Review article

**Brodalumab for the treatment of moderate to severe plaque psoriasis: an Evidence Review Group evaluation of a NICE Single Technology Appraisal**

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**Running heading: Brodalumab for the treatment of moderate to severe plaque psoriasis: an ERG perspective**

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# Abstract

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

(STA) process, brodalumab was assessed to determine the clinical and cost effectiveness of its use in the treatment of moderate to severe plaque psoriasis. The Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE) Technology Assessment Group at the University of York was commissioned to act as the independent Evidence Review Group (ERG). This article provides a summary of the ERG review of the company’s submission, the ERG report and the NICE Appraisal Committee’s subsequent guidance issued in March 2018. The main clinical effectiveness data were derived from three well conducted multicentre double-blind randomised controlled trials (RCTs). The trials demonstrated that brodalumab statistically significantly reduced the severity of psoriasis and its impact on health related quality of life, compared with placebo, at 12 weeks. In comparison with ustekinumab, statistically significantly more brodalumab patients had reduced psoriasis severity at 12 weeks. Psoriasis severity and quality of life also appeared improved at 52 weeks, although statistical significance was not assessed. Withdrawal rates were comparable with drug survival rates of other biological therapies and rates of adverse events were similar between brodalumab and ustekinumab. A network meta-analysis (NMA) was presented, comparing brodalumab with other therapies available at the same point in the treatment pathway (i.e. in patients for whom standard systemic therapy or phototherapy is inadequately effective, not tolerated or contraindicated). The NMA ranked treatments in order of effectiveness, in terms of achieving different levels of Psoriasis Area and Severity Index (PASI) response. The results indicated that brodalumab had a similar probability of response to ixekizumab, secukinumab and infliximab and a higher probability of response than ustekinumab, adalimumab, etanercept, apremilast, dimethyl fumarate (DMF) and placebo. The company’s economic model compared nine treatment sequences which included three lines of active therapy, consisting of brodalumab and other comparators recommended by NICE, followed by best supportive care. The sequence with brodalumab in the first line position dominated sequences which started with adalimumab, infliximab, secukinumab and ustekinumab. The incremental cost-effectiveness ratio (ICER) of the brodalumab sequence compared to less effective and non-dominated sequences ranged from £7,145 (versus the etanercept sequence) to £13,353 (versus the DMF sequence) per quality-adjusted life-year (QALY) gained. The ICER for the more costly and effective ixekizumab sequence was £894,010 per QALY gained compared to the brodalumab sequence. At a threshold of £20,000 per QALY gained, the brodalumab sequence had the highest probability of being cost-effective (96%). The main limitation of the company’s economic model was the restrictive nature of the sequences compared. Twelve separate scenarios based on key uncertainties were explored by the ERG. The only scenarios where brodalumab was ranked lower than first were not considered to be more appropriate or plausible than the assumptions or scenarios included in the company’s base-case. The treatment rankings identified in the ERG’s alternative base-case were identical to those derived from the company’s base-case model. At the first NICE Appraisal Committee meeting, the Committee concluded that brodalumab appears to be as effective as other anti-interleukin-17 agents and is cost effective, based on the discount agreed in the patient access scheme. Brodalumab is recommended as an option for treating adults with severe plaque psoriasis (defined by a total PASI score of 10 or more and a Dermatology Life Quality Index (DLQI) score of more than 10) that has not responded to other systemic non-biological therapies. Brodalumab should be stopped at 12 weeks if the psoriasis has not responded adequately.

**Key points for decision makers**

* Three well conducted double-blind randomised controlled trials demonstrated that brodalumab significantly reduced the severity of psoriasis compared with placebo or ustekinumab and improved health related quality of life.
* A network meta-analysis comparing brodalumab with other therapies available at the same point in the treatment pathway indicated that brodalumab had a similar probability of response to ixekizumab, secukinumab and infliximab and a higher probability of response than ustekinumab, adalimumab, etanercept, apremilast, DMF and placebo.
* An economic model compared nine treatment sequences which included three lines of active therapy, followed by best supportive care. The brodalumab sequence had the highest probability of being cost-effective at a threshold of £20,000 and £30,000 per quality-adjusted life-year (QALY) gained.
* The treatment rankings identified in the ERG alternative base-case were identical to those derived from the company base-case model, providing confirmation of the robustness of the company’s results.

# 1. Introduction

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

Single technology appraisals (STA) evaluate a single product, device or other technology. The manufacturer or sponsor of the technology (referred to as the company) submits evidence supporting the clinical and cost effectiveness of the product and an independent Evidence Review Group (ERG) is commissioned to produce a review and critique of the evidence submitted.

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

This article presents a summary of the ERG’s independent critique of the company’s submission to NICE and its role in the subsequent development of NICE guidance for the use of brodalumab for the treatment of moderate to severe plaque psoriasis. The key issues that arose during the review process and the subsequent Appraisal Committee decision making are summarised. Full details of the appraisal and the relevant documents can be found on the NICE website [[1](#_ENREF_1)].

# 2. The Decision Problem

Psoriasis is a chronic inflammatory, immune-mediated skin disorder, with a relapsing-remitting pattern [[2](#_ENREF_2)]. In the UK, the prevalence of psoriasis is estimated to be around 3% [[3](#_ENREF_3)]; around 20% of these patients have moderate to severe disease, corresponding to around 230,000 people in England [[4](#_ENREF_4)]. Chronic plaque psoriasis is the most common form of psoriasis, accounting for 90% of all cases [[4](#_ENREF_4)]. Symptoms can include scaling, itching, redness, tightness of the skin, bleeding and burning, which can affect sleep, physical functioning, activities of daily living and work productivity [[5-10](#_ENREF_5)].

In the UK, standard treatment includes topical therapy as a first line treatment [[11](#_ENREF_11)]. For patients with more severe psoriasis, phototherapy or systemic non-biological treatments are recommended. For adults with moderate to severe psoriasis (Psoriasis Area and Severity Index (PASI) score ≥ 10 and Dermatology Life Quality Index (DLQI) score >10) who do not respond to, are intolerant of or have a contraindication to standard systemic therapies and phototherapy, NICE recommends systemic biological therapies, apremilast or dimethyl fumarate (DMF) [[12](#_ENREF_12), [13](#_ENREF_13)].

There are several existing systemic biological therapies available for adults with severe psoriasis, including adalimumab, etanercept, ixekizumab, secukinumab, ustekinumab and infliximab (for patients with very severe disease; PASI ≥20 and DLQI >18) [[12](#_ENREF_12)]. These therapies target different parts of the IL-17-Th17 pathway, which plays a central role in amplifying the immune response in psoriasis patients. Many patients do not achieve complete skin clearance with tumour necrosis factor (TNF) antagonists (adalimumab, etanercept and infliximab) or the interleukin (IL)-12/-23 inhibitor ustekinumab [[14](#_ENREF_14)], and many stop treatment due to loss of response or adverse effects [[15-17](#_ENREF_15)]. Studies of secukinumab and ixekizumab, which target IL-17A activity, have shown higher response rates and complete skin clearance in some patients [[12](#_ENREF_12)]. Patients who do not experience primary failure, i.e. non-response evident within the first few weeks, may later experience secondary failure, where the therapy stops being effective after months or years of treatment [[12](#_ENREF_12)]; underlining the need for a range of treatment options.

Brodalumab is a fully human monoclonal antibody, which targets the IL-17-receptor-A [[18](#_ENREF_18)], with a different mechanism of action to the other IL-17A inhibitors. Brodalumab was granted a European marketing authorisation on 17 July 2017. The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1 and 2, followed by 210 mg every 2 weeks. The list price of brodalumab is £1280 per pack of 2 syringes and a confidential patient access scheme has been agreed. The company positioned brodalumab in the treatment pathway alongside the other biological therapies (although infliximab is only recommended for patients with very severe disease). If a patient does not respond adequately to the chosen treatment, physicians are advised to consider switching them to an alternative therapy [[12](#_ENREF_12)].

# 3. Evidence Review Group (ERG) Review

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

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

## Clinical Evidence

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

The main clinical effectiveness data were derived from three well conducted multicentre double-blind randomised controlled trials (RCTs): AMAGINE-1 compared brodalumab (140 mg every two weeks [Q2W] and 210 mg Q2W) with placebo [[19](#_ENREF_19)]; AMAGINE-2 and AMAGINE-3 both compared brodalumab (140 mg Q2W and 210 mg Q2W) with placebo and ustekinumab [[20](#_ENREF_20), [21](#_ENREF_21)]. The eligible population for all three trials was adults aged 18 to 75 who were candidates for biological therapy for stable moderate to severe plaque psoriasis of at least 6 months duration. Patients had to have a PASI score ≥ 12, a static Physician’s Global Assessment (sPGA) score ≥ 3 and involvement of ≥ 10% of the body surface area. Enrolment of patients with previous use of biological agents was capped at 50% of each study population.

The trials demonstrated that brodalumab (210 mg Q2W) statistically significantly reduced the severity of psoriasis and its impact on health-related quality of life, compared with placebo, at 12 weeks. In comparison with ustekinumab (AMAGINE-2 and AMAGINE-3 trials), a statistically significant greater number of patients on brodalumab (210 mg Q2W) experienced a reduction in psoriasis severity at 12 weeks. Quality of life appeared improved at 12 weeks, although statistical significance was not assessed. The AMAGINE-2 and AMAGINE-3 trials also assessed psoriasis severity and quality of life at 52 weeks; with both appearing to improve, although statistical significance was not assessed.

Across the three AMAGINE trials, withdrawal rates were low, with around 88% of brodalumab patients completing each study to week 52. During the 12-week induction phase of AMAGINE-2 and AMAGINE-3, the proportion of patients reporting adverse events was similar between the brodalumab and ustekinumab groups (57.8% and 59%, respectively), but higher than in the placebo group, as would be expected with a biological therapy. Rates were similar between brodalumab and ustekinumab during the maintenance phase of the trials. Rates of serious adverse events were similar between the brodalumab and ustekinumab groups.

Mild to moderate candida infections were more frequent with brodalumab than ustekinumab or placebo; IL-17 inhibitors are known to cause an increased risk of candida infection. Some patients in the AMAGINE trials experienced suicidal ideation and behaviour (SIB).

A network meta-analysis (NMA) using the random-effect approach was presented, comparing brodalumab with other therapies available at the same point in the treatment pathway. The NMA ranked treatments in order of effectiveness, in terms of achieving different levels of PASI response (percentage reduction in PASI score from baseline) at the end of the study-defined induction period. The length of the induction period varied by treatment, ranging from 10 weeks to 16 weeks. The base case NMA included data from 59 RCTs involving 28,346 patients, which included both licensed doses of the therapies, along with unlicensed doses and conventional systemic therapies, where their inclusion was considered to contribute additional indirect evidence for licensed doses. A sensitivity analysis was undertaken which included only licensed doses and dosing regimens currently recommended by NICE. When ranked in order of effectiveness, from most effective to least effective, (median probability of achieving a PASI 75 response, i.e. a 75% reduction in PASI score from baseline) the results for the base case NMA and the sensitivity analysis were consistent: ixekizumab, brodalumab, secukinumab, infliximab, ustekinumab, adalimumab, etanercept, apremilast, DMF, placebo. For PASI 50, PASI 90 and PASI 100 response, the results were similar; brodalumab had a similar probability of response to ixekizumab, secukinumab and infliximab and a higher probability of response than ustekinumab, adalimumab, etanercept, apremilast, DMF and placebo.

There was considerable variation in PASI response rates in the placebo arms of the trials included in the NMA, so a placebo adjusted model was compared with the unadjusted model. The results of both models were similar, indicating that patients treated with brodalumab had a similar probability of response than those treated with ixekizumab, secukinumab and infliximab and a higher probability of response than patients treated with ustekinumab, adalimumab, etanercept, etanercept, apremilast, DMF and placebo.

## Critique of the Clinical Evidence and Interpretation

The company’s systematic review did not appear to have missed any relevant RCTs of brodalumab. The included RCTs were good quality and the results are likely to be reliable. All three AMAGINE trials included brodalumab at the licensed dose (210 mg Q2W) in addition to lower doses; only results for the licensed dose were described in detail in the submission.

Trial inclusion criteria of the AMAGINE trials were generally appropriate and baseline patient characteristics were similar across treatment groups. However, the inclusion criteria relating to disease severity were not the same as the severity threshold specified in the NICE pathway to be considered for other biological therapies, apremilast and DMF (PASI score ≥ 10 and DLQI score > 10). The AMAGINE trials recruited a population with higher PASI scores (≥ 12) but did not specify a minimum DLQI score. The mean baseline DLQI scores for the different treatment groups across the trials were above 10, but it is likely that there were patients included with DLQI scores below the threshold specified by NICE. In addition, 17-35% patients in the AMAGINE trials had not received previous systemic therapy or phototherapy, which is not consistent with the proposed positioning of brodalumab in the treatment pathway. Therefore, the results may not be entirely generalisable to the proposed eligible population.

Patients in all three trials were eligible to enter an open-label extension phase, which was planned to last a further 4 years. However, all three trials were terminated on 22 May 2015, when Amgen announced that it had commenced termination of its participation in the co-development and commercialization of brodalumab with AstraZeneca. The decision was based on events of SIB in the brodalumab program, which Amgen believed likely to necessitate restrictive labelling. There is still uncertaintly regarding brodalumab and SIB. The company concluded that the data suggest the risk of SIB is not higher with brodalumab than with other biological therapies. However, the US Food and Drug Administration (FDA) and European Public Assessment Report (EPAR) reported that they were unable to draw firm conclusions on the relationship between brodalumab and SIB.

The NMA appeared to be conducted appropriately for the comparison of the treatments available at the same point in the treatment pathway as brodalumab, for the treatment of moderate to severe plaque psoriasis. The systematic searches and the methods used for the company’s NMA were appropriate and the quality assessment of the trials included in the NMA suggested that these were of good quality.

An important difference between the trials included in the NMA was the PASI response rates in the placebo arms of the trials; placebo was the common reference treatment across the majority of the trials. Variations in trial eligibility criteria, prior medication, average patient age and other relevant characteristics could contribute to differences in placebo response rates and, therefore, to differences in the relative efficacy of the interventions compared to placebo. Therefore, a placebo adjusted model was compared with the unadjusted NMA model, in order to explore the between-study heterogeneity. The ERG considered the company’s adjusted model to be more appropriate than the unadjusted model, although the results were similar. The ERG made some minor revisions to the company’s placebo adjusted synthesis model; the results were consistent with the results presented by the company, providing reassurance regarding the company analyses.

The ranking of therapies in order of effectiveness, based on results of the NMA, was consistent with other NMAs undertaken in other recent STAs of treatments for moderate to severe psoriasis in adults [[22-24](#_ENREF_22)], and a NMA undertaken for the development of British Association of Dermatologists’ guidelines, published in April 2017 [[25](#_ENREF_25)].

## Cost-Effectiveness Evidence

The company’s search for existing cost-effectiveness studies of brodalumab identified only one US modelling study undertaken prior to the EU marketing authorisation, in which assumptions were made in relation to the potential acquisition cost [[26](#_ENREF_26)]. Therefore, the company submitted a de novo economic model, using a Markov state-transition model structure, which the ERG considered to be appropriate. The model consisted of four treatment-related health states (induction, maintenance, best supportive care and death) with patients being allocated to one of five PASI response categories (PASI 0-49, PASI 50-74, PASI 75-89, PASI 90-99 and PASI 100).

The company’s economic model compared nine treatment sequences which included three lines of active therapy, followed by best supportive care. Brodalumab was included in the first line position alongside other comparators recommended by NICE for psoriasis patients who have failed to respond to conventional systemic therapies or who are intolerant or have a contraindication to these treatments. Brodalumab and each comparator treatment was then assumed to be followed by a second and third line biological therapy, selected by the company based on clinical guidelines and advice. Consideration was also given to including therapies with a different mechanism of action to the preceding line. To ensure comparability of the sequences evaluated, ustekinumab and secukinumab were always included as the second and third-line treatments, except in the two treatment sequences that started with either of these drugs.

At the end of the induction period (10-16 weeks) for each line of treatment in the sequence, individuals were assigned to one of five PASI response categories, based on the NMA results. In the base case analysis, the PASI 75 response rate was selected as the response threshold for treatment continuation beyond the induction period. Patients achieving a PASI 75 response were assumed to continue with the same treatment and enter the maintenance phase of the model. Patients who did not achieve a PASI 75 response were assumed to discontinue their treatment and then switch to the next treatment in the sequence. The impact of using PASI 50 as an alternative cut-off to switching to the next treatment line was explored in a scenario analysis. During the maintenance period, patients were assumed to continue to receive the same treatment and maintain the same PASI response as measured at the end of the induction period until the treatment was discontinued, at a constant annual rate of 18.7%, irrespective of the drug given. The discontinuation rate, which accounted for the loss of response over time and/or the incidence of adverse events, was informed by evidence on the long-term drug survival rates from a large UK registry (British Association of Dermatologists Biologic Interventions Register [BADBIR]) [[17](#_ENREF_17)]. Patients who experienced primary or secondary failure of the third line of treatment moved to best supportive care, with patients assumed to be treated with non-biological supportive therapies.

A time horizon of 40 years was chosen, as it was considered sufficient to capture all relevant differences in costs and benefits between comparators. Utility values used in the model were derived from EuroQol-5D (EQ-5D)-3L data (UK tariffs applied) collected in the AMAGINE-1 trial of brodalumab versus placebo. The utility values were based on the proportion of patients in the different PASI response categories and the change in utility from baseline associated with each PASI response category. The resource use and costs included in the model comprised drug acquisition, administration, monitoring, adverse events and best supportive care. Unit costs were sourced from relevant UK sources, including Department of Health Reference Costs 2015/2016, Monthly Index of Medical Specialties (MIMS), Personal Social Services Research Unit (PSRRU) and other published literature.

Fully incremental cost-effectiveness ratios (ICERs) and pairwise ICERs for the brodalumab sequence compared to each comparator sequence were reported. In the pairwise ICER comparisons, the brodalumab sequence dominated sequences which started with adalimumab, infliximab, secukinumab and ustekinumab. The ICER of the brodalumab sequence compared to less effective and non-dominated sequences ranged from £7,145 (versus the etanercept sequence) to £13,353 (versus the DMF sequence) per quality-adjusted life-year (QALY) gained. The ICER for the more costly and effective ixekizumab sequence was £894,010 per QALY compared to the brodalumab sequence.

At a threshold of £20,000 per QALY gained, the brodalumab sequence had the highest probability of being cost-effective (96%). At a threshold of £30,000, the brodalumab sequence was reported to have a 100% probability of being the most cost-effective.

## Critique of the Cost-Effectiveness Evidence

The main limitation of the company’s economic model was the restrictive nature of the sequences compared, in terms of the number of sequences included and the position of brodalumab within these. The ERG raised concerns that modelling selective sequences could provide misleading estimates of cost-effectiveness, particularly if there are treatments included in a sequence which are not cost-effective themselves. The ERG proposed an alternative approach, using the net benefit framework, as opposed to the conventional decision rules for cost effectiveness analysis which are based on the ICER. A key advantage of using the net-benefit framework is that this approach allowed the fully incremental ICER comparisons and the sequential treatment comparisons to be simplified, due to 2 key assumptions made in the company base-case; specifically: (i) the effectiveness of each treatment is independent of its position in any sequence; and (ii) the withdrawal rate of each treatment over the maintenance period is the same and constant over time. Employing these assumptions, the ERG proposed that the incremental net-benefits of each individual treatment versus BSC alone (and associated rankings) could also be used as a basis for establishing: (i) whether a specific treatment has the potential to be cost-effective within a sequence (i.e. whether a particular treatment appears cost-effective compared to BSC); (ii) the most efficient positioning of a treatment in a sequence (i.e. whether a particular treatment appears more or less cost-effective than another active comparator).

The results indicated that the following treatments would not appear in any efficient sequence using either a £20,000 or £30,000 per QALY threshold: infliximab, secukinumab and ixekizumab. However, these results do not include the confidential patient access schemes for secukinumab and ixekizumab. All of the remaining treatments have the potential to be in an efficient sequence depending on whether there are constraints on the overall length of a sequence. Constraining the sequence to three active lines of treatment, the optimal ranking based on the net monetary benefit, at a £20,000/QALY threshold is: brodalumab, DMF, adalimumab. At a £30,000/QALY threshold the optimal ranking is: brodalumab, ustekinumab, adalimumab.

The ERG also considered that the utility regression model used in the company base-case should have been adjusted for baseline EQ-5D. The results from the alternative regression approaches presented by the company showed that the regression model adjusting for baseline EQ-5D consistently performed better in terms of goodness of fit across a range of measures. The ERG also identified uncertainty regarding whether the EQ-5D data from the AMAGINE-1 trial could be generalised to the AMAGINE-2 and AMAGINE-3 trials which didn’t collect EQ-5D data. The ERG requested additional comparisons across the separate AMAGINE trials based on mapping between DLQI and EQ-5D-3L. The ERG considered that being able to show consistency across the separate studies and populations based on the mapped values would provide additional reassurance regarding the generalisability of the values from the single trial which included the EQ-5D-3L instrument. The results of the analyses provided by the company showed that AMAGINE-1 could be generalised to the other AMAGINE trials.

Regarding drug acquisition costs for brodalumab, the ERG considered that an adjustment to the dosing assumptions for brodalumab was appropriate based on the summary of product characteristics (SPC) wording and the provision of 2 pre-filled syringes within each pack. The assessment of response in the AMAGINE-trials at 12-weeks was taken after 10-weeks of treatment, which equates to 7 doses. However, each pack of brodalumab contains 2 pre-filled syringes. The SPC does not appear to allow provision for unit packs to be split. Therefore, it appears reasonable to assume that all individuals will be prescribed 8 doses of brodalumab (i.e. 4 packs of 2 pre-filled syringes), even if individuals who are not responding at week 12 discontinue and do not take the final dose. The company base case analysis assumes that all patients receive 7 doses and that only patients who are responders will continue to receive the 27 doses during the first year of treatment.

Finally, the ERG noted that there is uncertainty regarding the appropriateness of assuming a constant annual discontinuation rate (18.7%) for all treatments; the uncertainty concerns both the rate itself and whether there are important treatment or class specific differences. The discontinuation rate applied included drop-outs for any reason and was obtained by applying an exponential model to data from the BADBIR registry from years 2 and 3 [[17](#_ENREF_17)]. The company justified excluding the year 1 data to avoid potential double counting of discontinuations due to early non-response. This approach to discontinuation rates in the base-case model is reasonable and generally consistent with previous appraisals. However, the discontinuation rate applied in the model was marginally lower than in previous submissions (18.7% versus 20%). A scenario analysis explored the use of different discontinuation rates for different treatment classes; the BADBIR registry reported a lower rate of discontinuation with ustekinumab compared with anti-TNF therapies (adalimumab, etanercept and infliximab). The resulting discontinuation rates were 14.7% for the anti-TNF therapies (and DMF and apremilast) and 7.3% for all the IL-inhibitors (brodalumab, ixekizumab, secukinumab and ustekinumab). Therefore, the discontinuation rates applied in the scenario are lower for all therapies compared to the base case rate of 18.7%. In addition, there may be differences between discontinuation rates for therapies within the same drug class. Therefore, the ERG considered that the assumptions applied in the base case analysis appeared more justifiable than those considered by the scenario.

The key uncertainties identified by the ERG were explored in 12 additional separate scenarios using net-benefit calculations and associated rankings of each individual treatment compared with best supportive care. At a £20,000/QALY threshold, brodalumab was ranked first (i.e. the most efficient single treatment) in 11 of the 12 scenarios explored and at a £30,000/QALY threshold, brodalumab was ranked first in 10 of the 12 scenarios explored. The only scenarios where brodalumab was ranked lower than first were not considered to be more appropriate or plausible than the assumptions or scenarios included in the company’s base-case. The ERG produced an alternative base-case, which combined changes from six of the 12 separate scenarios, considered to provide more appropriate or plausible assumptions than the company’s base-case. The treatment rankings identified in the ERG alternative base-case were identical to those derived from the company base-case model, providing significant reassurance and confirmation of the robustness of the company’s results. Brodalumab was identified as the most efficient treatment in the ERG and company base-case analyses.

## Conclusions of the ERG Review

Evidence from three good quality RCTs demonstrated that brodalumab significantly reduces the severity of psoriasis compared with placebo or ustekinumab (which also targets the IL-17 receptor but with a different mechanism of action). Health related quality of life was significantly improved compared with placebo and also appeared improved compared with ustekinumab, although statistical significance was not assessed between brodalumab and ustekinumab. Withdrawal rates were comparable with other biological therapies and rates of adverse events were similar between brodalumab and ustekinumab. However, there is still uncertaintly regarding brodalumab and SIB.

The results of both the placebo-adjusted and unadjusted NMA models indicated that brodalumab had a similar probability of response to ixekizumab, secukinumab and infliximab and a higher probability of response than ustekinumab, adalimumab, etanercept, etanercept, apremilast, DMF and placebo.

The main limitation of the company’s economic model was the restrictive nature of the sequences compared. Twelve additional separate scenarios based on key uncertainties were explored by the ERG. At a threshold of £20,000 per QALY gained, the brodalumab sequence had the highest probability of being cost-effective (96%). The only scenarios where brodalumab was ranked lower than first were not considered to be more appropriate or plausible than the assumptions or scenarios included in the company’s base-case.

# 4. NICE Guidance

After considering the available evidence from the company’s submission, the ERG report, expert testimony and other consultees, the NICE Appraisal Committee concluded that brodalumab improves severe psoriasis more than placebo and ustekinumab and, when compared indirectly, it appears to be as effective as other anti-interleukin-17 agents. Cost-effectiveness estimates for brodalumab compared with other biological treatments, and with apremilast and DMF, show that it is generally more cost effective.

The Committee therefore recommended brodalumab as an option for treating plaque psoriasis in adults, only if:

* the disease is severe, as defined by a total PASI of 10 or more and a DLQI of more than 10 and
* the disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or these options are contraindicated or not tolerated and
* the company provides the drug with the discount agreed in the patient access scheme.

Brodalumab should be stopped at 12 weeks if the psoriasis has not responded adequately, defined as:

* a 75% reduction in the PASI score (PASI 75) from when treatment started or
* a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.

**5. ERG Conclusion**

This case study highlights that even where the company submission is relatively strong, the ERG still has a role in interpreting and assessing the robustness of the clinical and cost-effectiveness evidence submitted by the company.

The ERG was concerned about the considerable variation in PASI response rates in the placebo arms of the trials included in the NMA presented by the company. However, a placebo adjusted model was compared with the unadjusted model and the results were similar. Results were also consistent with other NMAs undertaken in other recent STAs of treatments for moderate to severe psoriasis [[22-24](#_ENREF_22)] and a NMA undertaken for the development of the British Association of Dermatologists’ recent guidelines [[25](#_ENREF_25)].

The main limitation of the company’s economic model was the restrictive nature of the sequences compared. The ERG concluded that the net-benefit approach more fully addresses concerns noted by previous ERGs and NICE committees regarding the possible implications of restricting sequences (as opposed to modelling all feasible sequences) and the potential for misleading estimates of cost-effectiveness for the treatment of interest (i.e. due to the inclusion of other treatments in a sequence which are not cost-effective themselves). The ERG produced an alternative base-case, which combined changes from six of 12 separate scenarios explored, which were considered to provide more appropriate or plausible assumptions than the company’s base-case. The treatment rankings identified in the ERG alternative base-case were identical to those derived from the company base-case model, providing reassurance in the robustness of the company’s results. Brodalumab was consistently identified as the most efficient treatment.

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**Author Contributions**

Ros Wade, Alessandro Grosso, Emily South, Claire Rothery, Pedro Saramago Goncalves, Laetitia Schmitt, Kath Wright and Stephen Palmer all formed part of the ERG that produced the ERG report that this paper describes. Stephen Palmer and Ros Wade took overall responsibility for the cost-effectiveness and clinical effectiveness parts of the project. Ros Wade wrote the draft of the manuscript. All authors commented on the manuscript and approved the final version. This summary has not been externally reviewed by PharmacoEconomics.

**Compliance with Ethical Standards**

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**Conflicts of Interest**

All authors (Ros Wade, Alessandro Grosso, Emily South, Claire Rothery, Pedro Saramago Goncalves, Laetitia Schmitt, Kath Wright and Stephen Palmer) have no potential conflicts of interest.

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