimumab, etanercept, golimumab, and best supportive care, and when using the Committees preferred assumption of some HAQ-DI progression for apremilast (at half the rate of best supportive care) there was a cost saving of £6739 in the apremilast sequence, but a QALY loss of -0.368, resulting in an ICER of £18,300 saved per QALY lost. The Committee considered this to be the most plausible scenario because it used its preferred assumptions, and also because the results were consistent with the clinical and cost data; that is, when compared with TNF-alpha inhibitors, apremilast cost less but was also the least effective active treatment. The Committee considered whether there was any evidence to consider apremilast as a treatment after TNF-alpha inhibitor therapy. It noted that evidence in this area was limited. The Committee noted that in all exploratory analyses by the ERG, the apremilast treatment sequence resulted in cost savings but a QALY loss. For example, a treatment sequence in which apremilast replaced golimumab in a sequence of adalimumab, etanercept, golimumab and best supportive care (assuming HAQ-DI progression at a rate equal to half that of best supportive care) resulted in a cost saving of £5343, a QALY loss of −0.362, and an ICER of £14,800 saved per QALY lost. The Committee agreed that this was the most plausible scenario that had been presented because it used the Committee's preferred assumptions about treatment sequences with an equal number of treatments and some HAQ-DI progression for apremilast, and also because of the limited evidence presented by the company. The Committee noted that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. The Committee agreed that the most plausible ICERs of £18,300	4.20, 4.21

	and £14,800 saved per QALY lost for apremilast, given before or after TNF-alpha inhibitors respectively, would not compensate for the clinical effectiveness that would be lost. It therefore concluded that apremilast could not be recommended as a treatment either before or after TNF-alpha inhibitors. It was unable to make recommendations for its use when people cannot take TNF-alpha inhibitors, because of a lack of evidence for its use in these circumstances.	
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	-
End-of-life considerations	Not applicable.	-
Equalities considerations and social value judgements	Not applicable.	-

5 Review of guidance

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

Andrew Dillon
Chief Executive
December 2015

6 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

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

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

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

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel
Institute of Brain and Behaviour Mental Health, University of Manchester

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Department of Primary Care and Population Health, University College London

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford
Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Patrick McKiernan
Consultant Paediatrician, Birmingham Children's Hospital

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Dr Suzanne Martin
Reader in Health Sciences

Dr Iain Miller
Founder & CEO, Health Strategies Group

Dr Paul Miller
Market Access Adviser

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr John Radford
GP, NHS Sheffield

Dr Claire Rothery
Research Fellow in Health Economics, University of York

Professor Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton
Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle
Lay Member

NICE project team

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

Dr Caroline Hall/Carl Prescott
Technical Leads

Fay McCracken/Nicola Hay/Fiona Pearce
Technical Advisers

Lori Farrar
Project Manager

7 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Centre for reviews and Dissemination and Centre for Health Economics, York:

Corbett M, Sideris E, Palmer S, Harden M, Woolacott N, Bojke L. Apremilast for treating active psoriatic arthritis: A Single Technology Appraisal. CRD and CHE Technology Assessment Group, 2015

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

I. Company:

- Celgene

II. Professional/expert and patient/carer groups:

- Psoriasis and Psoriatic Arthritis Alliance
- Psoriasis Association
- British Association of Dermatologists
- British Society for Rheumatology
- Primary Care Rheumatology Society
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Abbvie (adalimumab)
- Merck Sharp & Dohme (golimumab, infliximab)
- Centre for Reviews and Dissemination and Centre for Health Economics, York
- National Institute for Health Research Health Technology Assessment Programme

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

- Dr Phillip Helliwell, Senior Lecturer in Rheumatology, nominated by British Society of Rheumatology and Arthritis Research UK – clinical expert
- Dr Ruth Murphy, Consultant Dermatologist, nominated by British Association of Dermatologists and Royal College of Physicians – clinical expert
- David Chandler, Chief Executive, nominated by Psoriasis and Psoriatic Arthritis Alliance – patient expert
- Helen McAteer, Chief Executive, nominated by Psoriasis Association – patient expert

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

- Celgene

About this guidance

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

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

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

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

Your responsibility

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

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

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Accreditation

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient access scheme submission

Apremilast (Otezla®) for the treatment of active psoriatic arthritis

May 3rd 2016

1 Introduction

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

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

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

2 Instructions for manufacturers and sponsors

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

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

Please refer to the following documents when completing the template:

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

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

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

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

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

When making a patient access scheme submission, include:

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

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

3 Details of the patient access scheme

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

This patient access scheme (PAS) is for all preparations of apremilast (Otezla®) and concerns its use on the NHS in England and Wales, within its marketing authorisation, alone or in combination with Disease-Modifying Anti-Rheumatic Drugs (DMARDs), for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

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

A Single Technology Appraisal (STA) for apremilast for the treatment of adult patients with active PsA was submitted to NICE in January 2015. NICE Technology Appraisal guidance (TA372)[1] concluded that apremilast is not recommended within its marketing authorisation for treating PsA, that is, alone or in combination with DMARDs, for the treatment of active PsA in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. This outcome was based on the Appraisal Committee's conclusion that use of apremilast as part of a treatment sequence after the failure of DMARD therapy is associated with a cost saving compared with a sequence in which patients only receive biologic therapy after DMARD failure but also a reduction in health-related quality of life (HRQoL).

In section 4.11 of TA372, the Committee accepted that the use of treatment sequences was a valid approach to modelling. In section 4.12, the Committee stated that they considered it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence. The Committee scenario in which apremilast was used as a first-line therapy (post DMARD) in a treatment sequence consisting of adalimumab and etanercept was compared with a biologic strategy consisting of adalimumab, etanercept and golimumab.

The most plausible incremental cost-effectiveness ratio (ICER) for apremilast as a first-line therapy was considered to be approximately £18,300 (South-West quadrant). The Committee noted that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. However, the Appraisal Committee concluded that the cost saving

associated with replacing the first biologic therapy with apremilast was not sufficient to compensate for the reduction in efficacy associated with apremilast.

The PAS has been developed to improve the cost-effectiveness of apremilast and enable therapy with apremilast as a first-line treatment to be considered a cost-effective use of NHS resources within the licensed indication. Adopting the Appraisal Committee's preferred scenario and assumptions used for decision-making within TA372 and including the fixed price for apremilast provided by the PAS, the base case result indicates that the apremilast strategy is associated with a cost saving of [redacted] and a reduction in QALYs of [redacted] compared with a biologic strategy, resulting in an ICER of £39,052 (South-west quadrant), i.e. the apremilast strategy has a higher net benefit at a WTP threshold of £30,000/QALY compared with routine NHS practice (see section 4.6). Extensive sensitivity and scenario analyses show that apremilast remains cost-effective in all scenarios explored, providing a higher net benefit for the apremilast strategy at a WTP threshold of £30,000/QALY. Thus at the fixed price provided by the PAS, apremilast as a first-line therapy (post DMARD) represents a clinically-effective and cost-effective treatment option for active PsA for the NHS in England in Wales.

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

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

Drug acquisition cost of apremilast at PAS price versus routine NHS comparators

The PAS fixed price for apremilast offers a significant cost saving to comparator biologic therapies used in current routine NHS practice in the management of PsA in England and Wales, ranging from [redacted] to [redacted] per patient per year. Table 1 highlights this cost difference. Of note, apremilast has a [redacted] lower drug acquisition cost than the most widely used first-line biologic therapy for the management of PsA in England and Wales, adalimumab (Humira®).[2] Celgene considers that the cost-savings for apremilast at the PAS fixed price and the cost-effectiveness results detailed within this submission supports the positioning of apremilast as a first-line therapy (post DMARD).

Table 1 Annual drug acquisition costs and cost saving per patient for apremilast at the PAS fixed price over comparator biologic therapies

	Apremilast (Otezla®) at PAS price	Adalimumab (Humira®)	Etanercept (Enbrel®)	Golimumab (Simponi®)	Infliximab (Remicade®)	Ustekinumab (Stelara®)
Drug acquisition cost per patient per year*	[redacted]	£9,156	£9,295	£9,156	£13,638	£9,304
% difference in drug acquisition costs (Otezla versus comparator)	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Drug costs exclude VAT and are based on published NHS list price (MIMS April 2016) and at dosing detailed within the posology of the respective SPCs. Costs calculated on post year 1 dosing schedule. An average patient weight of 85.65kg is assumed. No administration costs are included. Infliximab would incur an additional cost associated with drug infusion

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

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

The PAS is applied to all patients with PsA receiving treatment on the NHS in England and Wales within the European marketing authorisation, i.e., patients with active PsA who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

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

- Why have the criteria been chosen?

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

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

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

All patients prescribed apremilast on the NHS, within its licensed indication, for management of active PsA in patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy, will meet the criteria for the scheme, in accordance with anticipated NICE Guidance.

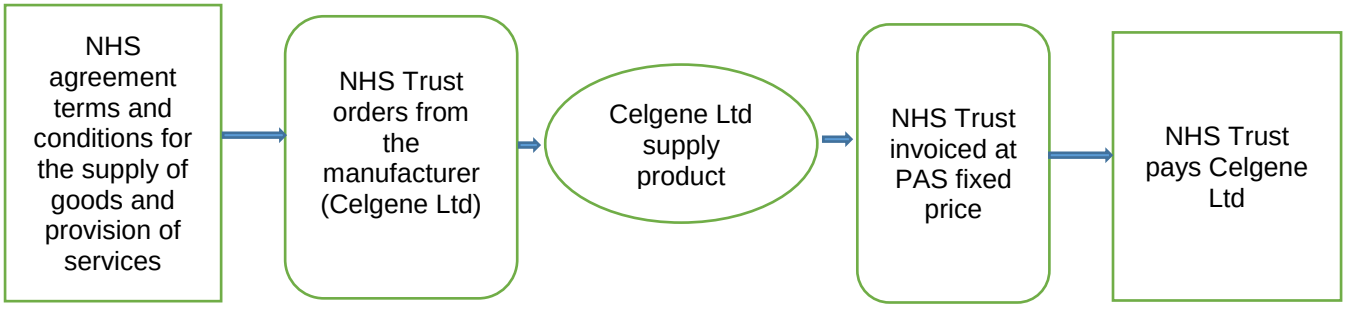
3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

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

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

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

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



3.10 Please provide details of the duration of the scheme.

The PAS will remain in place from the receipt of a positive recommendation from NICE for the use of apremilast, within its licensed indication, for the treatment of patients with active PsA who have had an inadequate response or who have been intolerant to a prior DMARD

therapy, until the recommendation is next reviewed by NICE and subject to the agreement of the DH.

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

No.

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

Not applicable

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

Not applicable

4 Cost effectiveness

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

Following a positive recommendation from NICE, the PAS will apply to all patients who receive apremilast for treatment of active PsA on the NHS within the NICE recommended population.

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

The economic model has been updated to reflect the assumptions that the Appraisal Committee considered to be most plausible for decision-making, as stated in TA372.[1] This has included:

1) comparing two treatment sequences of equal lengths (i.e. apremilast as a first-line therapy (post DMARD) in a treatment sequence consisting of adalimumab and etanercept with a biologic strategy consisting of adalimumab, etanercept and golimumab.)
2) using efficacy results from the NMA excluding the Schett et al trial [3]
3) using a utility function derived from the apremilast trial data
4) assuming the same monitoring for apremilast as for biologic therapy
5) assuming HAQ-DI progression on apremilast at half the rate of that on BSC
6) inclusion of a placebo response to BSC

No other changes have been made to the model, although an alternative assumption, which Celgene considers to be more appropriate, relating to the HAQ-DI score for golimumab has been made as explained below:

- Golimumab was not included in the manufacturer base case in TA372
- During NICE TA220, the manufacturer of golimumab marked the HAQ-DI change conditional on PsARC response as academic in confidence
- In the Committee's preferred scenario in TA372, which includes golimumab, it is assumed that the HAQ-DI score conditional on PsARC response for golimumab is

equal to the average of the score for the other TNF inhibitors in the model (i.e. adalimumab, etanercept and infliximab)

- However, in NICE TA220,[4] the Committee commented (section 4.8):

The Committee carefully considered the results of the mixed treatment comparison. It noted that for PsARC response and absolute change in PASI from baseline, the results showed that golimumab was generally equivalent to the other TNF inhibitors. However, it also noted that golimumab had the lowest HAQ score change from baseline (both in participants whose disease responded to treatment based on PsARC score and those whose disease did not respond based on PsARC score) compared with the other TNF inhibitors. (TA220, Section 4.8)

Thus, an assumption that the HAQ-DI score for golimumab corresponds to the average of that for the other TNF inhibitors is likely to overestimate the HAQ-DI response for golimumab. If this response for golimumab is set conservatively as being [redacted] – the results for the Committee's preferred base case in TA372 changes from £18,292/QALY (SW quadrant) to [redacted]/QALY (SW quadrant). **It should be noted that the PAS offer for apremilast supports cost-effectiveness using either assumption for golimumab HAQ-DI change.**

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

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

Appraisal Committee preferred scenario

Details of the changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible (as described in TA372) are summarized in Table 2.

Table 2 Summary of changes to the model to reflect the assumptions that the Appraisal Committee considered most plausible and the resulting ICER

Parameter	Company submission	Company consultation model	Considered most plausible by the Appraisal Committee	Rapid Review Model
Model structure	Assumes apremilast extends a sequence	Assumes apremilast extends a sequence	Assumes apremilast displaces a TNF inhibitor in a sequence	Assumes apremilast displaces a TNF inhibitor in a sequence
Efficacy	NMA	NMA excluding Schett et al[3]	NMA excluding Schett et al[3]	NMA excluding Schett et al[3]
Utility source	Linear function of the HAQ-DI and PASI scores, based on a multivariate linear regression model estimated by Wyeth.[163]	Apremilast trial data using UK tariffs	Apremilast trial data using UK tariffs	Apremilast trial data using UK tariffs
HAQ progression while on apremilast	None	None	Half the rate of BSC	Half the rate of BSC
BSC efficacy	None	Inclusion of placebo response in BSC health state	Inclusion of placebo response in BSC health state	Inclusion of placebo response in BSC health state
Physician visits/monitoring frequency	Assumed no monitoring for ongoing apremilast	Assumes the same frequency of monitoring for apremilast and biologic therapy	Assumes the same frequency of monitoring for apremilast and biologic therapy	Assumes the same frequency of monitoring for apremilast and biologic therapy

Parameter	Company submission	Company consultation model	Considered most plausible by the Appraisal Committee	Rapid Review Model
Model structure	Assumes apremilast extends a sequence	Assumes apremilast extends a sequence	Assumes apremilast displaces a TNF inhibitor in a sequence	Assumes apremilast displaces a TNF inhibitor in a sequence
HAQ-DI conditional on PsARC response for golimumab	N/A, golimumab not included in base case	N/A, golimumab not included in base case	Assumes HAQ-DI change equal to the mean of adalimumab, etanercept and infliximab	Assumes HAQ-DI change [redacted]
ICER, £/QALY (at apremilast list price)	14 691	19,510	£18,292; South-west quadrant	[redacted] South-west quadrant

AC, Appraisal Committee; BSC, Best supportive care; HAQ-DI, Health Assessment Questionnaire-Disability Index; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; QALY, quality-adjusted life year; TNF, tumour necrosis factor

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

The clinical effectiveness data resulting from the evidence synthesis used in the rapid review model are identical to that used in the Appraisal Committee preferred model and are not affected by the inclusion of the PAS. Clinical effectiveness data are based on the results of an NMA (see Table 3 to Table 6). No changes have been made to these efficacy data which were included in TA372.

Table 3 Probability of PsARC response according to treatment

	Mean	SD	Median	95% CrI
Placebo	0.30	0.01	0.30	(0.27, 0.32)
Apremilast 30 mg	0.49	0.03	0.49	(0.43, 0.55)
Adalimumab 40 mg	0.64	0.05	0.65	(0.55, 0.73)
Etanercept 25 mg	0.76	0.05	0.76	(0.65, 0.85)
Golimumab 50 mg	0.81	0.04	0.81	(0.71, 0.89)
Ustekinumab 45 mg	0.53	0.05	0.53	(0.43, 0.62)
Infliximab 5 mg/kg	0.80	0.04	0.81	(0.72, 0.88)

CrI, credible interval; SD, standard deviation.

Table 4 Probability of PASI response according to treatment

	Mean	SD	Median	95% CrI
Probability of PASI50				
Placebo	0.13	0.01	0.13	(0.11, 0.15)
Apremilast 30 mg	0.35	0.04	0.35	(0.27, 0.44)
Adalimumab 40 mg	0.72	0.07	0.73	(0.57, 0.85)
Etanercept 25 mg	0.37	0.07	0.37	(0.24, 0.53)
Golimumab 50 mg	0.70	0.07	0.70	(0.55, 0.84)
Ustekinumab 45mg	0.53	0.06	0.53	(0.4, 0.65)
Infliximab 5 mg/kg	0.90	0.03	0.91	(0.83, 0.96)
Probability of PASI75				
Placebo	0.04	0.01	0.04	(0.03, 0.05)
Apremilast 30 mg	0.17	0.03	0.17	(0.12, 0.23)
Adalimumab 40 mg	0.51	0.09	0.51	(0.34, 0.67)
Etanercept 25 mg	0.19	0.05	0.18	(0.1, 0.3)
Golimumab 50 mg	0.48	0.09	0.48	(0.32, 0.65)
Ustekinumab 45mg	0.30	0.06	0.30	(0.2, 0.42)

	Mean	SD	Median	95% CrI
Infliximab 5 mg/kg	0.77	0.06	0.77	(0.64, 0.87)
Probability of PASI90				
Placebo	0.01	0.00	0.01	(0.01, 0.01)
Apremilast 30 mg	0.05	0.01	0.05	(0.03, 0.08)
Adalimumab 40 mg	0.26	0.07	0.25	(0.14, 0.41)
Etanercept 25 mg	0.06	0.02	0.06	(0.02, 0.12)
Golimumab 50 mg	0.24	0.07	0.23	(0.13, 0.39)
Ustekinumab 45mg	0.12	0.03	0.12	(0.06, 0.19)
Infliximab 5 mg/kg	0.52	0.08	0.52	(0.38, 0.68)

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

Table 5 Mean change in HAQ-DI from baseline in PsARC responders according to treatment

	Mean	SD	Median	95% CrI
Placebo	-0.26	0.01	-0.26	(-0.29, -0.23)
Apremilast 30 mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	-0.46	0.04	-0.46	(-0.53, -0.38)
Etanercept 25 mg	-0.63	0.05	-0.63	(-0.73, -0.54)
Infliximab 5 mg/kg	-0.67	0.05	-0.67	(-0.76, -0.58)

bid, twice daily; biw, biweekly; CrI, credible interval; EOW, every other week; q12w, once every 12 weeks; QW, once weekly; SD, standard deviation.

Table 6 Mean change in HAQ-DI from baseline in PsARC non-responders according to treatment

	Mean	SD	Median	95% CrI
Placebo	0.01	0.01	0.01	(0, 0.03)
Apremilast 30 mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	-0.12	0.03	-0.12	(-0.17, -0.07)
Etanercept 25 mg	-0.18	0.05	-0.18	(-0.27, -0.09)
Infliximab 5 mg/kg	-0.18	0.04	-0.18	(-0.26, -0.1)

bid, twice daily; biw, biweekly; CrI, credible interval; EOW, every other week; PsARC, Psoriatic Arthritis Response Criteria; QW, once weekly; SD, standard deviation.

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

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

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

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

Summary results

Base-case analysis

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

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

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

A suggested format is shown below (table 3).

The base case corresponds to the Appraisal Committee's preferred assumptions as described in TA372 and compares the following two treatment strategies in patients with active PsA:

- Apremilast strategy: apremilast → adalimumab → etanercept → BSC
- Biologic strategy: adalimumab → etanercept → golimumab → BSC

Table 7 summarizes the results for the base-case analysis for apremilast at the list price according to the Appraisal Committee's most plausible scenario for apremilast as a first-line therapy, and Table 8 summarizes the results for the base case at the list price using the alternative value for HAQ-DI for golimumab (as discussed in section 4.1). In this latter scenario, the apremilast strategy is associated with a cost saving of [redacted] and a QALY loss of [redacted], resulting in an ICER of [redacted] (SW quadrant) at list price.

In considering these results it should be remembered that in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes.

All results presented within this document include an assumption of HAQ-DI progression = ½ BSC rate on apremilast treatment unless otherwise stated (as preferred by the Appraisal Committee).

Table 7 Base-case cost-effectiveness results for the Appraisal Committee's most plausible scenario: apremilast at the list price

	Apremilast strategy	Biologic strategy
Intervention cost (£)	£68,995	£76,862
Other costs (£)	£45,249	£44,121
Total costs (£)	£114,244	£120,983
Difference in total costs (£)	-£6,739	
QALYs	8.19	8.56
QALY difference	–0.37	
ICER (£)/QALY	£18,292; SW Quadrant	

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

Table 8 Base-case cost-effectiveness results for Appraisal Committee's most plausible scenario with alternative HAQ-DI change for golimumab: apremilast at the list price

	Apremilast strategy	Biologic strategy
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER (£)/QALY	[redacted]SW Quadrant	

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

From this point forward, the results for all scenarios will be based on the assumption that the HAQ-DI change conditional on PsARC response for golimumab [redacted] Celgene considers this to be a valid assumption based on conclusions presented in TA220. As previously mentioned, the PAS offer for apremilast supports cost-effectiveness using either assumption for golimumab HAQ-DI change.

Table 9 summarises the results for the base-case analysis for apremilast using the PAS fixed price [redacted] discount from NHS list price). In this analysis the apremilast strategy is associated with a cost saving of [redacted], resulting in an ICER of £39,052 (South-west quadrant) for the apremilast strategy compared with the biologic strategy. This reflects a reduction in the total incremental costs of [redacted] compared to apremilast at the list price, and hence a corresponding increase in the cost saving associated with the apremilast strategy. The PAS does not affect the incremental QALYs.

Table 9 Base-case cost-effectiveness results: apremilast with PAS

	Apremilast strategy	Biologic strategy
Intervention cost (£)	[redacted]	[redacted]

Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER (£)/QALY	Higher net benefit at 30K/QALY £39,052 SW quadrant	

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; SW, south-west

Net Monetary Benefit

The Net Monetary Benefit (NMB) allows us to move away from a ratio and places both costs and effects on a single scale. In NMB, the difference in effects between two options being evaluated is rescaled into monetary value using the cost-effectiveness threshold as a value for each unit of effect, and the difference in costs between the options is subtracted from this value. Thus the NMB of an intervention at a given WTP threshold is calculated using the following formula:

$NMB = \lambda . \Delta E - \Delta C$

Where:

λ = threshold

ΔE = Incremental effect

ΔC = Incremental cost

If the NMB is >0 for the intervention, it indicates that the intervention has a higher net monetary benefit at a given WTP threshold versus the comparator.

Using the cost-effectiveness result in Table 9, the NMB for the apremilast strategy is calculated as follows:

NMB = (£30,000 * [redacted]) – ([redacted]) = +£2,683

As the NMB is>0, this indicates that the apremilast strategy has a higher NMB compared with the biologic strategy at a WTP of £30K.

Thus at the PAS fixed price, apremilast, as a first-line therapy (post DMARD) is associated with a higher net benefit at a WTP threshold of £30K compared with routine NHS practice in England and Wales.

Sensitivity analyses

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

Deterministic sensitivity analyses (DSA) have been performed on the Appraisal Committee's preferred scenario including apremilast with and without the PAS using the parameters varied in the original evidence submission (see the manufacturer's submission section 7.6.2). Key parameters included treatment efficacy (i.e. PASI and PsARC response rates), changes in HAQ-DI scores by PsARC response category, and health care costs (Table 10).

Results for the DSA show that, for the analysis including apremilast at the PAS fixed price, the ICER was greater than £33,000/QALY (SW quadrant) for all conditions considered (Table 11). The range of ICER values for the DSA at list price was [redacted] to [redacted] and at the PAS fixed price was £33,643 to £50,168 (all South-West quadrant).

The main drivers of the cost-effectiveness include the efficacy measures relating to golimumab, namely PsARC response rate, long-term dropout rate and change in HAQ-DI score in PsARC responders, the HAQ-DI slope which determines costs and utilities in the model, and discount rates for both costs and outcomes (Figure 1).

Table 10 Values used in the deterministic sensitivity analyses

Input parameter/treatment	Base case	Lower value	Upper value	Rationale, Reference
PASI-50 response rates				
Apremilast	34.96%	26.91%	43.50%	95%CrI, Celgene, NMA results[5]
Adalimumab	72.23%	57.02%	84.95%	95%CrI, Celgene, NMA results[5]
Etanercept	37.47%	23.76%	52.81%	95%CrI, Celgene, NMA results[5]
Golimumab	70.01%	54.79%	83.54%	95%CrI, Celgene, NMA results[5]

Input parameter/treatment	Base case	Lower value	Upper value	Rationale, Reference
PASI-75 response rates				
Apremilast	16.72%	11.53%	22.85%	95%CrI, Celgene, NMA results[5]
Adalimumab	50.83%	34.27%	67.47%	95%CrI, Celgene, NMA results[5]
Etanercept	18.66%	9.72%	30.47%	95%CrI, Celgene, NMA results[5]
Golimumab	48.24%	32.20%	65.28%	95%CrI, Celgene, NMA results[5]
PASI-90 response rates				
Apremilast	5.04%	2.89%	7.92%	95%CrI, Celgene, NMA results[5]
Adalimumab	25.93%	13.79%	41.00%	95%CrI, Celgene, NMA results[5]
Etanercept	5.96%	2.35%	11.18%	95%CrI, Celgene, NMA results[5]
Golimumab	23.88%	12.57%	38.84%	95%CrI, Celgene, NMA results[5]
PsARC response rates				
Apremilast	48.67%	42.81%	54.53%	95%CrI, Celgene, NMA results[5]
Adalimumab	64.49%	54.98%	73.26%	95%CrI, Celgene, NMA results[5]
Etanercept	75.84%	65.14%	84.78%	95%CrI, Celgene, NMA results[5]
Golimumab	80.99%	71.36%	88.67%	95%CrI, Celgene, NMA results[5]
Correlation coefficient between PsARC and PASI-75 responses				
rho	0.44	0.36	0.51	95%CI, Rodgers *et al*.[6]
Annual withdrawal rates (%)				
Apremilast	16.5%	12.37%	20.62%	Assumption validated by clinical experts
Adalimumab	16.5%	12.37%	20.62%	95%CI, Rodgers *et al*.[6]
Etanercept	16.5%	12.37%	20.62%	95%CI, Rodgers *et al*.[6]
Golimumab	16.5%	12.37%	20.62%	95%CI, Rodgers *et al*.[6]
Change in HAQ-DI scores – PsARC responders				
Apremilast	[redacted]	[redacted]	[redacted]	95%CrI, Celgene, NMA results[5]
Adalimumab	–0.456	–0.529	–0.383	95%CrI, Celgene, NMA results[5]
Etanercept	–0.633	–0.729	–0.537	95%CrI, Celgene,

Input parameter/treatment	Base case	Lower value	Upper value	Rationale, Reference
				NMA results[5]
Golimumab	[redacted]	[redacted]	[redacted]	95%CrI, Celgene, NMA results[5]
Change in HAQ-DI scores – PsARC non-responders				
Apremilast	[redacted]	[redacted]	[redacted]	95%CrI, Celgene, NMA results[5]
Adalimumab	–0.120	–0.174	–0.065	95%CrI, Celgene, NMA results[5]
Etanercept	–0.182	–0.273	–0.092	95%CrI, Celgene, NMA results[5]
Golimumab	[redacted]	[redacted]	[redacted]	95%CrI, Celgene, NMA results[5]
BSC cost as a function of HAQ-DI – regression coefficients: Rodgers et al.				
Intercept	274.12	274.12	274.12	95%CI, Rodgers *et al*.[6]
HAQ-DI coefficient	121.18	–33.32	275.67	95%CI, Rodgers *et al*.[6]
Other health care costs as a function of HAQ-DI – regression coefficients: Rodgers et al.				
Intercept	274.12	274.12	274.12	95%CI, Rodgers *et al*.[6]
HAQ-DI coefficient	121.18	-33.32	275.67	95%CI, Rodgers *et al*.[6]
% of prescription cost	0.15	0.14	0.17	95%CI, Rodgers *et al*.[6]
Other health care costs as a function of HAQ-DI – cost of psoriasis: Rodgers et al.				
On TNF inhibitor, with PASI-75	16	14.04	17.96	95%CI, Rodgers *et al*.[6]
On TNF inhibitor, no PASI-75	198	180.36	215.64	95%CI, Rodgers *et al*.[6]
Not on TNF-inhibitor therapy	198	180.36	215.64	95%CI, Rodgers *et al*.[6]
Regression coefficients for utility estimation – apremilast trial				
Intercept	0.832	0.790	0.874	95%CI, Rodgers *et al*.[6]
HAQ-DI coefficient	–0.261	–0.288	–0.234	95%CI, Rodgers *et al*.[6]
PASI coefficient	–0.002	–0.004	0.001	95%CI, Rodgers *et al*.[6]
HAQ-DI progression when not on treatment				
HAQ-DI slope	0.006	0.001	0.011	95%CI, Rodgers *et al*.[6]
Increased mortality due to psoriatic arthritis				
Hazard ratio	1.36	1.12	1.64	95%CI, Ali *et al.*[7]

Input parameter/treatment	Base case	Lower value	Upper value	Rationale, Reference
Discount rate				
Costs and utilities	0.035	0.00	0.06	NICE[8]

CI, confidence interval; CrI, credible intervals; HAQ-DI, Health Assessment Questionnaire-Disability Index; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; PASI-50, 50% reduction in Psoriasis Area and Severity Index; PASI-75, 75% reduction in Psoriasis Area and Severity Index; PASI-90, 90% reduction in Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; TNF, tumour necrosis factor alpha.

Table 11 Univariate DSA results (costs saved/QALY lost): apremilast at list price and with PAS

Input parameters	List Price			PAS price		
	ICER at low value (£/QALY)	ICER at high value (£/QALY)	Range of variation (£/QALY)	ICER at low value (£/QALY)	ICER at high value (£/QALY)	Range of variation (£/QALY)
Efficacy						
PsARC - Apremilast	[redacted]	[redacted]	[redacted]	£35,327	£44,258	£8,931
PsARC - Adalimumab	[redacted]	[redacted]	[redacted]	£41,029	£37,594	£3,434
PsARC - Etanercept	[redacted]	[redacted]	[redacted]	£40,985	£37,703	£3,282
PsARC - Golimumab	[redacted]	[redacted]	[redacted]	£50,168	£34,732	£15,436
PASI50 - Apremilast	[redacted]	[redacted]	[redacted]	£38,909	£39,204	£296
PASI50 - Adalimumab	[redacted]	[redacted]	[redacted]	£39,086	£39,023	£63
PASI50 - Etanercept	[redacted]	[redacted]	[redacted]	£39,105	£38,993	£112
PASI50 - Golimumab	[redacted]	[redacted]	[redacted]	£39,245	£38,881	£364
PASI75 - Apremilast	[redacted]	[redacted]	[redacted]	£38,235	£39,743	£1,508
PASI75 - Adalimumab	[redacted]	[redacted]	[redacted]	£39,264	£38,855	£410
PASI75 - Etanercept	[redacted]	[redacted]	[redacted]	£39,227	£38,834	£393
PASI75 - Golimumab	[redacted]	[redacted]	[redacted]	£40,234	£37,986	£2,247
PASI90 - Apremilast	[redacted]	[redacted]	[redacted]	£39,025	£39,088	£63
PASI90 - Adalimumab	[redacted]	[redacted]	[redacted]	£39,067	£39,032	£35
PASI90 - Etanercept	[redacted]	[redacted]	[redacted]	£39,057	£39,044	£14
PASI90 - Golimumab	[redacted]	[redacted]	[redacted]	£39,126	£38,953	£173
Correlation coefficient between PsARC and PASI-75 responses	[redacted]	[redacted]	[redacted]	£39,013	£38,968	£45
Withdrawal rates						

Input parameters	List Price			PAS price		
	ICER at low value (£/QALY)	ICER at high value (£/QALY)	Range of variation (£/QALY)	ICER at low value (£/QALY)	ICER at high value (£/QALY)	Range of variation (£/QALY)
Long-term dropout rate - Apremilast	[redacted]	[redacted]	[redacted]	£42,778	£36,284	£6,494
Long-term dropout rate - Adalimumab	[redacted]	[redacted]	[redacted]	£39,775	£38,564	£1,210
Long-term dropout rate - Etanercept	[redacted]	[redacted]	[redacted]	£39,352	£38,806	£546
Long-term dropout rate - Golimumab	[redacted]	[redacted]	[redacted]	£33,821	£48,689	£14,868
Utilities						
Change in HAQ score - Apremilast PsARC responders	[redacted]	[redacted]	[redacted]	£42,817	£35,873	£6,944
Change in HAQ score - Adalimumab PsARC responders	[redacted]	[redacted]	[redacted]	£38,112	£40,038	£1,925
Change in HAQ score - Etanercept PsARC responders	[redacted]	[redacted]	[redacted]	£38,011	£40,160	£2,149
Change in HAQ score - Golimumab PsARC responders	[redacted]	[redacted]	[redacted]	£34,350	£45,174	£10,824
Change in HAQ score - Apremilast PsARC non-responders	[redacted]	[redacted]	[redacted]	£39,292	£38,814	£478
Change in HAQ score - Adalimumab PsARC non-responders	[redacted]	[redacted]	[redacted]	£39,009	£39,094	£86
Change in HAQ score - Etanercept PsARC non-responders	[redacted]	[redacted]	[redacted]	£38,496	£39,622	£1,126
Change in HAQ score - Golimumab PsARC non-responders	[redacted]	[redacted]	[redacted]	£39,052	£39,052	£0

Input parameters	List Price			PAS price		
	ICER at low value (£/QALY)	ICER at high value (£/QALY)	Range of variation (£/QALY)	ICER at low value (£/QALY)	ICER at high value (£/QALY)	Range of variation (£/QALY)
Utility estimation regression: intercept	[redacted]	[redacted]	[redacted]	£39,497	£38,636	£861
Utility estimation regression: HAQ-DI coefficient	[redacted]	[redacted]	[redacted]	£35,870	£43,085	£7,215
Utility estimation regression: PASI coefficient	[redacted]	[redacted]	[redacted]	£37,607	£40,612	£3,004
HAQ-DI slope	[redacted]	[redacted]	[redacted]	£45,969	£36,105	£9,864
Costs						
Other healthcare cost estimation regression: intercept	[redacted]	[redacted]	[redacted]	£39,052	£39,052	£0
Other healthcare cost estimation regression: HAQ-DI coefficient	[redacted]	[redacted]	[redacted]	£40,221	£37,883	£2,338
Other healthcare cost estimation - proportion of prescriptions in total estimated cost	[redacted]	[redacted]	[redacted]	£39,050	£39,053	£3
BSC cost estimation regression: intercept	[redacted]	[redacted]	[redacted]	£39,052	£39,052	£0
BSC cost estimation regression: HAQ-DI coefficient	[redacted]	[redacted]	[redacted]	£40,009	£38,094	£1,916
Psoriasis cost: on biologics, with PASI-75	[redacted]	[redacted]	[redacted]	£39,031	£39,072	£42
Psoriasis cost: on biologics, no PASI-75	[redacted]	[redacted]	[redacted]	£39,194	£38,909	£286
Psoriasis cost: not on biologics	[redacted]	[redacted]	[redacted]	£39,096	£39,007	£89
Discount rates						
Discount rate – costs and outcomes	[redacted]	[redacted]	[redacted]	£33,643	£42,317	£8,674
Increased mortality due to PsA						

Input parameters	List Price			PAS price		
	ICER at low value (£/QALY)	ICER at high value (£/QALY)	Range of variation (£/QALY)	ICER at low value (£/QALY)	ICER at high value (£/QALY)	Range of variation (£/QALY)
Hazard ratio for increased mortality	[redacted]	[redacted]	[redacted]	£38,640	£39,497	£857

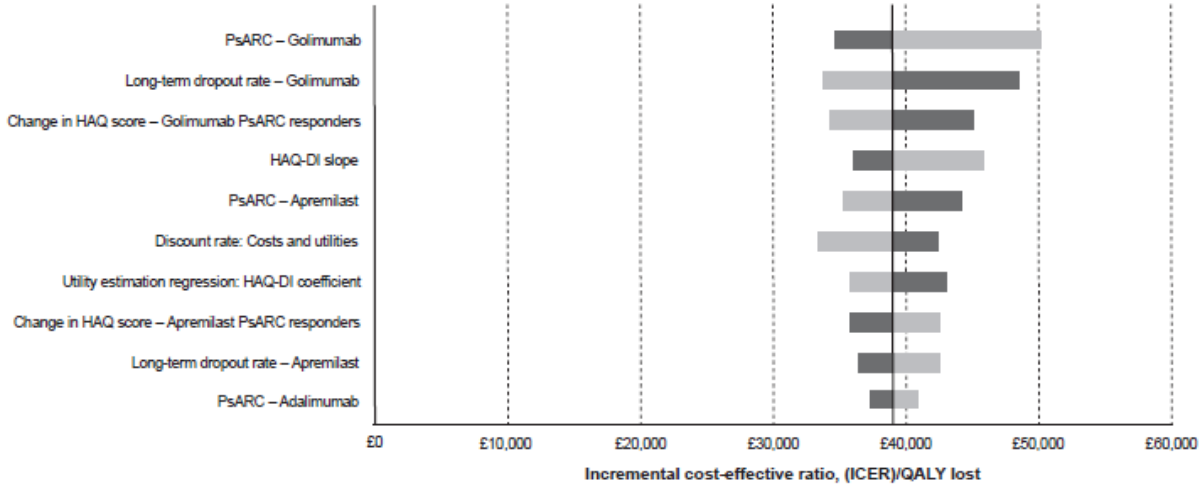
BSC, best supportive care; DSA, deterministic sensitivity analysis; HAQ-DI, Health Assessment Questionnaire Disability Index; ICER, incremental cost-effectiveness ratio; PASI-50/75; 50%/75% or greater improvement in Psoriasis Area and Severity Index Score; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; QALY, quality-adjusted life year.

Note: All ICERs presented in Table 11 are in the South-West quadrant

Figure 1 Tornado diagrams at a) the list price and b) with PAS

a)

b)



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

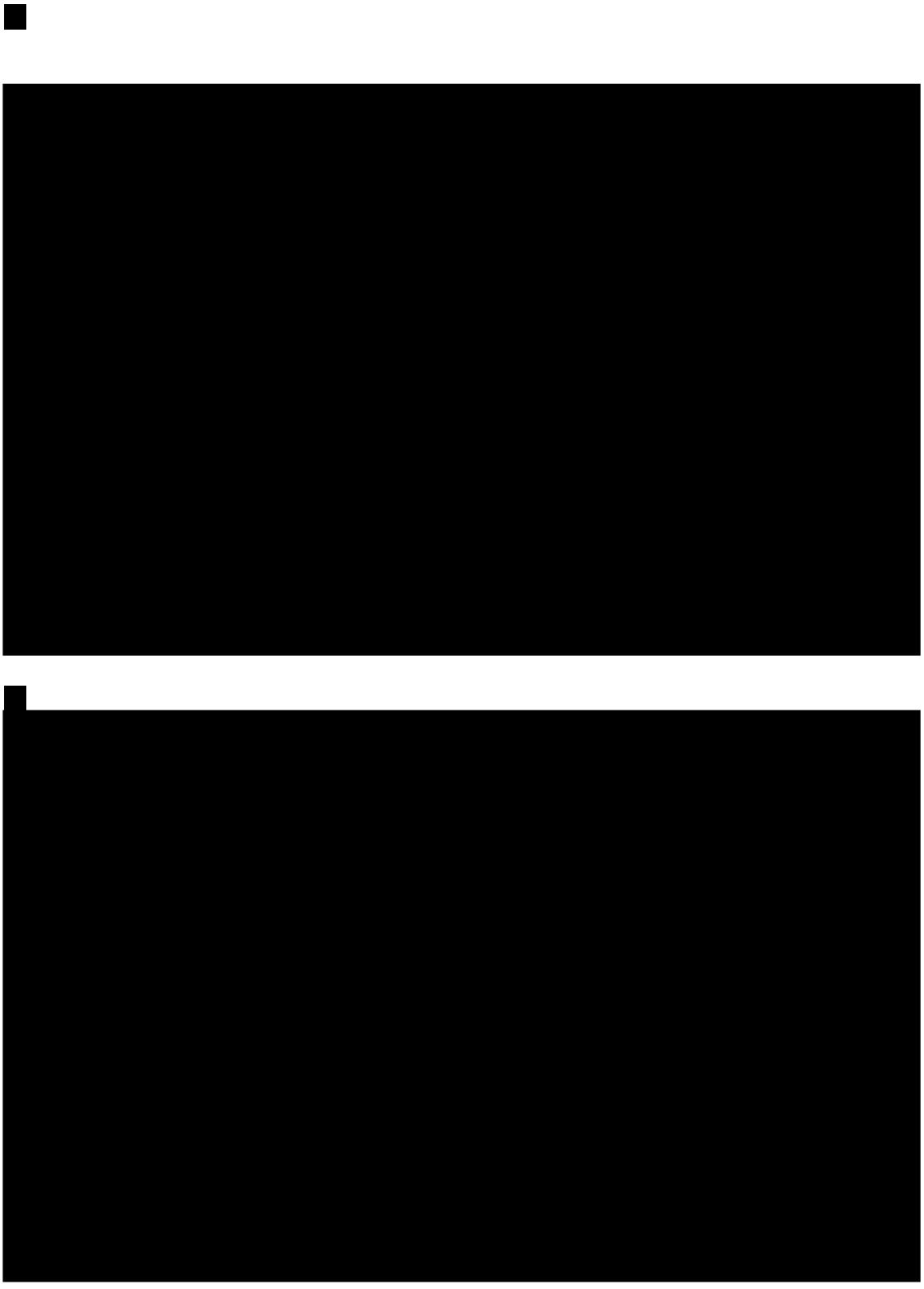
Probabilistic sensitivity analyses (PSA) were performed using the model corresponding to the Appraisal Committee's preferred assumptions and using the same parameter inputs as for the original submission (see manufacturer's submission section 7.6.3). A total of 5000 simulations were run.

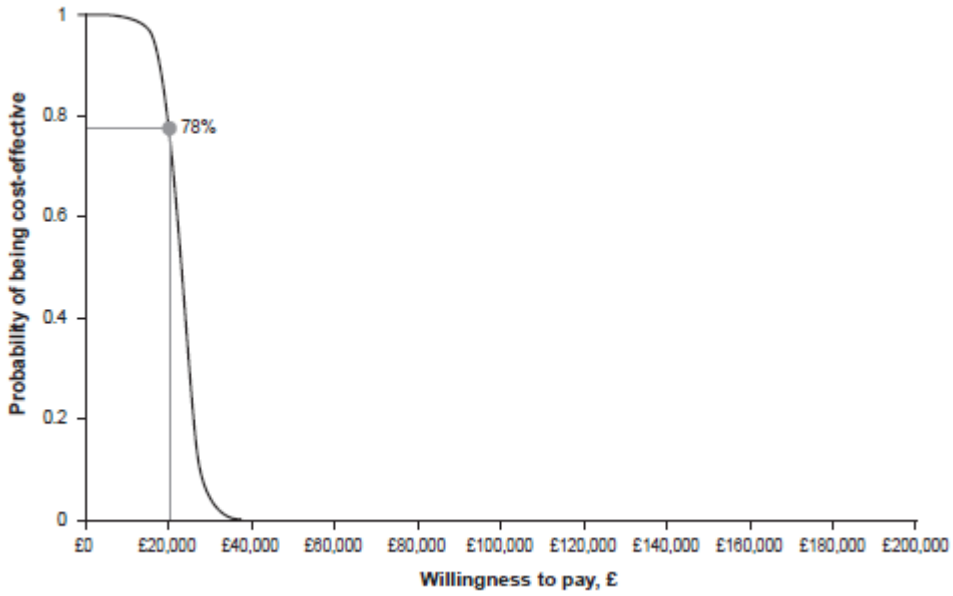
For the analysis for apremilast at the list price, the totality of the simulations is located in the south-west quadrant indicating a negative differential in costs and in outcomes (see Figure 2a). This implies that, based on the uncertainty associated with the model parameters modelled in the PSA, the inclusion of apremilast in the base case sequence, produces cost savings and a decrement in health benefits in all simulations considered. For the corresponding analysis for apremilast at the PAS fixed price, the cluster of simulation results moves downwards indicating that the price of apremilast included in the PAS increases the cost savings associated with the apremilast strategy (Figure 2b).

The probabilistic and deterministic ICERs are similar in both scenarios ([redacted] and [redacted], respectively, without the PAS, and £39,022 and £39,052, respectively with the PAS), indicating no issues with non-linearity within the model.

Cost-effectiveness acceptability curve plots indicated that at a willingness to pay threshold of £20,000, apremilast has a 78% probability of having a higher net benefit at the list price and this increases to 100% at the PAS fixed price (Figure 3). When considering a willingness to pay threshold of £30,000, apremilast has a probability of having a higher net benefit of 6% at the list price and 98% at the PAS fixed price (Figure 4).

Figure 2 a) Cost-effectiveness plane for analysis of apremilast at a) the list price and b) with PAS





b)

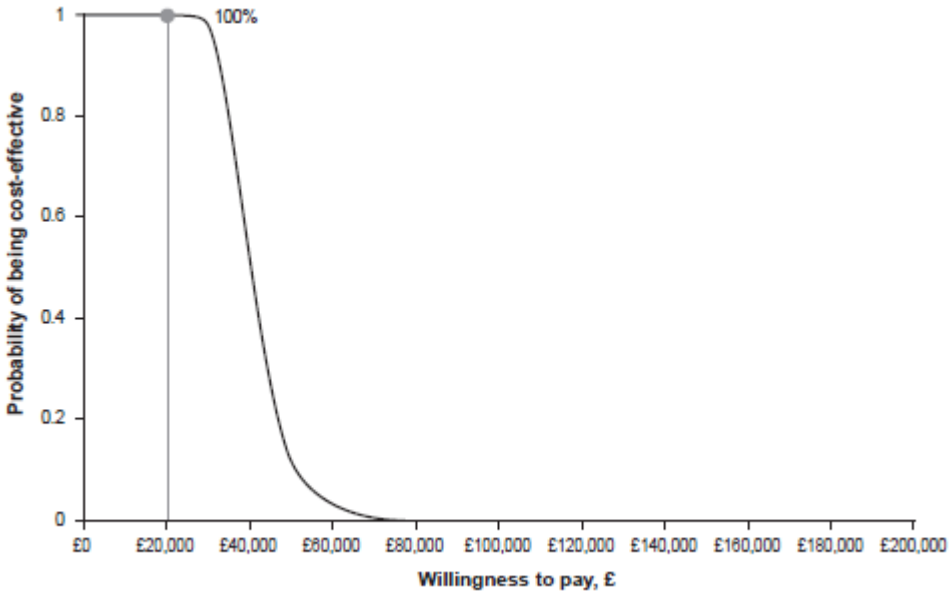
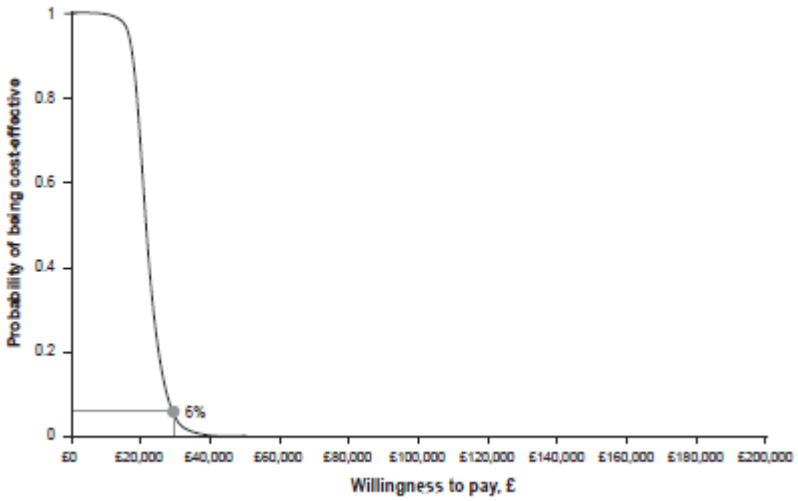
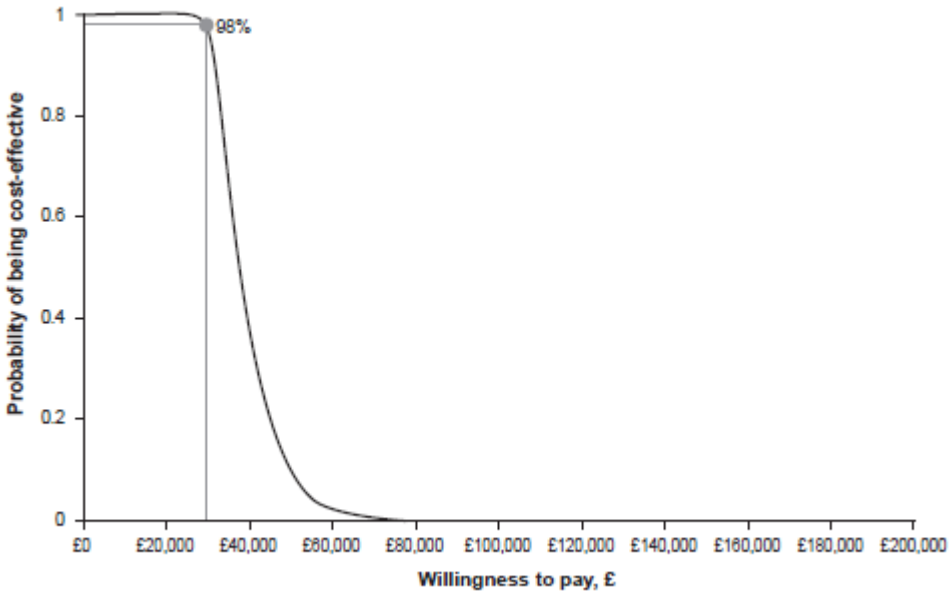


Figure 4 Cost-effectiveness acceptability curve for apremilast a) at list price and b) with PAS for a willingness to pay threshold of £30,000

a)



b)



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

Scenario analyses were performed to consider the effect of uncertainty around structural assumptions in the base case.

Table 12 presents the results of scenario analyses corresponding to those presented in the original submission (see manufacturer's submission section 7.7.9). These include: alternative treatment sequence and length of sequence, alternative time horizons, alternative criteria for treatment continuation, assuming HAQ-DI rebounds to natural history, alternative utility estimates, alternative estimates of costs for BSC and other healthcare costs, employing a 24-week trial period length for apremilast; using alternative assumptions for the apremilast long-term withdrawal probability, using an alternative baseline HAQ-DI score and assuming zero HAQ progression on apremilast treatment.

All scenario analyses have been conducted on the Appraisal Committee's preferred assumptions detailed in TA372, namely the comparison of sequences with an equal number of active treatments and **include an assumption of HAQ-DI progression = ½ BSC rate on apremilast treatment unless otherwise stated.**

For all of the 18 scenarios considered, the apremilast strategy using the PAS fixed price for apremilast was associated with a higher net benefit compared with the biologic strategy at a WTP of £30,000/QALY (ICER range for scenarios tested £31,943-£63,844).

Table 12 Results of scenario analyses at the list price and with the PAS fixed price corresponding to those performed for the initial submission

	List Price					PAS price				
Treatment strategy[1]	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**
Appraisal Committee preferred Base case										
Apremilast strategy (Apremilast→adalimumab→etanercept→ **BSC)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £39,052 SW quadrant
Biologic strategy (Adalimumab→etanercept→golimumab→ **BSC)**	[redacted]	[redacted]				[redacted]	[redacted]			
Apremilast versus adalimumab										
Apremilast strategy (Apremilast →BSC)	[redacted]	[redacted]	[redacted]	[redacted]	£21,832; SW Quadrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic strategy (Adalimumab →BSC)	[redacted]	[redacted]				[redacted]	[redacted]			
Comparison of 4-treatment strategies										
Apremilast strategy (Apremilast → adalimumab →etanercept→golimumab→BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £63,934 SW quadrant

	List Price					PAS price				
Treatment strategy[1]	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**
Biologic strategy (Adalimumab→etanercept→ golimumab→infliximab → BSC)	[redacted]	[redacted]				£146,246	9.18			
Scenario analysis: treatment continuation criteria defined as achievement of PsARC or PASI-75 response										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £37,280 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: ACR20 as a treatment response criteria										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £39,477 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: 1-year time horizon										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £75,669 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: 5-year time horizon										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net

	List Price					PAS price				
Treatment strategy[1]	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**
					[redacted]					benefit at 30K/QALY; £60,679 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: 10-year time horizon										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £50,363 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: HAQ rebound to natural history										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £37,857 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: utility estimation regression by Abbott										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £35,774 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			

	List Price					PAS price				
Treatment strategy[1]	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**
Scenario analysis: utility estimation by Schering-Plough										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £38,330 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: BSC and other healthcare costs estimated based on the regression model by Poole et al.										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £39,505 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: 24-weeks apremilast trial period length (consistent with apremilast SPC)										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £40,374 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: Alternative withdrawal probability for apremilast based on trial data in week 16 PsARC responders (10.9%)										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £44,264 SW quadrant

	List Price					PAS price				
Treatment strategy[1]	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: Alternative baseline HAQ-DI score based on Rodgers et al.(1.05)										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £38,902 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: No excess mortality is associated with PsA; mortality based on general population all-cause mortality										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £38,422 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: Correlation coefficient for PsARC and PASI75 based on apremilast trial data (ρ = 0.2356)										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £38,954 SW quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			
Scenario analysis: No HAQ progression on apremilast treatment										
Apremilast strategy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £63,844 SW

	List Price					PAS price				
Treatment strategy[1]	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**
					[redacted]					quadrant
Biologic strategy	[redacted]	[redacted]				[redacted]	[redacted]			

[1]Unless otherwise stated, Apremilast strategy: apremilast → adalimumab → etanercept → BSC; Biologic strategy: adalimumab → etanercept → golimumab →BSC.

ACR, American College of Rheumatology; BSC, best supportive care; HAQ-DI, Health Assessment Questionnaire-Disability Index; ICER, incremental cost-effectiveness ratio; N/A, not applicable; PASI-75, 75% or greater improvement in Psoriasis Area and Severity Index score; PsARC, Psoriatic Arthritis Response Criteria; QALYs, quality-adjusted life years; TNF, tumour necrosis facto

Single-treatment strategies: Pair-wise comparisons

Results for the pair-wise comparisons for single-line strategies, adopting the Appraisal Committees preferred assumptions (including HAQ-DI progression=1/2 BSC rate on apremilast treatment), with and without the PAS are summarised in Table 13.

Table 13 Single-treatment strategies: Pair-wise comparisons

	List Price					PAS price				
Sequence	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**	**Total costs (£)**	**Total QALYs**	**Δ costs (£)**	**Δ QALYs**	**ICER (£/QALY)**
Apremilast → BSC	[redacted]	[redacted]	[redacted]	[redacted]	£21,832; SW Quadrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab → BSC	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Apremilast → BSC	[redacted]	[redacted]	[redacted]	[redacted]	£19,373; SW Quadrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept → BSC	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Apremilast → BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,164; SW Quadrant
Golimumab → BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Apremilast → BSC	[redacted]	[redacted]	[redacted]	[redacted]	Higher net benefit at 30K/QALY; £40,116 SW Quadrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab → BSC	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	

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

Note, ustekinumab is not considered a relevant comparator in the single-line comparisons for patients eligible for a first-line TNF inhibitor therapy, consistent with recommendations detailed in TA340.

Single-treatment strategies: Fully incremental analysis

Results for fully incremental analysis for single-line comparisons, adopting the Appraisal Committees preferred assumptions (including HAQ-DI progression=1/2 BSC rate on apremilast treatment), with and without the PAS are summarised in Table 14 and Table 15.

Strategies highlighted in green are on the efficiency frontier and are cost-effective options at a WTP threshold of £30,000.

Etanercept and infliximab were found to be the on the cost efficiency frontier in the analysis at the list price, although the ICER of infliximab versus etanercept was very high ([redacted] per QALY gained, Table 14) and above conventional WTP thresholds of £20,000-£30,000/QALY. Apremilast was found to be extendedly dominated at the list price. At the PAS fixed price, apremilast is the most cost-effective treatment option at a WTP threshold of £20,000. Apremilast is also the only cost-effective treatment at a WTP of £20,000. Etanercept is the most cost-effective option at a WTP threshold of £30,000 with apremilast being the next most cost-effective option (ICER = [redacted] vs BSC) (Table 15).

Table 14 Fully incremental analysis for apremilast at list price: single-treatment strategies

Technologies	Total costs (£)	Total QALYs	ICER (£) versus BSC	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
BSC	[redacted]	[redacted]			
Apremilast	[redacted]	[redacted]	£21,698	£21,698	Extended dominance
Adalimumab	[redacted]	[redacted]	£21,746	£21,746	Extended dominance
Etanercept	[redacted]	[redacted]	£20,532	£20,532	£20,532
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	£31,728	£150,456	ICER greater than £30,000/QALY

BSC: Best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Table 15 Fully incremental analysis for apremilast with PAS: single-treatment strategies

Technologies	Total costs (£)	Total QALYs	ICER (£) versus BSC	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
BSC	[redacted]	[redacted]			
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	£21,746	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	£20,532	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	£31,728	[redacted]	[redacted]

BSC: Best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Alternative HAQ-DI progression assumptions

Presented below (tables 16 and 17) are fully incremental analyses assuming alternative HAQ-DI progression scenarios whilst on apremilast treatment including an assumption of zero HAQ-DI progression (supported by 3-year clinical trial data previously presented) and HAQ-DI progression=BSC (highly conservative and not supported by any evidence base).

Table 16 Fully incremental analysis for apremilast at PAS price: single-treatment strategies (assumes no HAQ progression on apremilast treatment)

Technologies	Total costs (£)	Total QALYs	ICER (£) versus BSC	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	£21,746	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	£20,532	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	£31,728	[redacted]	[redacted]

Table 17 Fully incremental analysis for apremilast at PAS price: single-treatment strategies (assumes HAQ progression=BSC on apremilast treatment)- exploratory analysis

Technologies	Total costs (£)	Total QALYs	ICER (£) versus BSC	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
BSC	[redacted]	[redacted]			
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	£21,746	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	£20,532	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	£31,728	[redacted]	[redacted]

Results show that, at the PAS price, apremilast remains the most cost-effective option at a WTP of £20K, even in the highly conservative exploratory analysis which assumes HAQ progression=BSC. **It should be noted that this scenario is exploratory in nature and not supported by any evidence and should therefore be interpreted with caution**. Apremilast has shown a statistically significant difference on disease activity compared with placebo. HAQ-DI is driven by disease activity, as is evident from data from the apremilast phase 3 trials. In these trials, apremilast provided a statistically significant improvement on disease activity at week 16 (e.g. ACR20, swollen joint count and tender joint count) and this improvement is sustained to week 102. This was accompanied by a statistically significant improvement in HAQ-DI compared with placebo at week 16 and the initial improvement in HAQ-DI was sustained to week 102 in patients who remained on treatment (all data previously presented as part of consultation response). This is also supported by published literature which indicate that strong and persistent control of disease symptoms improves both long term functional and joint damage outcomes.[9] Celgene therefore consider it clinically implausible to suggest that the rate of HAQ-DI deterioration is the same on apremilast and BSC. The analysis has been developed to show that even in the most conservative scenario, apremilast is likely to represent a cost-effective treatment option based on a conventional direct comparison versus NICE recommended TNF-inhibitor comparator therapies.

Three-treatment strategies

In section 4.11 of TA372, the Committee accepted that the use of treatment sequences was a valid approach to modelling. In section 4.12, the Committee stated that it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence. Celgene considers that a comparison of treatment sequences is more reflective of routine NHS practice. To assess the potential for variation in the ordering of therapies within a sequence, Celgene have conducted a fully incremental analysis based on

comparing sequences of equal length containing 3 active treatments (as in the Committees preferred base case).

The positioning of ustekinumab has been restricted to post one TNF-inhibitor, consistent with NICE Guidance in TA340.[10] The positioning of apremilast within the sequence has been restricted to first-line (post DMARD) consistent with its likely positioning in clinical practice based on drug cost, safety profile, route of administration and consistent clinical expert feedback. Furthermore, the single line displacement shows that apremilast is a cost-effective option at a WTP £20,000-£30,000 when TNF inhibitor therapies are considered as comparators (at PAS price). The objective of the sequential analysis is to determine whether apremilast is cost effective as a first-line (post DMARD) treatment option within a treatment sequence.

At the list price, two apremilast strategies were found to be on the efficiency frontier: apremilast followed by adalimumab and etanercept (ICER vs cheapest sequence, [redacted] per QALY gained), and apremilast followed by etanercept and adalimumab (ICER versus next most cost-effective strategy, [redacted], Table 18). Celgene note that the first of these sequences was considered not to be cost effective by the Appraisal Committee in TA372 although results from the fully incremental analysis show that this is a cost-effective choice. Both these ICERs were below the [redacted] /QALY threshold. In addition, the sequence preferred by the Committee (adalimumab followed by etanercept followed by golimumab) is extendedly dominated. The most cost-effective strategy at a WTP of £30,000 appears to be etanercept followed by golimumab followed by adalimumab.

Table 18 Fully incremental analyses for apremilast at list price: three-treatment strategies

Technologies	Total costs (£)	Total QALYs	ICER (£) versus cheapest treatment	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
Apremilast, Adalimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Ustekinumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Adalimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Ustekinumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Adalimumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Etanercept,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	ICER (£) versus cheapest treatment	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
Ustekinumab					
Adalimumab, Etanercept, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Etanercept, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Golimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Golimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Ustekinumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Golimumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Adalimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Ustekinumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Adalimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Etanercept, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Golimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Etanercept, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Ustekinumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Golimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Ustekinumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Adalimumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Adalimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Golimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Etanercept,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	ICER (£) versus cheapest treatment	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
Ustekinumab					
Etanercept, Golimumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Etanercept, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Ustekinumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Adalimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Infliximab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Etanercept, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Ustekinumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Golimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Ustekinumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Adalimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Etanercept, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Infliximab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Adalimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Infliximab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Golimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Infliximab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Infliximab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Infliximab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Ustekinumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Infliximab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Infliximab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Adalimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	ICER (£) versus cheapest treatment	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
Etanercept, Golimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Etanercept, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Infliximab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Infliximab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Infliximab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Ustekinumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Ustekinumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Infliximab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Adalimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Infliximab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Etanercept, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Adalimumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Etanercept, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Golimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Golimumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Etanercept, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Golimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

In the analysis with apremilast at the PAS fixed price, apremilast followed by etanercept and then golimumab was the most cost-effective strategy at a WTP of £30K, with an ICER of [redacted] per QALY gained versus the next most cost-effective strategy on the frontier (Table 19). Results indicate that at the PAS fixed price, there were no biologic strategies on the efficiency frontier as all were ruled out by dominance, extended dominance or had ICERs which exceeded a WTP of £30K (versus the next most cost-effective strategy).

Table 19 Fully incremental analyses for apremilast with PAS: three-treatment strategies

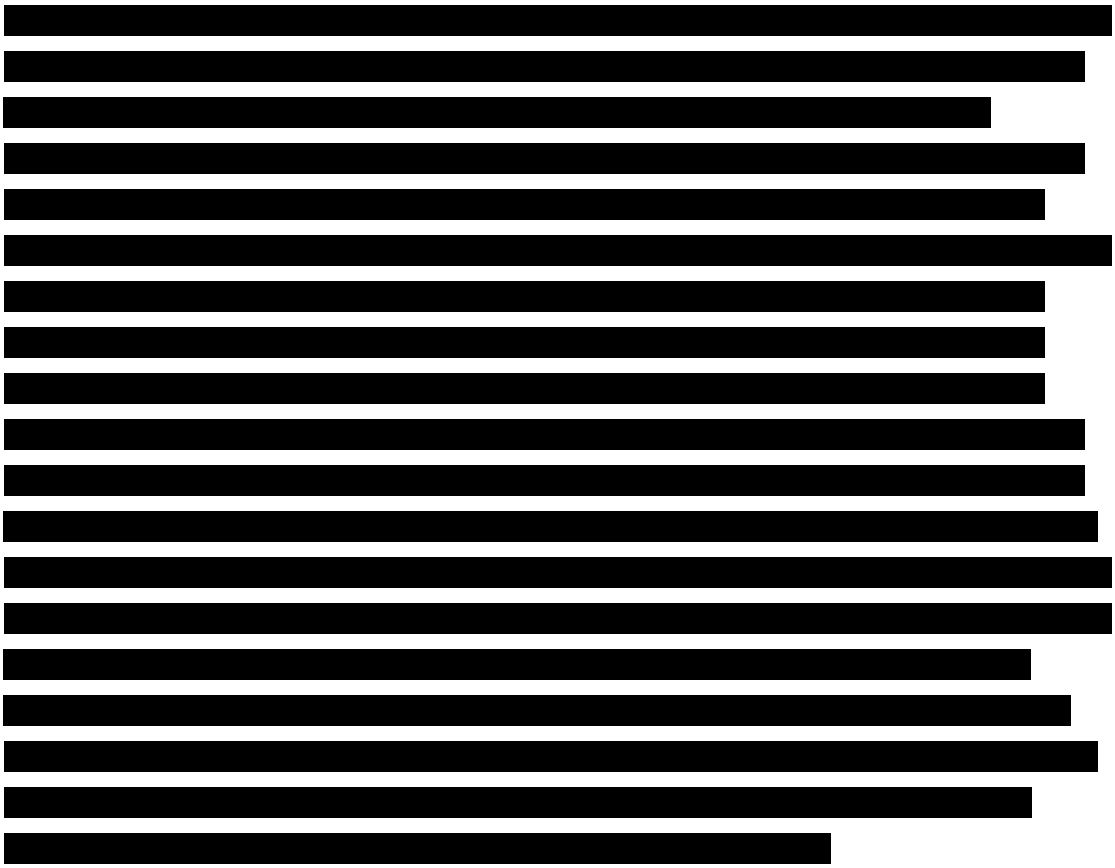
Technologies	Total costs (£)	Total QALYs	ICER (£) versus cheapest treatment	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
Apremilast, Adalimumab, Ustekinumab	[redacted]	[redacted]			
Apremilast, Adalimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Adalimumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Etanercept, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Etanercept, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Golimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Golimumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Ustekinumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Ustekinumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Etanercept, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Etanercept, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Golimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Ustekinumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Golimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Adalimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Ustekinumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Adalimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	ICER (£) versus cheapest treatment	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
Adalimumab, Etanercept, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Golimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Ustekinumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Ustekinumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Adalimumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Adalimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Golimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Etanercept, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Adalimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Golimumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Etanercept, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Ustekinumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Etanercept, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Infliximab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Golimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Infliximab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Infliximab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Etanercept, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Ustekinumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Golimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Ustekinumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Adalimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Adalimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Infliximab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab, Infliximab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast, Infliximab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	ICER (£) versus cheapest treatment	ICER (£) incremental (QALYs) versus next most cost-effective strategy	Frontier
Adalimumab, Infliximab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Infliximab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Ustekinumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Infliximab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Adalimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Golimumab, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Etanercept, Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Infliximab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Infliximab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Ustekinumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Ustekinumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept, Infliximab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Adalimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab, Infliximab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Etanercept, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Adalimumab, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Etanercept, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Golimumab, Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Golimumab, Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Etanercept, Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab, Golimumab, Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-years

NHS Budget Impact as a result of approval of apremilast in psoriatic arthritis



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

Note: All data presented in this section have been presented previously during NICE TA372. This section does not contain any new data

Apremilast has a novel PDE-4 mechanism of action, targeting multiple steps in the pathogenesis of PsA, and represents a significant innovation for the treatment of active PsA.[11]

Apremilast, being an oral therapy, may support patient preferences for route of administration. Empirical research indicates that many patients with PsA have a preference to avoid injectable medications for their condition. For example in the MAPP study,[12,13] half of patients in the UK who had received injectable biologic therapies indicated that these therapies were burdensome, primarily because of AEs, inconvenience and anxiety associated with injections and preparation for self-injection. A preference for an oral route of administration compared to injectable therapy is not captured into the QALY calculation.

Apremilast reduces the impact of PsA on productivity loss and work limitations. The impact of apremilast treatment on work limitations and productivity were assessed using the Work Limitations Questionnaire (WLQ)-25. Pooled data from the three Phase 3 RCT, PSA-002/003/004 indicates that patients with active PsA receiving apremilast experienced increased work productivity and reduced work limitations compared with placebo suggesting a favourable wider societal benefit associated with apremilast treatment.[14] These wider societal benefits were conservatively not incorporated into the economic evaluation.

The analysis, consistent with the Rodgers et al. model, excludes costs or disutility associated with adverse events. This is considered to be conservative toward apremilast based on the available data. A recent publication highlights an increase in serious infection rates associated with biologic treatment.[15] Celgene have previously presented 3-year safety data as part of the response to the appraisal consultation document during TA372. These data were based on a pooled analysis of PSA-002/003/004 studies and reported that the results indicated no new safety signals between weeks 102-156 beyond those previously identified. In addition, the SPC for apremilast does not have any requirements for screening at treatment initiation or routine laboratory monitoring with treatment. The base case analysis, assumes equal monitoring requirements for apremilast and biologic comparators and can therefore be considered as conservative toward apremilast.

The additional benefits highlighted in this section relating to the novel mechanism of action of apremilast, a preference for an oral route of administration, overall safety and laboratory monitoring advantages and the wider societal benefit of apremilast treatment on work productivity are not captured in the base case QALY calculation. Thus the estimates of cost-effectiveness of apremilast presented in this submission can be considered as conservative.

Overall Conclusion

The analysis presented within this submission shows that in England and Wales apremilast as a first-line therapy (post DMARD), at the fixed PAS price, is likely to have a higher net benefit at a WTP threshold of £30K compared with routine NHS practice. This conclusion is robust to a series of extensive sensitivity and scenario analyses based on varying key parameters and includes scenarios that are based on a set of highly conservative assumptions. This conclusion, based on a comparison of treatment sequences, is further supported by the results from a conventional, fully incremental analysis comparing apremilast directly with TNF-inhibitor therapies in a single-line displacement.

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

Not relevant

Impact of patient access scheme on ICERs

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

This information is presented in section 4.9.

5 References

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ERG review of the PAS submission of apremilast for the treatment of active psoriatic arthritis

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Date 30/6/2016

1 Introduction

Following the decision not to recommend apremilast for the treatment of active psoriatic arthritis (PsA) in NICE Technology Appraisal Guidance 372, the company (Celgene) has proposed a Patient Access Scheme (PAS) within the rapid review facility of the Single Technology Appraisal (STA) process. According to the company PAS submission, the PAS is intended to be applied to all patients with active PsA receiving treatment with apremilast on the NHS in England and Wales, within its licensed indication.

The ERG was requested by NICE to review the company submission. Due to the limited resource available, the additional work undertaken by the ERG does not constitute the same level of formal critique that was applied to the original submission. The ERG review should also be read in conjunction with the company's PAS submission.

In Table 1, the ERG provides a summary of the changes introduced by the company in the PAS submission. These are further discussed in Sections 2 to 4 of this document.

Table 1 Summary of changes in the company PAS submission

1)	Lower acquisition costs for the 56 and 27 tablet packs of apremilast, based on the proposed PAS
2)	Adjustments to reflect the NICE Appraisal Committee's preferred assumptions, as detailed in the TA Guidance 372
3)	An alternative assumption, introduced by the company, relating to the HAQ-DI score change for golimumab

The ERG has identified a number of additional issues and uncertainties related to the NICE Appraisal Committee's (AC) preferred assumptions that have not been fully addressed within the company PAS. These are listed in Table 2 and are discussed in more detail in Sections 5 and 6.

Table 2 List of additional issues considered relevant by the ERG

1)	The potential positioning of apremilast within a treatment sequence
2)	The HAQ progression for patients on treatment with apremilast
3)	The length of the treatment sequences being compared

2 PAS Implementation

2.1 PAS scheme

Apremilast is administered orally. The recommended dosage is 30 mg twice daily after an initial titration schedule. A single 10-mg dose is given on the first day of treatment; this is titrated to 30 mg twice daily over 5 days (see the summary of product characteristics for the dose titration schedule).

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

2.2 Patient population to which the PAS applies

As per the company's PAS submission, the PAS is intended to be applied to all patients with PsA receiving treatment with apremilast on the NHS in England and Wales within its licensed indication, for the management of active PsA in patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

2.3 Administration costs

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

3 Model changes based on NICE Appraisal Committee's deliberations

In addition to the PAS submission, the company submitted an updated economic model. The updated model was stated to incorporate the PAS price for apremilast, as well as the adjustments to the company base-case analysis that the NICE AC considered most plausible, as stated in TA37. These adjustments included:

1. comparing two treatment sequences of equal lengths (i.e. the company base-case evaluates apremilast as pre-biologic treatment as part of a treatment sequence consisting of adalimumab and etanercept with a biologic-only sequence consisting of adalimumab, etanercept and golimumab.)
2. using efficacy results from the NMA excluding the Schett et al trial
3. using a utility function derived from the apremilast trial data
4. assuming the same monitoring for apremilast as for biologic therapy
5. assuming HAQ-DI progression on apremilast at half the rate of that on BSC
6. inclusion of a placebo response to BSC.

In addition to the NICE AC preferred assumptions, an alternative assumption relating to the HAQ-DI score (change from baseline) for golimumab was also incorporated in the updated company model. In their original submission, the company assumed that the HAQ-DI score for golimumab, conditional on PsARC response, is equal to the average of the score for the other TNF inhibitors included in the model (i.e. adalimumab, etanercept and infliximab). An assumption was required because the actual HAQ-DI change score for golimumab used in a previous TA (TA220) was marked as academic in confidence. In their PAS submission, the company have revisited this assumption. The rationale provided by the company is that golimumab was not included in the company's base case in TA372,

but is now included in the NICE AC preferred scenario. Hence, the company argues that the appropriateness of their original assumption is now more relevant in the context of the analyses presented based on the NICE AC preferred assumptions.

The company now make the case in their PAS submission that in a previous NICE appraisal (TA220), despite the fact that the HAQ-DI change for golimumab was marked as academic in confidence, the Committee commented that "golimumab had the lowest HAQ score change from baseline compared with the other TNF inhibitors. (TA220, Section 4.8)". The company considered that their previous assumption that the HAQ-DI score for golimumab is equal to the average of that for the other TNF inhibitors is likely to overestimate the HAQ-DI response for golimumab. Consequently in their updated economic model in the PAS submission, they assume the HAQ-DI change for golimumab as [redacted].

A summary of all the adjustments that were made to the economic model in the company PAS submission are detailed in Table 3.

Table 3 Summary of changes to the company updated model

Parameter	Company original submission (TA372)	Company model following consultation (TA372)	Considered most plausible by the NICE AC (TA372)	PAS submission
Model structure	Assumes apremilast extends a sequence	Assumes apremilast extends a sequence	Assumes apremilast displaces a TNF inhibitor in a sequence	Assumes apremilast displaces a TNF inhibitor in a sequence
Efficacy	NMA	NMA excluding Schett et al	NMA excluding Schett et al	NMA excluding Schett et al
Utility source	Linear function of the HAQ-DI and PASI scores, based on a multivariate linear regression model estimated by Wyeth.	Apremilast trial data using UK tariffs	Apremilast trial data using UK tariffs	Apremilast trial data using UK tariffs
Physician visits/monitoring frequency	Assumed no monitoring for ongoing apremilast	Assumes the same frequency of monitoring for apremilast and biologic therapy	Assumes the same frequency of monitoring for apremilast and biologic therapy	Assumes the same frequency of monitoring for apremilast and biologic therapy

HAQ progression while on apremilast	None	None	Half the rate of BSC	Half the rate of BSC
BSC efficacy	None	Inclusion of placebo response in BSC health state	Inclusion of placebo response in BSC health state	Inclusion of placebo response in BSC health state
HAQ-DI conditional on PsARC response for golimumab	N/A, golimumab not included in base case	N/A, golimumab not included in base case	Assumes HAQ-DI change equal to the mean of adalimumab, etanercept and infliximab	Assumes HAQ-DI change [redacted]

AC, Appraisal Committee; BSC, Best supportive care; HAQ-DI, Health Assessment Questionnaire-Disability Index; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; QALY, quality-adjusted life year; TNF, tumour necrosis factor

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

4 Results from the company PAS submission

In the company PAS submission, the base-case compares the following two treatment sequences, based on the NICE AC's preferred scenario in TA372:

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

In Table 7 of their PAS submission, the company summarised the deterministic base-case results for the scenario considered most plausible by the NICE AC in TA372, as presented in the final appraisal determination (FAD) document. This scenario incorporates the NICE AC preferred assumptions and does not include the PAS price for apremilast and the alternative company HAQ change assumption for golimumab. This comparison was associated with a cost saving of £6,739 for the apremilast sequence and a QALY loss of 0.37, and resulted in an ICER £18,292 (South-west (SW) quadrant of the cost-effectiveness plane) for the apremilast sequence, at list price for apremilast. Since the apremilast sequence is in the SW quadrant, the ICER of £18,292 refers to the comparison of the higher cost and more effective sequence (comparator sequence) compared to the lower cost and less effective sequence (apremilast sequence).

Given that the ICER for the apremilast sequence in this comparison is less than the conventional cost-effectiveness threshold range (£20,000-£30,000 per QALY), the comparator sequence is the most cost-effective strategy, using the list price for apremilast. That is, the expected cost savings at list price with the apremilast sequence are not sufficient to offset the expected loss in QALYs. Consequently, in situations where a treatment option is less effective and less costly than its comparator, the conventional decision rule of demonstrating cost-effectiveness with an ICERs below a given threshold is reversed; thus the higher the ICER under these circumstances, the more cost effective the treatment option in the SW quadrant becomes. For a treatment option to be considered cost-effective in the SW quadrant, the estimate of the ICER has to be greater than the cost-effectiveness threshold considered.

The company base-case analysis in the PAS submission included the NICE AC's preferred assumptions in TA372, but it additionally included the assumption that the HAQ-DI change for golimumab is [redacted] (as discussed in Section 3). Table 4 summarises the deterministic results of the company base-case, with and without the PAS price applied for apremilast. At list price for apremilast, in the company base-case analysis the apremilast sequence is associated with a cost saving of [redacted] and a QALY loss of [redacted], resulting in an ICER of [redacted] (SW quadrant). The difference in the company base-case ICER at list price for apremilast versus the NICE AC preferred scenario (ICER of £18,292, SW quadrant) is driven by the different in the HAQ assumption for golimumab.

Applying the PAS discount for apremilast ([redacted]) in the company base-case, the apremilast sequence is associated with a cost saving of [redacted], resulting in an ICER of £39,052 (South-west quadrant) compared with the comparator (biologics-only) sequence. This reflects a reduction in the total incremental costs of [redacted] compared to apremilast at list price, and hence a corresponding increase in the cost saving associated with the apremilast sequence. The PAS does not affect the incremental QALYs. As a result, the magnitude of cost savings based on the PAS price now is now sufficient to offset the expected loss in QALYs such that the apremilast sequence is now the most cost-effective strategy. The ERG has successfully replicated these results.

Table 4 Company base-case deterministic results (including alternative HAQ-DI change assumption for golimumab) – with and without apremilast PAS

	No PAS discount		PAS discount applied ( )	
	Apremilast sequence	**Comparator sequence**	**Apremilast sequence**	**Comparator sequence**
Intervention cost (£)				
Other costs (£)				
Total costs (£)				
Difference in total costs (£)				
QALYs				
QALY difference				
ICER (£)/QALY	; SW Quadrant		£39,052 SW quadrant	

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

Net Monetary Benefit

Given some of the issues and challenges associated with ratio based statistics (i.e. the ICER) and issues of interpreting results in the SW-quadrant, the company also reported results in terms of Net Monetary Benefit (NMB). The NMB places both costs and effects on a single monetary scale and avoids the statistical and interpretation issues of ratios. In NMB, the difference in health effects between two options being evaluated is rescaled into monetary value using the cost-effectiveness threshold as a value for each unit of effect, and the difference in costs between the options is subtracted from this value. If the NMB is >0 for the intervention, it indicates that the intervention has a higher net monetary benefit at a given threshold versus the comparator (i.e. it is cost-effective). The advantage of the NMB approach is that there is no ambiguity in the interpretation.

Using the company base-case results with the PAS discount for apremilast (as shown in Table 4) and a cost-effectiveness threshold of £30,000 , the NMB for the apremilast sequence is calculated as follows: NMB = (£30,000 *) – = +£2,683. Since the NMB is>0, this indicates that the apremilast sequence is cost-effective compared to the comparator sequence. Similarly, the NMB for the apremilast sequence at a cost-effectiveness threshold of £20,000 is NMB = (£20,000 *) – = +£5,699.

Deterministic sensitivity analyses

A number of deterministic sensitivity analyses were presented, with and without the PAS discount, using the parameters that were varied in the original evidence submission (original company submission, section 7.6.2). Key parameters included treatment efficacy (i.e. PASI and PsARC response rates), changes in HAQ-DI scores by PsARC response category, and health care costs. The deterministic sensitivity analyses results are presented in detail in Tables 10 and 11 of the company PAS submission (p20-26). The apremilast sequence at the PAS fixed price appeared to be cost-effective in all scenarios considered by the company in their deterministic sensitivity analyses. The ICER results for the apremilast sequence were all located in the SW quadrant and ranged between £33,643 and £50,168 per QALY.

Probabilistic results

The company additionally conducted PSA in their updated model, on their base-case analysis with and without the PAS discount. The same parameter inputs as the PSA in their original submission were used. A total of 5,000 simulations were run. The additional assumption of HAQ change for golimumab, introduced in the PAS submission, was not tested in the company PSA. The probabilistic and deterministic ICERs were reported to be similar ([redacted] and [redacted], respectively, without the PAS, and £39,022 and £39,052, respectively with the PAS), indicating no issues with non-linearity within the model.

The PSA base-case results indicated that at the list price apremilast has a 78% probability of being cost-effective at a cost-effectiveness threshold of £20,000/QALY which increased to 100% at the PAS discounted price. These probabilities were respectively 6% at the list price and 98% at the PAS discounted price, for a threshold of £30,000/QALY.

Scenario analyses

Scenario analyses were presented to consider the effect of uncertainty around structural assumptions in the base case. The scenario analyses selected by the company and presented in the PAS submission corresponded to those presented in the original company submission. These included:

- alternative treatment sequence and length of sequence
- alternative time horizons
- alternative criteria for treatment continuation
- assuming HAQ-DI rebounds to natural history

- alternative utility estimates
- alternative estimates of costs for BSC and other healthcare costs
- employing a 24-week trial period length for apremilast
- using alternative assumptions for the apremilast long-term withdrawal probability
- using an alternative baseline HAQ-DI score and
- assuming zero HAQ progression on apremilast treatment.

The scenario analyses results are presented in Table 12 (p34-39) of the company PAS submission.

All the company scenario analyses were conducted on the company base case i.e. the NICE AC preferred scenario detailed in TA372, including the assumption of HAQ-DI progression of apremilast equal to half the BSC rate and the additional company assumption that the HAQ-DI change for golimumab [redacted]. For all of scenarios considered by the company, the apremilast sequence at the PAS price was associated with a higher NMB compared with the comparator sequence at a cost-effectiveness threshold of £30,000/QALY. The ICER results for these scenarios were all located in the SW quadrant and ranged between £31,943and £75,669.

Single-treatment comparisons

The company presented single-treatment comparisons, that is head-to-head comparisons, of apremilast versus anti-TNF therapies, adopting the NICE AC preferred assumptions (i.e. including HAQ-DI progression for apremilast equal to half the rate for BSC), with and without the PAS price. Table 5 summarises these results. These comparisons indicated that, when including the PAS price, apremilast is cost-effective compared to all biologic therapies at a threshold of £20,000, but not versus etanercept and golimumab when considering a threshold of £30,000.

Table 5 Single-treatment pair-wise comparisons (company analysis; replication of Table 13, p40 in company PAS submission)

	ICER (£/QALY)	
Sequence	**List Price**	**PAS price**
Apremilast → BSC vs. Adalimumab → BSC	£21,832*	[redacted]
Apremilast → BSC vs. Etanercept → BSC	£19,373*	[redacted]
Apremilast → BSC vs. Golimumab → BSC	[redacted]	£28,164*
Apremilast → BSC vs. Infliximab → BSC	£40,116*	[redacted]

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

* ICER is located in the south west quadrant

A fully incremental analysis of single-treatment comparisons, when including the PAS price for apremilast, indicated that while apremilast is the most cost-effective treatment option at a cost-effectiveness threshold of £20,000, etanercept is the most cost-effective option at a threshold of £30,000 (Table 6).

Table 6 Fully incremental analysis of single-treatments; apremilast at PAS price (company analysis; replication of Table 15, p43 in company PAS submission)

Treatment	Total costs (£)	Total QALYs	ICER (£) versus BSC	ICER (£) versus next most cost-effective strategy	Frontier
BSC	[redacted]	[redacted]			
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	£21,746	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	£20,532	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	£31,728	[redacted]	[redacted]

BSC: Best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

The company also considered fully incremental analyses of single-treatments, assuming alternative HAQ-DI progression scenarios for apremilast. This is the only section of the company PAS submission where less optimistic HAQ progression scenarios for apremilast have been considered. Whereas the base case PAS assumed apremilast to have HAQ-DI progression equal to half the BSC rate, the company presented fully incremental results when an assumption of no HAQ-DI progression while on treatment with apremilast is considered (Table 7, also in p43 of company PAS submission) and another set of fully incremental results assuming that patients on treatment with apremilast have the same HAQ-DI score progression as BSC (i.e. assuming that apremilast does not have an impact on disease progression; Table 8, also in p44 of company PAS submission).

Table 7 Fully incremental analysis of single- treatments; apremilast at PAS price. Scenario with no HAQ progression for apremilast (company analysis; replication of Table 16, p43 in company PAS submission)

Technologies	Total costs (£)	Total QALYs	ICER (£) versus BSC	ICER (£) versus next most cost-effective strategy	Frontier
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC: Best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Table 8 Fully incremental analysis of single- treatments; apremilast at PAS price. Scenario with HAQ progression for apremilast equal to BSC (company analysis; replication of Table 17, p44 in company PAS submission)

Technologies	Total costs (£)	Total QALYs	ICER (£) versus BSC	ICER (£) versus next most cost-effective strategy	Frontier
BSC	[redacted]	[redacted]			
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	£21,746	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	£20,532	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	£31,728	[redacted]	[redacted]

BSC: Best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

This latter scenario, assuming HAQ progression for apremilast equal to BSC, was argued by the company to be "highly conservative and not supported by any evidence base". Results showed that, at the PAS price, apremilast was the most cost-effective option at a cost-effectiveness threshold of £20,000 for both HAQ-DI progression scenarios. However, for a threshold of £30,000 etanercept was consistently shown to be the most cost-effective option.

Three-treatment sequence comparisons

Based on the NICE Committee statement in TA372, that it is more informative to make inferences from modelling the same number of active comparators in each treatment sequence, the company presented a fully incremental analysis, comparing sequences of equal length of 3 active treatments. This analysis was intended to assess the potential for variation in the ordering of therapies within a sequence. In this analysis however, the company restricted apremilast to first-line (pre-biologic) position within the sequence, claimed to be in line with its likely positioning in clinical practice based on drug cost, safety profile, route of administration and consistent clinical expert feedback. Ustekinumab was also included in this fully-incremental analysis and was restricted to post one TNF-inhibitor, consistent with NICE Guidance in TA340.

Among the treatment sequences selected by the company, when considering the list price for apremilast, the most cost-effective sequence at a threshold of £30,000 appeared to be a sequence not including apremilast: etanercept followed by golimumab followed by adalimumab (Table 18 of company PAS submission). When taking into account the PAS price for apremilast, the sequence of apremilast followed by etanercept and then golimumab was the most cost-effective sequence at a cost-

effectiveness threshold of £30,000, with an ICER of £24,212 per QALY gained versus the next most cost-effective sequence on the frontier (Table 19 of company PAS submission).

5 ERG critique of company's PAS submission

5.1 ERG verification checks

The ERG undertook a series of verification checks in relation to the inclusion of the PAS scheme and the proposed model amendments. The ERG is satisfied that the company appropriately implemented the PAS scheme and the specific adjustments that the NICE AC considered to be most plausible. The ERG was able to validate the findings of the company's base-case analysis, confirming that (i) the introduction of the PAS discount of [redacted] for apremilast (ii) the implementation of the adjustments to the economic model to reflect the NICE AC's preferred assumptions and (iii) the implementation of the alternative company HAQ-DI assumption for golimumab, resulted in an ICER of £39,052 per QALY (SW Quadrant) versus an ICER of £18,292 /QALY (SW Quadrant) in the NICE AC preferred scenario in TA372. These results represent an improvement from a negative NMB of -£4,313 to a positive NMB of +£2,683 in the company PAS submission base-case, at a cost-effectiveness threshold of £30,000/QALY.

Due to time constraints the ERG did not attempt to replicate all the individual sensitivity and scenario analyses reported in Tables 11 and 12 of the company's submission or all the results of fully incremental analyses of treatment sequences provided in Tables 18 and 19 of the company PAS submission. Instead, the ERG focused on replicating and verifying the company base-case results and all the single-treatment scenarios that the company presented in Tables 7-9 and Tables 12-17 of the company PAS submission. The ERG successfully replicated these results.

5.2 ERG critique

Although the ERG is satisfied that the company appropriately implemented the PAS scheme and the model adjustments based on the NICE AC preferred assumptions, the ERG has concerns on a number of remaining uncertainties that have not been fully addressed by the company in their PAS submission. Specifically these relate to:

1) The potential positioning of apremilast within a treatment sequence
2) HAQ progression for apremilast
3) The length of the treatment sequences being compared

Issue 1: The potential positioning of apremilast within a treatment sequence

Throughout their PAS submission, the company has evaluated apremilast only as pre-biologic treatment within a treatment sequence, claiming that this is in line with clinical expert feedback and that it reflects the likely positioning of apremilast in clinical practice. No alternative positioning was evaluated for apremilast within a treatment sequence, either in the fully incremental analyses that the company presented or in any of their scenario analyses that were explored.

However, the NICE AC clearly noted in Section 4.10 of the final appraisal determination (FAD) document in TA372 that *"The Committee considered the lack of radiographic assessment in the apremilast trials. It heard from the clinical experts that it would be difficult to justify using apremilast early in the treatment pathway (before TNF-alpha inhibitors) without evidence that it can prevent radiological progression, because there is evidence to show that TNF-alpha inhibitors slow disease progression."* and the AC concluded in the end of Section 4.10 that *"the lack of radiographic evidence and the clinical-effectiveness evidence did not support the use of apremilast before TNF-alpha inhibitors in clinical practice.".*

In addition, the company in their PAS submission has presented the comparison of the apremilast sequence (apremilast → adalimumab → etanercept → BSC) versus the comparator sequence (adalimumab → etanercept → golimumab → BSC) as the only preferred scenario by the NICE AC in TA372. However, the Committee in the FAD (Section 4.21) also considered apremilast as a treatment after TNF-alpha inhibitor therapy, or for people who could not take TNF-alpha inhibitors.

Issue 2: HAQ progression for apremilast

The company, throughout their analyses in the PAS submission, use the assumption of HAQ-DI progression for apremilast at a rate equal to half the rate for BSC. This is referred to by the company

as the NICE AC preferred assumption. However, it has been stated by the NICE Committee, that the HAQ trajectory for patients remaining on treatment with apremilast is uncertain. In Section 4.14 of the FAD document in TA372 the Committee states that "*The Committee was aware that the assumption that TNF-alpha inhibitors halt disease progression was supported radiographically and also by clinical practice evidence over a number of years. However, there was uncertainty about whether this assumption was equally relevant for apremilast, which has a different mechanism of action and limited evidence of use in clinical practice because it is a relatively new treatment".*
The ERG would like to highlight that this assumption of HAQ-DI progression for apremilast (i.e. at a rate half of the HAQ-DI progression for BSC) was chosen by the NICE AC as the most plausible scenario, from a limited set of analyses that were presented to the Committee. The actual rate of HAQ-DI progression for apremilast remains uncertain.
The company, within the PAS submission, did not present alternative HAQ progression assumptions for apremilast within the context of a treatment sequence. The only scenarios where the company considered alternative HAQ progression assumptions for apremilast in the PAS submission were within single-treatment comparisons. Specifically, the scenario that included a less optimistic HAQ assumption for apremilast was described by the company as "highly conservative and not supported by any evidence base".

Issue 3: The length of the treatment sequences being compared

In Section 4.12 of the FAD the NICE Committee stated that *"in order to prevent the model being confounded by any QALY gain occurring only because of one group in the model having an additional active treatment in a selected and an unrealistically short sequence, it was more informative to make inferences from modelling the same number of active comparators in each treatment sequence."*. This ERG interprets this to mean that the NICE AC preferred comparing sequences of equal length but did not formally state the exact/optimal length of the sequences.

The ERG considers that the fact that the company have only considered sequences including three active treatments in their base case analysis is a partial representation of the decision problem.

6 ERG additional analyses

In order to address the remaining areas of uncertainty and inform the most efficient use and position of apremilast, all issues discussed in Section 5 would need to be addressed simultaneously. However, while the updated model submitted by the company is sufficiently flexible to address independently all key issues raised, namely: (i) the position of apremilast within sequences, (ii) the rate of HAQ-DI

progression for apremilast and (iii) the length of the treatment sequences themselves, it cannot appropriately address all issues simultaneously. This is of key importance, especially with respect to addressing issues (i) and (ii) at the same time.

The updated version of the company model only permits the rate of HAQ-DI progression for apremilast to be altered when apremilast is used first in a treatment sequence, but not at any other position. Hence, while it is possible to alter the position apremilast in any given sequence in the updated model, the alternative HAQ-DI progression assumptions for apremilast cannot be subsequently applied at these different positions. The ERG is therefore not able to assess the cost effectiveness for apremilast in any position within a treatment sequence other than being first and at the same time include alternative HAQ-DI progression assumptions. The importance of testing different HAQ-DI progression assumptions for apremilast has been underlined by both the NICE AC and the ERG, due to the lack of radiographic assessment evidence to indicate the longer-term effect of apremilast on HAQ-DI progression.

We consider that this limitation in terms of the model functionality significantly constrains the ERG review. Similar concerns regarding model functionality were noted by the ERG previously in TA372 (see Section 4.16 of the ACD). Following the company PAS submission, the ERG made a request to NICE that the company should provide an updated version of the economic model, with the additional functionality to test alternative HAQ-DI progression for apremilast at any position within a treatment sequence. An updated version of the model with such functionality was, however, not provided. Therefore, given the aforementioned constraints, the ERG has only been able to explore a limited set of additional scenarios on the company base case, i.e. in a sequence comparison where apremilast is positioned as a first-line treatment.

Additional analyses were performed by the ERG to explore the impact of alternative HAQ progression assumptions for apremilast on the company's base-case comparison (i.e. apremilast → adalimumab → etanercept → BSC versus adalimumab → etanercept → golimumab → BSC). However, only a very limited set of alternative HAQ progression scenarios for apremilast were presented by the company prior to the publication of the FAD, namely (i) no HAQ progression for apremilast (ii) HAQ progression for apremilast equal to half the rate for BSC and (iii) HAQ progression for apremilast equal to the rate for BSC. Based on this limited set of scenarios, the NICE AC considered in the FAD that scenario (ii) was the most plausible HAQ progression assumption for apremilast. Given though that the actual rate of HAQ-DI progression for apremilast remains uncertain (see Section 5.2), the additional analyses performed by the ERG in this review present a more detailed

set of five alternative HAQ progression scenarios for apremilast, to further explore the potential impact of the long-term HAQ progression for apremilast on cost-effectiveness results.

The results of those scenarios are summarised in Table 9. The third scenario in Table 9, where the HAQ progression rate for apremilast is assumed to be equal to half the rate of BSC, represents the company's base-case in the PAS submission. As shown in Table 9, when taking into account all company base-case assumptions and only modifying HAQ progression assumptions for apremilast, the apremilast sequence remains cost-effective at a threshold of £30,000 even at the scenario where a HAQ progression rate equal to BSC is assumed for apremilast.

Table 9 Alternative HAQ progression assumptions for apremilast, on company's base-case comparison

	Apremilast: No HAQ progression		**Apremilast HAQ progression: 25% of BSC**		**Apremilast HAQ progression: 50% of BSC**		**Apremilast HAQ progression: 75% of BSC**		**Apremilast HAQ progression: equal to BSC**	
	Apremilast sequence	Comparator sequence	Apremilast sequence	Comparator sequence	Apremilast sequence	Comparator sequence	Apremilast sequence	Comparator sequence	Apremilast sequence	Comparator sequence
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	-	[redacted]	-	[redacted]	-	[redacted]	-	[redacted]	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	-	[redacted]	-	[redacted]	-	[redacted]	-	[redacted]	-
ICER (£)/QALY	£63,839*	-	£48,497*	-	£39,052*	-	£33,351*	-	£30,043*	-
NMB at £20,000	£8,155	-	£6,921	-	£5,699	-	£4,658	-	£3,912	-
NMB at £30,000	£6,295	-	£4,493	-	£2,683	-	£1,169	-	£17	-

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NMB: Net Monetary Benefit

Note: scenario with apremilast HAQ progression equal to 50% of BSC is the company's base-case analysis)

* ICER is located in South-West (SW) Quadrant

Given that the ERG cannot assess the impact of alternative HAQ progression assumptions for apremilast at any other position within a treatment sequence other than first, the ERG believes that the single (i.e. head-to-head) treatment comparisons of apremilast versus the other biologic therapies included in the treatment sequences can provide further supportive analyses. The results from head-to-head comparisons of apremilast versus biologic therapies, when considering the PAS price and alternative HAQ assumptions for apremilast, are presented in Tables 10-12. Apremilast is cost-effective versus all biologic therapies at any HAQ progression assumption, when considering a threshold of £20,000 (Table 11). However, as Table 12 shows, at a threshold of £30,000 apremilast is not cost-effective versus etanercept at any of the HAQ progression scenarios and it is also not cost-effective versus adalimumab and golimumab for a subset of the alternative HAQ progression assumptions.

Table 10 Single-treatment comparisons; PAS price and alternative HAQ assumptions for apremilast – ICER results

	HAQ progression assumption for apremilast				
ICER	No progression	25% of BSC	50% of BSC	75% of BSC	Equal to BSC
vs. Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs. Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs. Golimumab	£33,103	£30,431	£28,164	£26,457	£25,280
vs. Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio; HAQ: Health Assessment Questionnaire

All ICER results are located in South-West (SW) Quadrant

Table 11 Single-treatment comparisons; PAS price and alternative HAQ assumptions for apremilast – Net Monetary Benefit results at £20,000 threshold

	HAQ progression assumption for apremilast				
NMB at £20,000	No progression	25% of BSC	50% of BSC	75% of BSC	Equal to BSC
vs. Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs. Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs. Golimumab	£8,959	£7,724	£6,508	£5,493	£4,756
vs. Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NMB: Net Monetary Benefit; HAQ: Health Assessment Questionnaire

Table 12 Single-treatment comparisons; PAS price and alternative HAQ assumptions for apremilast – Net Monetary Benefit results at £30,000 threshold

	HAQ progression assumption for apremilast				
NMB at £30,000	No progression	25% of BSC	50% of BSC	75% of BSC	Equal to BSC
vs. Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs. Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs. Golimumab	£2,122	£319	-£1,463	-£3,013	-£4,251
vs. Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NMB: Net Monetary Benefit; HAQ: Health Assessment Questionnaire

Although the company has only presented a partial set of sequencing strategies (where apremilast is considered only as a pre-biologic treatment option), it might logically follow from Table 12 that at a threshold of £30,000 and depending on the HAQ progression assumption for apremilast, any sequence in which apremilast replaces a biologic therapy versus which it is not cost-effective, would not be cost-effective compared to the comparator (biologics-only) sequence.

The reason that this logic does not appear to apply in the context of exploring alternative HAQ progression assumptions for apremilast on the company's base-case comparison (Table 9) is due to the fact that the company has included a declining efficacy assumption for any treatment following first line, in their analysis. This was done by applying a hazard ratio from an external study (Hyrich et al) to the efficacy of biologic therapies following first-line. The ERG has already critiqued the use of this hazard ratio in their original review (Section 5.2.6.3, p71-73) on the basis that: (i) the Hyrich et al analysis is based on rheumatoid arthritis rather than PsA patients, and (ii) the data are observational

rather than from a RCT. There was also no mention in the original company submission of any search for an alternative source to inform the efficacy reduction assumption. Consequently, the presence and possible magnitude of any decline in efficacy remains highly uncertain.

To further understand the logic of the sequence results, the ERG replicated the set of scenarios shown in Table 9, excluding the declining efficacy assumption for treatments after first-line. The results of these updated analyses are presented in Table 13 at thresholds of £20,000 and £30,000. At a threshold of £20,000, the apremilast sequence appears optimal across the scenarios. However, at a threshold of £30,000 the comparator sequence becomes optimal for the scenarios where HAQ progression for apremilast is assumed to be 75% of BSC or equal to BSC (last two columns). Given that apremilast replaces adalimumab in the company base-case comparison, these treatment sequence results are expected, based on the logic outlined from the single-treatment comparison results of apremilast versus adalimumab presented in Table 12.

By implication, in the scenarios where HAQ progression for apremilast is assumed to be 75% of BSC or equal to BSC (see last two columns of Table 12) the optimal sequence of three treatments would include only the biologic therapies adalimumab, etanercept and golimumab. Apremilast would not be included in the optimal sequence in such a context, regardless of its position within the sequence.

As is evident, the optimal sequence is influenced by the HAQ progression assumptions for apremilast and the potential decline in efficacy for treatments used at different points in the sequence. The ERG considers that the presence and possible magnitude of declining efficacy remains uncertain. There also exists uncertainty surrounding the possible decline in efficacy for apremilast at different positions. However, given the limitations in the model functionality, the ERG has not been able to fully explore this aspect further.

Table 13 Alternative HAQ progression assumptions for apremilast, on company's base-case comparison. No declining efficacy assumed after first-line.

	Apremilast: No HAQ progression		**Apremilast HAQ progression: 25% of BSC**		**Apremilast HAQ progression: 50% of BSC**		**Apremilast HAQ progression: 75% of BSC**		**Apremilast HAQ progression: equal to BSC**	
	Apremilast strategy	Comparator strategy	Apremilast strategy	Comparator strategy	Apremilast strategy	Comparator strategy	Apremilast strategy	Comparator strategy	Apremilast strategy	Comparator strategy
ICER (£)/QALY	£38,323*	-	£34,164*	-	£30,818*	-	£28,403*	-	£26,845*	-
NMB at £20,000	£8,987	-	£7,752	-	£6,529	-	£5,485	-	£4,739	-
NMB at £30,000	£4,082	-	£2,279	-	£494	-	-£1,042	-	-£2,184	-

QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; NMB: Net Monetary Benefit

* ICER is located in South-West (SW) Quadrant

7 ERG summary

The ERG is satisfied that the company appropriately implemented the PAS scheme and the specific adjustments that the NICE AC considered to be most plausible. The ERG successfully replicated the company base-case and the single-treatment comparisons that the company presented. The ERG however identified additional issues and uncertainties that were not fully addressed by the company. These relate to the positioning of apremilast within a treatment sequence, the HAQ progression assumption for apremilast, the length of the treatment sequences being compared and the presence and magnitude of a decline in efficacy for treatments following first-line.

The ERG was severely constrained in its review by limitations in the model functionality of the updated company model. Although the ERG could not assess the impact of alternative HAQ progression assumptions for apremilast at any position other than first within a treatment sequence, they performed additional analyses of head-to-head comparisons of apremilast versus the other biologic therapies, including alternative HAQ assumptions for apremilast. The ERG concludes that the optimal treatment sequence and the positioning of apremilast depends on the HAQ progression assumptions for apremilast and the potential decline in efficacy for treatments used at different points in the sequence. The partial analyses from the ERG, together with the opinions of clinical experts (as stated in the FAD), demonstrate that there remains uncertainty regarding the appropriate position of apremilast and the ERG does not consider that the analyses presented by the company are sufficient to demonstrate that the most cost-effective position for apremilast is a pre-biologic therapy.