

**Evidence Review Group Report commissioned by the
NHS R&D HTA Programme on behalf of NICE**

Adalimumab for the treatment of psoriasis

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None

Information that was submitted to the National Institute for Health and Clinical Excellence in confidence has been removed from this version of the report. Black bars in the text indicate where this has occurred.

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LIST OF ABBREVIATIONS

AAD	American Academy of Dermatology
BAD	British Association of Dermatologists
BIW	Twice weekly
BNF	British National Formulary
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CIC	Commercial in confidence
CSR	Clinical study report
DLQI	Dermatology life quality index
EADV	European Academy of Dermatology and Venerology
EMA	European Medicines Agency
EOW	Every other week
EQ-5D	Euro quality of life questionnaire
ERG	Evidence review group
EVPI	Expected value of perfect information
FDA	Food and Drug Administration
HEED	Health economic evaluations database
HES	Hospital episode statistics
HTA	Health technology assessment
IHCIS	Integrated healthcare information services
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
kg	kilogram
LOCF	Last observation carried forward
MCS	Mental component score
MEIP	Medline in process
mg	milligram
MS	Manufacturer's submission
N or n	Number
N/A	Not applicable
NHS	National Health Service
NHS EED	NHS economic evaluation database
NICE	National Institute for Health and Clinical Excellence
NRR	National research register

PASI	Psoriasis area and severity index
PCS	Physical component score
PDF	Portable document format
PGA	Physician's global assessment
PRLIT	Manufacturer's in-house product literature database
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PT	Publication type
PUVA	Psoralen ultraviolet (light) A
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SC	Supportive care
SE	Standard error
SD	Standard deviation
SF-36	Short form (version) 36
SG	Standard gamble
SMC	Scottish Medicines Consortium
SPC and SmPC	Summary of product characteristics
STA	Single technology appraisal
TAR	Technology assessment report
TTO	Time trade off
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
VS	Versus

SUMMARY

Scope of the submission

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE), and is appropriate to the National Health Service (NHS). The intervention is adalimumab for adults with moderate to severe chronic plaque psoriasis. The decision problem defines the population and intervention in relation to the proposed licensed indication. The population currently proposed is adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA, a more tightly defined group than that stated in the NICE scope. The participants in the trials were largely those with moderate to severe psoriasis but the manufacturer defined this slightly differently in each trial. The ERG is not clear whether all participants meet the criterion for previous therapy of having failed to respond, or having a contraindication to, or being intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA. The intervention, comparators and outcomes are as appropriate and clinically meaningful as possible.

Summary of submitted clinical-effectiveness evidence

- The main evidence on efficacy in the submission comes from three randomised controlled trials (RCTs) comparing adalimumab with placebo. One of these three RCTs also compares adalimumab with methotrexate. One further RCT contributes evidence on efficacy and time to relapse. Additionally two extension studies and one ongoing open-label extension study were included. Other than the one RCT mentioned above which included a methotrexate arm no trials of potential comparator treatments were included.
- A higher proportion of patients on adalimumab 40mg every other week achieved an improvement on the Psoriasis Area and Severity Index (PASI) of at least 75% (PASI 75) when compared to placebo groups after either 12 weeks (two trials) or 16 weeks (two trials) of treatment. There was also a statistically significant difference in favour of adalimumab for the proportion of patients achieving a PASI 50 (three trials) and 90 (four trials).
- The MS did not present a narrative or quantitative synthesis of the data from the four trials except in the mixed treatment comparison. The mixed treatment comparison result for treatment with adalimumab 40mg every other week was a mean probability of achieving a PASI 75 response treatment of 67% (2.5%-97.5%

credible interval of 57-74%) in comparison to supportive care where the mean probability of achieving PASI 75 was 5% (2.5%-97.5% credible interval of 4-6%). The mixed treatment comparison results for PASI 50 and PASI 90 were also in favour of adalimumab over supportive care. For each PASI outcome in the mixed treatment comparison the probability of a response was greater for infliximab 5 mg/kg/day than adalimumab, but the probability of response with adalimumab was greater than etanercept, efalizumab and the non-biologic systemic therapies.

- In terms of secondary outcomes, there were statistically significant differences between adalimumab and placebo in Physician's Global Assessment (PGA) score, Dermatology Life Quality Index (DLQI), EuroQoL quality of life questionnaire (EQ-5D) and Short form version 36 (SF-36) quality of life outcomes. The incidence of any adverse event was similar in treatment and placebo arms; serious adverse events were comparable; and discontinuations due to adverse events were low and comparable between groups. The MS reports that the incidence of adverse events at least possibly related to study drug was statistically significantly higher in the adalimumab treatment group than the placebo groups.

Summary of submitted cost-effectiveness evidence

- The cost-effectiveness analysis estimates the mean length of time that an individual would respond to treatment, and the utility gains associated with this response. The model is based closely upon the model reported in the NICE appraisal of etanercept and efalizumab for psoriasis.¹ The results are presented for adalimumab compared to other biological therapies including intermittent etanercept, based upon utility values obtained from two clinical trials.
- The model is generally internally consistent and appropriate to psoriasis, in terms of structural assumptions. The cost-effectiveness analysis generally conforms to the NICE Reference Case, the scope and the decision problem.
- Treatment effectiveness is reported in terms of the numbers of patients achieving PASI 50, 75 and 90 goals at the end of the trial period. Evidence was synthesised from a variety of trials for all therapies considered in the model using a mixed treatment comparison model.
- Patients who achieve improvements in PASI score were assigned an associated improvement in quality of life with higher responses associated with larger improvements in quality of life.

- The base case incremental cost-effectiveness ratio (ICER) for adalimumab compared to supportive care, for patients with severe psoriasis was £30,538 per Quality Adjusted Life Year (QALY).
- Scenario analysis reported in the MS shows the model was most sensitive to the utility values used (with DLQI \leq 10 having much higher cost-effectiveness ratios than DLQI $>$ 10).

Commentary on the robustness of submitted evidence

Strengths

- The MS conducted a systematic search for clinical- and cost-effectiveness studies of adalimumab. It appears unlikely that the searches missed any additional trials that would have met the inclusion criteria.
- The four key adalimumab trials identified were of reasonable methodological quality, and measured a range of outcomes that are as appropriate and clinically relevant as possible.
- Overall, the MS presents an unbiased estimate of treatment efficacy for adalimumab based on the results of the placebo-controlled trials.
- The economic model presented with the MS used an appropriate approach for the disease area given the available data.
- The measure of utility gain was taken from two randomised clinical trials that directly linked changes in PASI score to changes in utility using the EQ-5D.

Weaknesses

- The processes undertaken by the manufacturer for screening references, data extraction and quality assessment of included studies were not well reported in the MS. However, the manufacturer was able to provide details when requested.
- The MS did not undertake a systematic review of the comparator trials and reported very limited information on the comparator trials that were included in the mixed treatment comparison.
- The MS provided very little in the way of a narrative synthesis of outcome data from the key trials and did not perform a meta-analysis. A mixed treatment comparison was conducted but few methodological details were provided on this.
- The assumptions made to estimate the cost-effectiveness of intermittent etanercept used inconsistent methodology for costs and benefits. The estimation of QALYs and costs generated were based upon different estimates of the length

of time individuals would spend on etanercept, with the estimate used for costs greater than that used for QALYs.

- There were no clear data on the amount of inpatient care required under supportive care.
- A fourth infusion for infliximab was included in the trial period at fourteen weeks. This would last for the first eight weeks of the treatment period and hence is most appropriately included in the treatment period costs. The clinical expert consulted believed that generally in clinical practice the fourth infusion would only be given after the individual's response category was assessed.

Areas of uncertainty

- As a standard meta-analysis was not conducted the overall treatment effect of adalimumab achieved across the trials is unknown. A meta-analysis might also have identified whether there is heterogeneity across the trials. If heterogeneity were found to be present the appropriateness of conducting a mixed treatment comparison would need to be reconsidered.
- The limited descriptions of both the comparator trials included in the mixed treatment comparison and the methodological assumptions underlying the mixed treatment comparison make it difficult for the ERG to critique the model outputs.
- The extent to which the trial populations of the included adalimumab trials match the population specified in the decision problem, in terms of prior treatment with systemic therapy, is uncertain.
- A regression model was used to relate changes in PASI scores to EQ5D data. However, few details were given of this model so the ERG could not be sure of the appropriateness of the approach taken.
- Uncertainty exists as to the correct way to model key alternatives to adalimumab, particularly intermittent etanercept. It is unclear how widely intermittent etanercept is used in clinical practice and the degree to which costs are avoided with intermittent therapy. It is also unclear as to how much utility is lost due to psoriasis flare-ups.
- There appears to be a paucity of data regarding the need for inpatient stays in psoriasis patients. The assumption is that individuals who are not responders to treatment receive twenty-one days per year and those who on treatment receive no inpatient stays. The model is sensitive to changes in the length of supportive care inpatient stay.

Key issues

- The majority of the trials of adalimumab efficacy presented by the MS were placebo-controlled trials. Only one head-to-head RCT was included that directly compared adalimumab to methotrexate. No studies were identified that directly compared adalimumab to the other possible comparators listed in the scope. The manufacturer carried out an indirect comparison, but because of the limited information presented on the included comparison trials and the methodological assumptions the ERG have reservations about this.
- The precise definition of the severity of the psoriasis patients included in the model is unclear. A clear specification of this and a tailoring of the effectiveness, quality of life, and cost data, to reflect specific severities would improve the applicability of the model.
- There is a need for better data relating to the need for inpatient stay for non-responders with various severities of disease.
- The assumptions made in estimating the values for key parameters used for the comparators are important in determining the relative cost-effectiveness of adalimumab compared to other biologic treatments, particularly the costing assumptions made for intermittent etanercept.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Abbott on the clinical-effectiveness and cost-effectiveness of adalimumab for psoriasis. It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the Evidence Review Group (ERG) and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 08/10/07. A response from the manufacturer via NICE was received by the ERG on 25/10/07 and this has been included as an appendix in the ERG report. Annotations referring to the appendix occur throughout the ERG report where applicable.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The MS provides a generally clear description of psoriasis. The overview summarises the aetiology and epidemiology of psoriasis, describes the features of the most common type of psoriasis (plaque psoriasis), and the classification of plaque psoriasis into different levels of disease severity. The three main therapeutic modalities (topical agents, phototherapy/photochemotherapy, and systemic medications) are summarised and the place of the new technology (adalimumab) with respect to current treatments is described.

The MS states that obtaining estimates for psoriasis prevalence is difficult and reports that in Northern Europe and Scandinavia where psoriasis tends to be more frequent the prevalence of psoriasis is estimated to be between 1.5% and 3% of the general population. The MS goes on to cite the NICE guidance on the use of etanercept and efalizumab which indicates that approximately 2% of the UK population have psoriasis.¹ Although the MS states that patients with severe disease constitute approximately 20-30% of all patients with psoriasis and often require systemic treatment, the MS does not at this stage indicate how many patients would be eligible for treatment with adalimumab. The ERG notes however that in a later section of the MS (Section 7.2, MS p134) the manufacturer has used a prevalence figure for psoriasis of 1.5% as the starting point in deriving the number of people with psoriasis in England and Wales as 789,155, and a figure of 1.1% of patients (8,681) with severe disease who would be eligible for treatment with adalimumab.

It is not clear from the MS whether the manufacturer has been consistent in the approach to defining disease severity. The ERG recognises that defining what constitutes mild, moderate and severe psoriasis is problematic as a number of different criteria are available and differing approaches are taken. One of the main accepted systems for classifying the severity of psoriasis is the Psoriasis Area and Severity Index (PASI). The limitations of this measure have been well documented,² but despite its shortcomings it is the measure used in most clinical trials. Body Surface Area (BSA) and the Dermatology Life Quality Index (DLQI) are also commonly used as systems for classifying the severity of psoriasis. The guidance for the use of biological therapies in psoriasis issued by NICE in July 2006 defines severe psoriasis as a PASI of ≥ 10 combined with a DLQI > 10 .¹ A 2005 review of the PASI alone (i.e. without DLQI or BSA) as an instrument in determining severity of chronic plaque-type psoriasis defines severe psoriasis as PASI > 12 and moderate psoriasis as PASI ranging from 7-12.³ Within the MS, in the disease overview the British Association of Dermatologists (BAD) guidelines (MS p12) are highlighted which suggest a PASI score of ≥ 10 correlates to severe disease, but in discussing topical agents (MS p13) disease severity is described in terms of body surface area affected with $< 5\%$ BSA affected classified as mild disease, 5-10% BSA as moderate disease, and $> 10\%$ BSA as severe disease. In describing the suggested place for adalimumab with respect to other currently available treatments (MS section 4.4, p 15) the criteria for treatment are given as a PASI of ≥ 10 together with a DLQI of > 10 , in line with current NICE guidance on the use of etanercept and efalizumab.¹

2.2 Critique of manufacturer's overview of current service provision

The manufacturer provides a brief overview of current service provision and describes the three main types of therapeutic option (topical agents, phototherapy/photochemotherapy, and systemic medication). The different agents available within each therapy type are listed. A detailed treatment algorithm is not provided although a brief description on the use of the different therapeutic options for psoriasis of differing severities is provided. The main adverse events associated with the non-biological therapies are summarised but the main adverse events associated with biological therapies are not discussed. Some areas of uncertainty in current clinical practice are described.

The MS states that adalimumab should be recommended as a treatment option for use in patients that have failed to respond to systemic therapies, or are intolerant to

these treatments and have a PASI ≥ 10 and DLQI > 10 in line with the current NICE recommendation for the use of etanercept and efalizumab. The MS goes on to suggest some potential advantages that adalimumab may have over other biological treatments for psoriasis

- adalimumab is licensed for psoriatic arthritis and Crohn's disease which are co-morbidities of psoriasis (advantage over efalizumab)
- adalimumab is a fully human antibody so immunogenicity may be reduced in comparison to monoclonal antibodies containing non-human sequences e.g. infliximab (The ERG notes that although no supporting literature is cited this is a logical suggestion to make)
- adalimumab has a long half life enabling every other week dosing (advantage over etanercept)
- adalimumab can be administered by the patient at home (after training) (advantage over infliximab)

The areas of uncertainty relating to current clinical practice highlighted by the manufacturer in the MS are

- the role of biological agents in treating other forms of psoriasis
- limitations with current methods for assessing and defining disease severity, and the lack of a "gold standard" quality of life measure in dermatology
- limitations with current therapies
- role of psychological factors on treatment outcome
- relative importance of psoriasis therapies and lifestyle factors on risk of cardiovascular disease and malignancy
- whether psoriasis therapy can have a disease modifying effect

The manufacturer acknowledges that at the time of writing the MS adalimumab was unlicensed and therefore there are no guidelines on its use. Guidelines which contain recommendations on the use of biological agents generally, or other biological agents specifically are mentioned:

- British Association of Dermatologists (BAD) guidelines for the use of biological interventions in psoriasis⁴
- NICE guidance on etanercept and efalizumab for the treatment of adults with psoriasis¹
- Scottish Medicines Consortium (SMC) assessment of infliximab 100mg powder for intravenous infusion (Remicade®) No. (318/06).⁵ Infliximab

(Remicade®) is accepted for restricted use within NHS Scotland for the treatment of severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapy including ciclosporin, methotrexate or psoralen ultraviolet A (PUVA).

- SMC assessment that efalizumab (Raptiva®) is not recommended for use within NHS Scotland for the treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or have a contra-indication to, or are intolerant to other systemic therapies, including ciclosporin, methotrexate and PUVA (photochemotherapy).⁶

The manufacturer has not mentioned that on publication of the NICE guidance on etanercept and efalizumab for the treatment of psoriasis, NHS Quality Improvement Scotland advised that the NICE appraisal was as valid for Scotland as for England and Wales and that the NICE guidance on efalizumab therefore supersedes the advice issued by the SMC 10 December 2004.⁷

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The final scope issued by NICE states that the population under consideration should be adults with moderate to severe chronic plaque psoriasis. The decision problem for the MS defines the patient group only by saying that the MS will address the clinical- and cost-effectiveness of treatment with adalimumab in accordance with the licensed indication. During the ERG's assessment of the MS (October to November 2007) adalimumab had not yet received its licence. The proposed licensed indication was stated in the MS (MS Section 1.3 p4)

- the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA

Providing there is no further change in the proposed licensed indication, the patient group described in the MS decision problem will be adults with moderate to severe chronic plaque psoriasis who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA, a more tightly defined group than that stated in the final NICE scope which is 'Adults with moderate to severe chronic plaque psoriasis'. However, the MS does not provide a definition of moderate to severe chronic plaque psoriasis and does not use disease severity as a criterion for including studies in the

systematic review. In addition the MS does not make it clear in the systematic review inclusion criteria that eligible patients are those who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.

2.3.2 Intervention

The final scope issued by NICE and the decision problem both state that the intervention should be adalimumab. The decision problem again suggests that treatment will be within the proposed licensed indication. The proposed course of treatment (MS section 1.8 p5) is an initial 80mg adalimumab loading dose at baseline followed by 40mg adalimumab at Week 1, and then subsequent doses of 40mg adalimumab every other week via subcutaneous injection. Adalimumab should be used as a maintenance therapy in patients with psoriasis. Available data suggest that clinical response is usually achieved within 16 weeks of treatment. Continued therapy should therefore be carefully reconsidered in a patient not responding within this time period.

The proposed course of treatment is subject to regulatory approval by the European Medicines Agency (EMA).

Adalimumab is already licensed for use in psoriatic arthritis and Crohn's disease. The British National Formulary (BNF) states that the recommended doses of adalimumab by subcutaneous injection are:

- rheumatoid arthritis, adult over 18 years, 40 mg on alternate weeks; if necessary increased to 40 mg weekly in patients receiving adalimumab alone
- psoriatic arthritis, adult over 18 years, 40 mg on alternate weeks
- ankylosing spondylitis, adult over 18 years, 40 mg on alternate weeks

The proposed use of adalimumab for psoriasis is therefore inline with its use for other indications.

2.3.3 Comparators

The NICE scope specifies the comparators as the standard therapies acitretin, ciclosporin, hydroxycarbamide, methotrexate, and photo(chemo)therapy (PUVA), plus the biologic therapies etanercept, efalizumab, and infliximab. The decision problem states that all standard and biologic therapies were considered for inclusion in the evidence synthesis, which is used to inform the cost-effectiveness modelling.

The ERG notes however that only one RCT was included which compared adalimumab with placebo and with methotrexate. Methotrexate was therefore the only comparator included in the systematic review of the MS. No other comparator trials were included in the systematic review of the MS and a standard meta-analysis was not carried out. Comparator trials were included in the mixed-treatment comparison but it was not possible to include acitretin, hydroxycarbamide and PUVA because the appropriate data are not available. The comparator described in the decision problem therefore only partially meets the remit defined in the NICE scope.

2.3.4 Outcomes

The final scope issued by NICE lists four outcomes that should be considered: measures of severity of psoriasis; remission rate; adverse effects of treatment; and health-related quality of life. The decision problem outcomes reflect those of the NICE scope; they included PASI 50/75/90/100 response, and both the Physician's and Patient's Global Assessment of Disease Activity. Three different measures of health related quality of life were used between the included trials (DLQI, SF-36, EQ-5D) and adverse events were reported.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach

3.1.1 Description of manufacturer's search strategy

The clinical-effectiveness searches are thorough and based on sound and reproducible search strategies, but few terms are used in the cost-effectiveness searches (see below).

3.1.1.1 Clinical-effectiveness searches

The minimum database search criteria that are specified by NICE (Medline, Embase, Medline in Progress (MEIP) and Cochrane) for undertaking clinical-effectiveness searches have been fully adhered to by the manufacturer. The manufacturer has exceeded the remit by undertaking searches on additional databases. The three key dermatology conference proceedings (American Academy of Dermatology [AAD], European Academy of Dermatology and Venerology [EADV], British Association of Dermatology [BAD]) are recorded as having been searched. The manufacturer also records additional searching having been undertaken on their in-house database ("PRLIT" – product literature).

Clinical-effectiveness searches for the systematic review were undertaken on the 8th August 2007. Databases were searched from 1996 to the search date. The MS states that it was not deemed necessary to search older databases as the clinical phase of adalimumab began in 1997. No start date is given for searches of conference abstracts but results are presented for AAD 2004-2007, for EADV 2005-2007, and for BAD 2006-2007. No start date or end date is given for the in house database search.

An additional search undertaken in September 2006 for the indirect/mixed treatment comparisons section of the MS is referred to (MS p77) but these searches are not listed in the Appendices. The ERG requested clarification and asked the manufacturer to supply these search strategies. The manufacturer responded and supplied the search strategy (Appendix 1, section A5 p87-93). For the mixed treatment comparison databases were searched from their inception to September 2006. Hand searching took place but the MS does not state which sources were hand searched and no search dates for the hand searching are given.

The search terms selected by the manufacturer include appropriate descriptor and free text terms (the latter were adequately truncated) for the disease area. The terms selected to identify clinical trials represent an adequate filter for the search. The documented strategies are appropriately run on the specified databases. All steps of the search strategy have been carefully recorded and the numbers from each search line have been recorded. The publication type (PT) has been applied in Medline to RCTs and controlled trials, which has good retrieval potential of relevant studies. The search could possibly have been extended to include follow up, cross over and meta analysis.

Cochrane was searched and a simple strategy is recorded in Table 9.2.4 of the MS (MS p142). The ERG re-ran the first two lines of the search strategy and obtained the same number of results in Cochrane Central.

Ongoing Trials

The manufacturer has manually searched the conference abstracts for three major dermatology meetings: AAD, EADV and BAD and records the number of hits for each conference year searched (MS p142-143). The manufacturer's in-house data and database (PRLIT) were also searched, which should comprehensively retrieve all ongoing trials that the manufacturer is undertaking pertaining to adalimumab. Biosis

is charted as having been searched which contains conference & meeting abstracts which might present interim data before the studies are fully published in journals.

There is no record in the MS Appendix 9.2 of the manufacturer searching other sources such as the National Research Register (NRR), Clinical Trials.gov, or Clinical study results.org, to seek ongoing trials. However, this is not a pre-requisite in the NICE instructions.

3.1.1.2 Cost-effectiveness searches

The cost-effectiveness searches (MS Appendix 9.3 p144) run by the manufacturer meet the minimum database criteria set by NICE (Medline, Embase, MEIP, NHS Economic Evaluations Database [NHS EED] and the Health Economic Evaluations Database [HEED]). No additional searches were made in the company database PRLIT. The searches are recorded as undertaken on the 4th September 2007. The databases Medline (PubMed), Medline (R) InProcess, and Embase were searched from 1996 to the search date. No start date is given for the databases HEED and NHS EED and the ERG assumes that these were searched from inception to the search date of 4th September 2007.

The manufacturer clearly states that scoping searches revealed a paucity of literature on cost studies for the drugs and hence it seems sensible to extend this to the disease area of psoriasis. However the search strategy contains only a few search terms: the free text terms “cost” and “effectiveness” and “Psoriasis”; the search string “cost adj effectiveness”; and finally cost or effectiveness appearing anywhere in the indexing or abstract. Cost-effectiveness could have been truncated to cost\$ effective\$. There are no free text synonyms used such as price, pricing, economic\$ pharmaco-economic\$ fee\$ charges, budget\$, expenditure\$, resources, utility, utilities. For the sake of being systematic a full cost filter could have been applied using the mix of index and free text terms for the drugs and then for the disease area in order to overtly spell out the absence or paucity of relevant results. The full economic filters always produce a large amount of irrelevant hits but the ERG feels the process should have been recorded. There is no strategy recorded for HEED and NHS EED (N/A is recorded for these two databases, however the number of retrieved items is recorded).

The ERG re-ran the manufacturer’s search strategy on Medline and obtained similar numbers of hits.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The MS treats the systematic review and the mixed treatment comparison as separate pieces of work, and describes the inclusion criteria slightly differently for each one. No details are provided regarding how the inclusion criteria were applied i.e. how references were screened for inclusion in the systematic review or the mixed treatment comparison. The manufacturer was asked to clarify their process for including studies. The manufacturer responded stating that selection of studies was conducted by one researcher and validated by a second researcher (Appendix 1, section A2 p79)

Systematic Review

Inclusion criteria (specified MS p20 &27)

- all RCTs comparing adalimumab to an alternative treatment or placebo for the treatment of psoriasis
- open-labelled controlled trials, prospective studies, crossover studies, and comparative studies also included in the search (and RCTs then extracted manually)

Exclusion criteria (specified MS p20 & 27)

- trials of patients with psoriatic arthritis, reviews, studies not fitting inclusion criteria, studies on juveniles (0-17 years)

The specified inclusion/exclusion criteria for the systematic review were appropriate and reflect some of the information given in the decision problem. However:

- psoriasis severity (stated in the decision problem as moderate to severe) was not an inclusion criterion
- the MS does not specify dose of adalimumab as an inclusion criterion (unlicensed at the time of the Single Technology Appraisal [STA]) and therefore includes information from trials where the dose does not reflect the anticipated licensed dose
- comparator trials that are included in the mixed-treatment comparison are not included in the systematic review
- although the MS initially states RCTs as a criterion for study identification (MS p20) and inclusion (MS p27) both these sections go on to indicate that other study designs i.e. open-labelled controlled trials, prospective studies,

crossover studies, and comparative studies were also included. This adds to the lack of clarity over the way in which inclusion criteria were applied.

- reasons for study exclusion were provided (MS p29) but no figures for how many references were excluded for each reason and no list of excluded studies was provided. The ERG requested clarification from the manufacturer. The manufacturer had to try and replicate the original literature search in order to supply a more detailed flow chart. Consequently there are slight discrepancies between the flow chart in the MS and the more detailed flow chart provided subsequently (Appendix 1, section A2 p80).

Mixed-treatment Comparison

Inclusion criteria (specified MS p77)

- RCTs of patients with moderate-to-severe psoriasis. The ERG notes that because psoriasis can be graded as moderate, moderate-to-severe, and severe, it is unclear whether the use of hyphens is meant to suggest that only the specific severity group of moderate-to-severe is being considered in this instance.
- trials had to have a primary endpoint of between eight and 16 weeks
- trials took place in a developed country. No reason for this was provided in the MS.
- patients must have inadequately responded to topical treatments alone, and had received prior systemic therapy or phototherapy, or were candidates for such treatment
- trials must have reported at least one of the PASI response values
- all potential treatments for psoriasis with Food and Drug Administration (FDA) or EMEA approval were initially considered eligible, but in the final analysis only treatments and dose regimens that are licensed and recommended for use in psoriasis patients in the UK were examined (MS p78-79)
- although not licensed as the time of analysis, adalimumab was also included and trial data on adalimumab supplemented the results. Only the anticipated licensed dose of adalimumab was included. This adalimumab dose inclusion criterion for the mixed treatment comparison is at odds with the inclusion criteria for the systematic review which did not include adalimumab dose.

Exclusion criteria

- no exclusion criteria are explicitly mentioned, although the MS does state the 19 papers were excluded because they could not be linked to a placebo (MS p78)

The specified inclusion/exclusion criteria for the mixed-treatment comparison were appropriate and reflect most of the information given in the decision problem.

However:

- no justification is given for the choice of inclusion and exclusion criteria. Whilst in most cases this is clear, in other cases such as the restriction to trials that took place in a developed country, the reasoning is not clear.
- a detailed search strategy for the mixed-treatment comparison was not present in the MS Appendix 9.2 (MS p137-144) although a literature flowchart is provided (MS p78). The ERG requested the search strategy from the manufacturer which the manufacturer supplied (Appendix 1, section A5 p87-93).
- It is not clear whether the MS statement p78 that “19 papers were excluded because they could not be linked to placebo” is an accurate description of the methodology. Papers should have been excluded because they could not be linked to placebo or another common comparator within the chain of evidence. A list of excluded studies was not supplied. The ERG requested clarification from the manufacturer who supplied the search strategy but did not supply a list of studies excluded from the mixed treatment comparison. Therefore the ERG has been unable to check this. If papers were excluded because they could not be linked to placebo, there is a chance that relevant trials which could link into the chain of evidence by a common comparator are excluded.
- quality assessment of studies included in the mixed treatment comparison did not appear to have been conducted. The ERG requested clarification about the methods used. The manufacturer responded by providing an updated version of Table 5.6.1 (Appendix 1, section A6 p96-97) which contains a Jadad quality rating for each of the included trials.
- little detailed information is presented about the comparator trials that are included in the mixed-treatment comparison such as patient characteristics (e.g. prior treatment history), psoriasis severity and treatment regimens.
- the MS does not describe the criteria used to classify and identify moderate-to-severe psoriasis

- an etanercept high dose (50mg twice weekly) is listed among the treatments and dose regimens that the manufacturer has included in the mixed treatment comparison. NICE guidance only recommends the use of etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly for the treatment of adults with plaque psoriasis (and only when specific criteria are met). Therefore it is the ERG's view that the etanercept high dose does not meet the manufacturer's stated objective for the mixed treatment comparison of including only treatments and dose regimens that are licensed and recommended for use in psoriasis patients in the UK. However, the clinical expert consulted by the ERG confirmed that etanercept 50mg twice weekly is used in a number of cases where the low dose is not effective.
- it not clear why results for ciclosporin 5mg/kg/day have been presented when the MS suggests that only the 3mg/kg/day dose would be under consideration since doses greater than this are related to high toxicities (MS p79). The ERG's clinical expert confirmed that ciclosporin is routinely used at doses ranging from 2.5 to 5mg/kg for psoriasis in the UK. Despite the potential for toxicity a number of patients do require the 5mg/kg dose.

3.1.2.1 Identified studies

The systematic review section of the MS includes five studies that contribute to the evidence base on efficacy:

- 3 RCTs (M02-528 [phase II], M03-656 REVEAL [phase III], and M04-716 CHAMPION [phase III])
- 1 extension study including both RCT and open-label periods (M02-529, which is a continuation of the phase II RCT M02-528)
- 1 ongoing open-label extension study (M03-658 which is a continuation of all the phase II and phase III trials within the Adalimumab Psoriasis Clinical Trial Programme)

An additional two studies are included which contribute to the evidence base on time to relapse following dose reduction or withdrawal from adalimumab, and evidence on re-treatment with adalimumab following relapse

- 1 study including both RCT and open-label periods (M02-538 [phase II])
- 1 open-label study (M03-596, which is a continuation of the phase II RCT M02-538)

This ERG report will concentrate on the randomised comparisons only, i.e. RCTs M02-528, M02-538, M02-538, periods A and C of M03-656 REVEAL, and M04-716 CHAMPION.

PDFs of published reports relating to the included clinical trials were provided. However, some of these reports were short summary documents that contained very few details. Clinical study reports (CSRs) were referenced in the MS but not provided. The manufacturer was asked to supply the CSRs and these were received on 10/10/07. The CSRs provide greater detail about trial methodology and results so consequently are long documents. The CSRs of the RCTs that the ERG has concentrated on ranged in size from 168 to 426 pages, and we have therefore not assessed these in detail.

The MS presents tables of summary details for key elements of the RCTs e.g. trial design, intervention, population, patient number flow charts, outcomes, sample size calculations and statistical analysis (MS p31-59). For the key efficacy RCTs (M02-528, M03-656 REVEAL, and M04-716 CHAMPION), the extension study including both RCT and open-label periods (M02-529), and the dose reduction/withdrawal RCT (M02-538) no differences in baseline characteristics of patients and controls are reported in the MS.

Although the ERG has not checked every detail, the information presented in the MS systematic review seems to be representative of the information in the published trial reports. Some details were not present in the published trial reports but were found in the CSRs. For the baseline demographics and disease characteristics of the three included RCTs (MS Table 5.3.2, p38-42), which the ERG has checked in detail against the trial publications (or CSRs if information not present in trial publications), only a few minor discrepancies were found:

- study M02-528. Baseline PGA% not reported in full in the MS, only the percentages of patients in the PGA categories of 'Severe' and 'Moderate to Severe' are provided. There are very minor discrepancies in baseline DLQI and EQ-5D scores between two tables within the CSR but the information in the MS matches the data in one of the CSR tables.
- study M02-538. The confidence interval for the baseline PASI score of the Not Randomised group is misreported as 15.1, 17.7 which is the overall 95% CI for the mean PASI score of all subjects. The correct 95% CI for the Not Randomised group is [REDACTED]

- study M04-716. Baseline body weight standard deviations were not present in the trial publication or the CSR so could not be checked. In the MS baseline PGA is presented for the 'severe' and 'very severe' groups combined whereas in the CSR these data are separate. A minor error has been made in adding together the values for the methotrexate group (the MS says 51, values in CSR suggest this should be ■ and consequently the percentage figure in the MS based on this value is also incorrect. The MS footnote (a) states that the percentage value for PGA of the combined 'severe' and 'very severe' groups is calculated on 107 subjects, but has actually been calculated on 108 subjects in this instance.

The processes undertaken by the manufacturer for the extraction of data from the included trials are not detailed in the MS. The ERG requested further information from the manufacturer about the processes used. The manufacturer responded stating that data had been extracted by one researcher and validated by a second researcher (Appendix 1, section A1 p79)

Table 1 Characteristics of the included adalimumab RCTs

Reference	Methods	Participants	Outcomes†
MO2-528 ⁸⁻¹³	<p><i>Design:</i> phase II, multicentre, RCT</p> <p><i>Interventions:</i> 1) adalimumab 40mg weekly 2) adalimumab 40mg every other week (eow) 3) placebo</p> <p><i>Duration:</i> 12 weeks</p>	<p>Adults with clinical diagnosis of moderate to severe chronic plaque psoriasis; ≥5% BSA affected for at least 1-year, active psoriasis despite topical therapies.</p> <p><i>Numbers:</i> 1) 50 2) 45 3) 52</p>	<p><i>Primary:</i> % achieving PASI 75 at week 12</p> <p><i>Secondary:</i> % achieving: PASI 50; PASI 90; PGA of <i>clear or almost clear</i></p> <p>Change from baseline score on: DLQI; SF-36; EQ-5D</p>
MO2-538 ^{14,15‡}	<p><i>Design:</i> Phase II, multicentre, RCT (withdrawal study following open-label period with adalimumab 40mg weekly).</p> <p><i>Interventions:</i> 1) adalimumab 40mg eow 2) placebo</p> <p><i>Duration:</i> 12 weeks</p>	<p>Adults with clinical diagnosis of moderate-to-severe plaque psoriasis for 1 year; ≥5% BSA for at least 2-months before screening. PASI ≥8 at screening & baseline, active disease despite topical therapies</p> <p><i>Numbers:</i> 1) 68 2) 68</p>	<p><i>Primary:</i> Time to relapse after adalimumab withdrawal (PASI <50 response)</p> <p><i>Secondary:</i> % achieving: PASI 75; PASI 50; PASI 90; PGA of <i>clear or almost clear</i></p> <p>Proportion who relapsed</p>
M03-656 REVEAL ¹⁶⁻¹⁹	<p><i>Design:</i> Phase III, multicentre, RCT with two placebo controlled periods (A and C) and one open-label period (B).</p>	<p>Adults with clinical diagnosis of moderate-to-severe plaque psoriasis for at least 6-months; stable for at least 2 months; ≥10% BS, PASI ≥12 and PGA at</p>	<p><i>Primary:</i> Period A: % achieving PASI 75 at week 16 Period C: % losing adequate response</p>

	<p>Period A and C only reported here.</p> <p><i>Interventions:</i> 1) adalimumab 40mg eow 2) placebo</p> <p><i>Duration:</i> Period A 16 weeks Period C 19 weeks</p>	<p>least 'moderate' at baseline</p> <p><i>Numbers:</i> Period A: 1) 814 2) 398</p> <p>Period C: 1)250 2)240</p>	<p><i>Secondary:</i> Period A&C: % achieving: PASI 75 (period C only); PASI 50; PASI 90; PASI 100; PGA of <i>clear</i> or <i>minimal</i>; DLQI =0</p> <p>Change from baseline score on: DLQI;SF-36</p>
MO4-716 CHAMPION ²⁰ -24	<p><i>Design:</i> Phase III, multicentre, RCT</p> <p><i>Interventions:</i> 1) adalimumab 40mg eow 2) methotrexate 7.5 rising to maximum 25.0mg weekly 3) placebo</p> <p><i>Duration:</i> 16 weeks</p>	<p>Adult candidates for systemic therapy or phototherapy with active psoriasis despite topical treatments; moderate-to-severe clinical psoriasis for at least 1-year; stable for at least 2-months; ≥10% BSA, PASI ≥10 at baseline.</p> <p><i>Numbers:</i> 1) 108 2) 110 3) 53</p>	<p><i>Primary:</i> % achieving PASI 75 at week 16</p> <p><i>Secondary:</i> % achieving: PASI 50; PASI 90; PASI 100; PGA of <i>clear</i> or <i>minimal</i></p> <p>Change from baseline score on: DLQI; EQ-5D</p>

† Primary outcomes, with selected key secondary outcomes are listed. Additional secondary outcomes were also reported by trials.

‡ The ERG has included data from this withdrawal trial because it is an RCT and it reports the outcomes that are reported in the other three trials

The MS systematic review does not comment on potential differences in patient characteristics between trials. However, the ERG notes that:

- Inclusion criteria for patients vary between the included trials. Although there is a diagnosis inclusion criterion of “Moderate to severe chronic plaque psoriasis” for all trials (as summarised in Table 5.2.1, MS p24-26), this level of disease severity is then defined slightly differently in the different trials (Table 1) by either a %BSA value alone, a %BSA value in combination with a PASI value, or a combination of %BSA, PASI value and PGA. The ERG’s clinical expert suggests that since the PGA is a subjective measure this would only become relevant in defining severity if patients had scores of less than 10 for each of PASI, BSA and DLQI.

• [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The ERG requested further details about how many of

the trial participants had severe, or moderate to severe psoriasis. The manufacturer responded by providing an additional table of baseline data relating to disease severity (Appendix 1, Table A4.1 p82). The manufacturer confirms that some of the patients enrolled in M02-528 would not have qualified under the BAD guidelines to receive biologic therapy for psoriasis but point out that this is why a post-hoc sub-analysis (MS p64) had been conducted on those patients who met some of the BAD guideline criteria. In addition the manufacturer notes that M02-528 was a dose-finding phase II study and not one of the pivotal phase III trials.

- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- In general, participants in the M02-528, and M02-538 studies appear to have slightly lower BSA% and PASI scores than participants in other studies.
- It is difficult to compare baseline PGA values because in studies M02-528 and M02-538 the PGA score has seven categories defined in the MS, but baseline values are not provided in the MS for M02-538 [REDACTED]
[REDACTED]. In studies M03-656 REVEAL and M04-716 CHAMPION PGA is categorised on a six point scale which is not defined in the MS. Overall the proportion of participants with a PGA of very severe, severe, or moderate in the CHAMPION and REVEAL studies is similar.
- M02-528 had higher proportions of participants having had prior systemic treatments (36.5% in the placebo and 42.2% in the eow adalimumab arm) compared to the other three trials where overall between 22.8% and 33.9% of trial participants had prior systemic therapy (% over whole trial population, not separate arms). In addition 26.5% of participants in trial M02-538 had received biologic treatments in the past 12 months, whereas in the REVEAL trial only 12.4% had and in CHAMPION only 2.2% had.
[REDACTED]
[REDACTED] The ERG requested further details from the manufacturer about how many of the trial participants had failed to respond to a prior systemic therapy in order to determine how closely the trial populations meet the anticipated licensed indication for treatment. The manufacturer responded that most patients who have a history of use of systemic therapy, but who

subsequently discontinued and enrolled in the adalimumab clinical trials, can be inferred to have failed to respond, developed a contra-indication, or acquired an intolerance to the agent they had been using. Additional tables were provided showing how many of the trial participants had received prior systemic therapy (Appendix 1, Tables A4.3 to A.4.6 p83-85). The ERG notes that in these tables the category of systemic therapy includes PUVA treatment.

- Other baseline characteristics e.g. %Male, age, and duration of psoriasis presented appear to be broadly similar between trials.

The MS does not provide summary details of the key elements of the RCTs that contributed data to the mixed treatment comparison, apart from the MS Table 5.6.1 which lists the data contributing to the mixed treatment comparison. The ERG requested further details about the processes of study inclusion and quality assessment of studies, and also whether the comparator trial populations would meet the anticipated indication for treatment with adalimumab, from the manufacturer. The manufacturer responded stating that selection of studies and extraction of data were conducted by one researcher and verified by a second researcher. For the key adalimumab studies included in the mixed treatment comparison (M02-528, REVEAL and CHAMPION), the Jadad scoring tool was used to assess the quality of the trials. (Appendix 1, section A1, p79). In addressing the ERG's query about whether the comparator trial populations would meet the anticipated indication for treatment with adalimumab, the manufacturer responded that the mean baseline characteristics for the comparator trial populations are in line with the anticipated licensed indication for adalimumab. For all these trials, the mean baseline BSA is >10% and the baseline PASI is >10 (Appendix 1, section A6 p95). Whilst this indicates that the trial populations may meet the psoriasis severity criteria the ERG has not been able to ascertain whether these populations meet the other criterion of being adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.

3.1.2.2 Details of any irrelevant studies that were included in the submission

Although the included RCTs appear to meet the inclusion criteria for the MS systematic review the ERG has noted that open-label studies were also included, which we have not assessed. The RCTs we have concentrated on relate to the short-term efficacy of adalimumab, the open-label studies provide some longer term

data which we have not been able to assess within the available timeframe. The ERG also notes that the withdrawal dose-reduction study M02-538 started with an open-label period of treatment with adalimumab 40mg weekly – this is not the dose specified in the draft SPC which is 40mg every other week.

3.1.2.3 Ongoing studies

The MS provides details of two ongoing trials (MS p28):

- **M03-658** – This 2-year, multicentre, open-label extension trial is currently ongoing at sites in Europe, Canada and the USA. As of 29 June 2006, a total of [REDACTED] patients were enrolled on this study, preliminary data for which are available.
- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

There is no record of the manufacturer searching sources such as NRR, Clinical Trials.gov, or Clinical study results.org, to seek out ongoing trials. Searches of these databases were undertaken by the ERG and the following studies were found which may be of relevance:

- Canadian Open-Label Access Program to Evaluate Adalimumab When Added to Inadequate Therapy for the Treatment of Psoriasis (PRIDE). The purpose of this non-randomised, open-label study is to evaluate the safety profile, the effectiveness and the economic impact of adalimumab when used for the treatment of subjects with active plaque psoriasis who have not adequately responded to prior psoriasis therapy. This Abbott sponsored study is recorded as being due to start August 2007 with a proposed total enrolment of 250 people. (Found listed on ClinicalTrials.gov)
- STRU-09-06. Adalimumab for psoriasis patients who are non-responders to etanercept: An open-label study. The purpose of this open-label study is to test the hypothesis that psoriasis patients who are non-responders to etanercept achieve a clinically useful response with adalimumab. The study aims to recruit 20 patients. The funders of this study are Abbott Laboratories Ltd and NHS R&D Support Funding. The study is recorded as Starting 17

April 2007 with an end date of 1 October 2007 given. (Found listed on National Research Register)

3.1.2.4 Additional studies

The ERG has identified one record from ClinicalTrials.gov which may be a relevant study.

- Adalimumab in Adult Japanese Subjects with Moderate to Severe Chronic Plaque Psoriasis. This phase 2/3, Randomized, Double-Blind, Placebo Controlled, Multicentre Study is listed as starting November 2005 and being complete. It was due to enrol 160 subjects. The ClinicalTrials.gov Identifier is NCT00338754.

3.1.3 Description and critique of manufacturer's approach to validity assessment

The MS provides a formal appraisal of the validity of the included trials using the quality assessment criteria developed by NICE. The process of applying quality criteria was not reported in the MS so the ERG requested further information from the manufacturer about the process used. The manufacturer responded stating that the quality of trials was assessed by one researcher. The ERG assessment of the four trials (M02-528;⁸⁻¹³ M02-538;^{14,15} REVEAL;¹⁶⁻¹⁹ CHAMPION²⁰⁻²⁴) can be seen below and differs from the MS for some of the trials but is generally in agreement.

- How was allocation concealed?

The focus of the MS response to this question is on blinding not allocation concealment *per se*, however the ERG assessment is that it is likely to be adequately concealed in all four RCTs as this was undertaken by an off-site provider.

- What randomisation technique was used?

The MS notes that computerised randomisation was used in each of the four trials by an off-site provider (Clinphone). The ERG concurs with this as an appropriate mechanism but also notes that the randomisation schedule itself was generated by Abbott (the manufacturer).

- Was a justification of the sample size provided?

The MS reports that justification of the sample size was reported in each of the trials but doesn't comment on the adequacy of these calculations. The ERG comment that power calculations were reported in the publications of two of the included trials (M02-528⁸⁻¹³; M02-538^{14,15}) and in the CSR (in confidence) for the other two trials

(REVEAL; ¹⁶⁻¹⁹ CHAMPION²⁰⁻²⁴). In the two published trials the sample size calculation was appropriate (although one group in the M02-528 trial had slightly fewer participants than the calculation assumed).

- Was follow-up adequate?

The MS reports that follow-up was adequate and concurs with EMEA recommendations. The EMEA recommendation states that “a duration of eight to 12 weeks... is generally sufficient to show short-term efficacy, except for drugs with slow onset of action, where longer study duration may be needed” (p5, <http://www.emea.europa.eu/pdfs/human/ewp/245402en.pdf>). The ERG assess the trial durations of the four trials as having adequate follow-up by this definition. The ERG also notes the number of participants not followed-up (due to withdrawal for example) was in the region of 4-10% in each of the four trials.

- Were the individuals undertaking the outcome assessment aware of allocation?

The ERG agrees with the MS that those undertaking the assessments of outcomes were unaware of the allocation to the randomised groups.

- Was the design parallel-group or crossover?

The ERG agrees with the MS that the studies were of a parallel design.

- Was the RCT conducted in the UK?

The MS reports that trials were multinational studies and notes that the countries taking part did not include the UK.

- How do the included RCT participants compare with patients who are likely to receive the intervention in the UK?

The MS reports that the participants in the trials were broadly similar in terms of baseline disease severity and demographics to those in England and Wales. The ERG agrees with this observation. The MS also acknowledges that participants in CHAMPION may differ from patients in the UK as they were methotrexate naïve. The MS does not discuss if clinical practice is likely to differ in anyway to the UK, the ERG assumes it is likely to be similar.

- Were the study groups comparable?

The MS notes that the study groups within each trial had similar demographic and clinical profiles to which the ERG would concur.

- Were the statistical analyses used appropriate? Was an intention-to-treat (ITT) analysis undertaken?

The MS notes that statistical analyses were appropriate and that intention-to-treat analyses were undertaken for each of the trials. The ERG would suggest that full ITT analysis was only used in the CHAMPION trial and for binary outcomes in the REVEAL trial, the other outcomes were either analysed with a modified ITT or Last Observation Carried Forward (LOCF) approach.

- Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

The MS does not discuss if any confounding factors may attenuate the interpretation of the results and the ERG suggests this is unknown, although in the CHAMPION trial folate was used in all treatment groups and the MS (page 94, interpretation of clinical evidence) attributes a high placebo response rate as possibly linked to this.

- For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?

The MS reports that in each trial (for the randomised treatment comparisons) there is at least one treatment arm that meets the dose of adalimumab recommended in the draft SPC. These data are not highlighted as Commercial in Confidence (CIC) in this section (Table 5.3.6, page 61) but has been treated as such by the ERG in line with the information elsewhere in the MS.

In addition, the MS also reports double blinding (patients and drug administrators) and this is adequate across the four trials, although the ERG notes that participants dropped out of placebo groups due to 'unsatisfactory therapeutic effect' (not defined).

3.1.4 Description and critique of manufacturer's outcome selection

The MS presents all relevant outcome measures reported in the four trials and these are appropriately reproduced in the MS with only minimal differences (for example some data were rounded). Three trials reported the proportion achieving a PASI 75 response as their primary outcome (M02-528; ⁸⁻¹³ REVEAL; ¹⁶⁻¹⁹ CHAMPION²⁰⁻²⁴); trial M02-538^{14,15} reported this as a secondary outcome. The primary outcome of this latter trial, time to relapse after randomisation, reflects the objective of the study to

evaluate the duration of effect of adalimumab treatment. The PASI 75 response was a secondary outcome in this trial. Other outcomes reported in the trials included PASI 50, 90, 100 response, PGA, DLQI, SF-36, and EQ-5D.

3.1.5 Description and critique the statistical approach used

The MS presents results from each trial independently, little narrative summary or tabulation of the overall effect of treatment from the trials is reported. In general the data presented in the MS reflects the data reported in the trial publications. In the MS the achievement of PASI 50, 75 and 90 are reported as proportions of patients (numbers and proportion in REVEAL¹⁶⁻¹⁹) with p-values reported for comparisons between groups in most cases (in some, p-values were only presented in the confidential CSRs). Quality of life outcomes (DLQI, EQ-5D, SF-36) were presented as change from baseline scores. For the CHAMPION trial²⁰⁻²⁴ the p-values alone for quality of life outcomes were presented in the MS. The variance around point estimates was not presented in many cases (see Tables 3 to 9 below). There is no discussion in the MS of whether or not it was necessary or appropriate to make adjustments to the level of statistical significance in order to correct for multiple comparisons in the analyses, but this was not discussed in the trial publications either.

The MS also reports data from post-hoc subgroup analyses. In the M02-528 trial⁸⁻¹³ an analysis of those meeting the criteria for biological therapy following the BAD guidelines was undertaken, and in the CHAMPION trial²⁰⁻²⁴ a subgroup analysis on those with baseline BSA >20%. These analyses have not been considered by the ERG as they were not predefined subgroup analyses and it is unknown whether there would have been enough statistical power to analyse these.

Meta-analysis

There was no meta-analysis undertaken on the data from the included trials for any of the outcomes. The manufacturer does not give any reasons for not undertaking a meta-analysis except to state that one was not conducted because Section 5.6 of the MS contains a mixed treatment comparison. Although the mixed treatment comparison would still have been needed to inform the cost-effectiveness analysis a meta-analysis might have been a useful addition to the MS particularly since the MS does not provide much in the way of a narrative summary of overall effect. A meta-analysis would also have provided information about any potential statistical heterogeneity between studies.

Indirect comparison/mixed treatment comparison

Evidence was collected for a mixed treatment comparison from the results of a different systematic literature search to the one which informed the systematic literature review (ERG report section 3.1.1.1 p18). Although a publication is referenced in which a mixed treatment comparison is described, full methodological details were not supplied in the MS. It was not clear what the processes were for determining which studies would be included (ERG report section 3.1.2 p20-22) and for performing the data extractions so the ERG requested clarification from the manufacturer. The manufacturer responded by providing some additional information about how data abstraction and quality assessment were carried out (Appendix 1, section A6, p94). The MS reports that the search identified 52 distinct RCTs providing evidence on the efficacy of 12 drugs. The literature flow chart documents that 36 sources (22 trials) had useable information on outcome for meta-analysis and states that these were finally used in the evidence synthesis. However, Table 5.6.1 (MS p81-82) lists only 18 included studies. The ERG suggests that this apparent discrepancy maybe because the MS goes on to report that final analysis examined only treatments and dose regimens that are licensed and recommended for use in psoriasis patients in the UK which may have excluded further studies, although this is not explicitly stated in the MS.

It is not clear in the MS how the trials which report outcomes for ciclosporin 1.25mg/kg/day, 2.5mg/kg/day and 3-5mg/kg/day have been incorporated into the evidence synthesis to provide outcomes for ciclosporin 5mg/kg/day and ciclosporin 3mg/kg/day.

Details are not provided regarding the comparator trials that contributed to the mixed treatment comparison. In particular the characteristics of the patient groups in the comparator trials are not described so it is not possible for the ERG to determine how similar the participants in the comparator trial arms are to those in the included adalimumab trial arms. The ERG requested clarification from the manufacturer, in particular whether the comparator trial populations would meet the anticipated indication for treatment with adalimumab. The manufacturer responded that the mean baseline characteristics for the comparator trial populations are in line with the anticipated licensed indication for adalimumab. For all these trials, the mean baseline BSA is >10% and the baseline PASI is >10 (Appendix 1, section A6 p95). Whilst this indicates that the trial populations may meet the psoriasis severity criteria the ERG

has not been able to ascertain whether these populations meet the other criterion of being adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.

A tabular or diagrammatic representation of the network of trials contributing to the chain of evidence would have been a useful addition to this section. The processes used and the methods of the mixed treatment comparison are not described in sufficient detail for the ERG group to review the approach taken and therefore the outcomes of the analysis.

3.2 Summary statement of manufacturer's approach

The manufacturer's approach to the systematic review was restricted to a review of clinical trials including adalimumab as an intervention. The manufacturer appears to have identified all the relevant published trials meeting their inclusion criteria. The information was supplemented by unpublished data from clinical study reports. There were some discrepancies between the scope and the decision problem however the ERG would suggest that these would not have resulted in any studies involving adalimumab being missed. The clinical-effectiveness searches for the systematic review are viewed by the ERG as sound. Search dates were provided for the main database searches. A separate set of searches was conducted for the mixed treatment comparison but these searches were not listed in the MS. Therefore it is less clear whether the approach will have identified all the relevant trials that could be considered for inclusion in the mixed treatment comparison. The manufacturer did not provide a systematic review of the comparator trials included in the mixed treatment comparison. Details of searches for ongoing studies were also provided. The search strategy for cost-effectiveness literature contained only a few search terms. Nevertheless, it is likely that all the relevant cost-effectiveness studies were identified.

Five adalimumab studies that contributed to the evidence base on efficacy were included by the manufacturer, with two further studies included which contributed to the evidence base on time to relapse. However, several of these were open-label studies which the ERG has not reviewed in detail.

The included studies meet the inclusion criteria, however psoriasis severity was not a specified inclusion criterion. Although all trials included participants with 'moderate to severe' psoriasis, the definition of this level of disease severity was defined differently

in each trial (Table 1 ERG report p25-26). In general participants in the M02-528 and M02-538 studies appeared to have slightly lower BSA% and PASI scores than participants in the other studies. The proportion of male to female participants and the age ranges of participants were similar.

Inclusion criteria were specified for the trials contributing to the mixed treatment comparison, however little information was provided on these so it has not be possible for the ERG to determine whether the included trials matched the specified inclusion criteria.

Quality assessment

The ERG has assessed the MS for its quality as a systematic review using the questions in CRD report 4.²⁵ For the included adalimumab trials, the quality of the MS was reasonable (see Table 2). However the ERG point out again that there was no systematic review of the comparator trials, no critical appraisal/quality assessment of these studies in the MS and very little detail was presented. The ERG requested further information from the manufacturer who responded and provided some additional information (Appendix 1, section A1 p79)

Table 2 Quality assessment (CRD criteria) of the MS review of adalimumab studies

CRD Quality Item; score Yes/No/Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Partially – inclusion criteria for study design (RCT) and intervention (adalimumab). But none stated for severity of disease or outcomes.
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes – follows suggested NICE checklist
4. Is sufficient detail of the individual studies presented?	Partially (Yes for adalimumab studies, No for comparator studies in the mixed treatment comparison)
5. Are the primary studies summarised appropriately?	Uncertain – very little attempt made to synthesise results from the included studies. No meta-analysis, a narrative summary for individual studies, but inadequate overview summary.

The submitted evidence generally reflects the decision problem defined in the MS. The lack of head-to-head comparisons has led to an indirect comparison but little information has been presented regarding the comparator trials that were included in this analysis. The ERG has some reservations about the comparator trials included in this analysis as discussed in section 3.1.2 (ERG report p22-23).

3.3 Summary of submitted evidence

3.3.1 Summary of results

In this section of the report, the ERG concentrates primarily on the main outcomes of the included RCTs of adalimumab. The MS notes on page 30 that no claim for efficacy was intended based on trial M02-538, however the ERG has included data from this trial because it is an RCT and it reports the outcomes that are reported in the other three trials. The additional non-RCT evidence is not described here but can be seen in the MS (pages 71-75). Data are summarised for each of the key outcomes below. Trial data are presented from groups that fall into the anticipated license for adalimumab only (40mg every other week) and any comparator arms. In

each summary table the data are taken from the MS and/or the trial publication and rounded to one decimal place (where reported). Occasionally data are presented from the CSR in confidence where it was not available in the MS or the trial publication. Information presented in *italics* was estimated by the ERG using data from the trials.

3.3.1.1 PASI

PASI 75

The primary outcome in the M02-528 trial,⁸⁻¹³ period A in the REVEAL trial,¹⁶⁻¹⁹ and the CHAMPION trial²⁰⁻²⁴ was the proportion achieving a PASI 75 response. The proportion achieving a PASI 75 was also a secondary outcome in the M02-538 trial.^{14,15} Outcomes were measured after 12 weeks of treatment in the M02-528 and the M02-538 trials; and at 16 weeks in the REVEAL (period A) and CHAMPION trials. It is important to note that participants had previously had 12-weeks open-label treatment before randomised treatments in the M02-538 trial. Table 3 shows that a higher proportion of participants on adalimumab 40mg every other week had achieved an improvement on the PASI of at least 75% (PASI 75) when compared to the placebo groups. This was statistically significantly different in all four trials. In the CHAMPION trial the likelihood of achieving a PASI 75 was also statistically significantly better in the adalimumab arm compared to the methotrexate treatment arm. In the M02-538 trial it can be observed that there is some degree of a carry-over effect in the placebo arm from the open-label treatment prior to randomisation. The proportion of participants in the placebo arm to achieve a PASI 75 was 48.5%. However, this is based purely on observation of the data and has not been tested statistically. In the CHAMPION trial it is apparent that the placebo group had a high response as measured by the PASI 75. The MS (page 94, interpretation of clinical evidence) suggest this may be due to the use of folate which was used in each of the trial arms.

Table 3 PASI 75

Study	Adalimumab 40mg eow	Placebo	Methotrexate	P-Value vs. placebo
M02-528 ⁸⁻¹³ (12 weeks)	53.3% (24/45)	3.8% (2/52)	n/a	p<0.001
M02-538† ^{14,15} (12 weeks)	67.6% (46/68)	48.5% (33/68)	n/a	p=0.032
REVEAL ¹⁶⁻¹⁹ (16 weeks) Period A[70.9% (578/814)	6.5% (26/398)	n/a	p<0.001
CHAMPION ²⁰⁻²⁴ (16 weeks)	79.6% (86/108)	18.9% (10/53)	35.5% (39/110)	p<0.001‡

† all patients previously given adalimumab for 12 weeks, PASI 75 not the primary outcome.

‡ adalimumab versus placebo; and adalimumab versus methotrexate

The MS did not present a narrative or quantitative synthesis of the data from the four trials on this outcome, except in the mixed treatment comparison (on page 83 of the MS and discussed below). The data in these trials suggests proportions within the region of 54-80% achieve a PASI 75 which is comparable to data from trials of comparator drugs used in the mixed treatment comparison (on page 83 of the MS). The MS does not discuss what they would consider a meaningful threshold to be for the proportion of patients responding on this measure.

PASI 50

Attainment of a 50% reduction in PASI response was measured as a secondary endpoint in all four trials (in REVEAL this was measured in period A and period C). In all trials a higher proportion of participants on adalimumab achieved a PASI 50 response compared to placebo. This was statistically significant in the two periods of the REVEAL trial at 16 weeks and 19 weeks respectively (data for period C was CIC but p-value was reported in the MS) and the CHAMPION trial at 16 weeks. Care is required in interpreting data from period C in the REVEAL trial as participants were a selected group who had all had previous treatment with adalimumab and were classed as ‘responders’. In the CHAMPION trial adalimumab treatment also led to a statistically significant benefit on PASI 50 compared to methotrexate treatment. Data from the M02-528 trial demonstrates a higher proportion of participants in the adalimumab treatment arm achieving a PASI 50 than those in the placebo treatment arm but no p-value is reported [REDACTED]. There were no statistically significant differences on PASI 50 between the adalimumab treated participants and the placebo treated participants in the M02-538 trial. As noted above it would appear that there was a carry-over effect on PASI response from the earlier open-label treatment in this trial.

Table 4 PASI 50

Study	Adalimumab 40mg eow	Placebo	Methotrexate	p-value vs. placebo
M02-528 ⁸⁻¹³ (12 weeks)	76% (34/45)	17% (9/42)	n/a	Not reported in the MS. [REDACTED]
M02-538† ^{14,15} (12 weeks)	77.9% (53/68)	66.2% (45/68)	n/a	p=0.173
REVEAL ¹⁶⁻¹⁹ (16 weeks) Period A	82.4% (671/814)	15.1% (60/398)	n/a	p<0.001
REVEAL ¹⁶⁻¹⁹ (19 weeks) Period C*	87.2% 218/250	66.3% 159/240	n/a	p<0.001
CHAMPION ²⁰⁻²⁴ (16 weeks)	88% (95/108)	30.2% (16/53)	61.8% (68/110)	p<0.001‡

† all patients previously given adalimumab for 12 weeks

* all patients previously given adalimumab for 32 weeks and classed as 'responders', re-randomised group only reported.

‡ adalimumab versus placebo; and adalimumab versus methotrexate

PASI 90

All four trials reported the achievement of a PASI 90 response as an outcome at endpoint, and the REVEAL trial reported this at endpoint of both period A and period C. As noted above caution is recommended in interpreting the outcome on PASI 90 from period C of this trial. Response rates on the PASI 90 are observably (and expectedly) lower than on the PASI 75 and 50 however the data would suggest that the benefit of adalimumab treatment remains. At 12-weeks in the M02-528 trial the data show a higher proportion achieving a PASI 90 in the adalimumab arm compared to the placebo arm, although the p-value is not reported [REDACTED]. The effect on PASI 90 response was statistically significantly better with adalimumab compared to placebo in all other trials (no data were presented for period C of REVEAL in the MS only the p-value [REDACTED]) and in the CHAMPION trial between adalimumab and methotrexate.

Table 5 PASI 90

Study	Adalimumab 40mg eow	Placebo	Methotrexate	P-Value vs. placebo
M02-528 ⁸⁻¹³ (12 weeks)	24% (11/45)	0	n/a	Not reported in the MS. [REDACTED]
M02-538† ^{14,15} (12 weeks)	47% (32/68)	28% (19/68)	n/a	p<0.05
REVEAL ¹⁶⁻¹⁹ (16 weeks) Period A	45% 366/814	1.8% 7/398	n/a	p< 0.001
REVEAL ¹⁶⁻¹⁹ (19 weeks) Period C*	53.6% 134/250	18.3% 44/240	n/a	p<0.001
CHAMPION ²⁰⁻²⁴ (16 weeks)	51.9% (56/108)	11.3% (6/53)	13.6% (15/110)	p<0.001‡

† all patients previously given adalimumab for 12 weeks

* all patients previously given adalimumab for 32 weeks and classed as 'responders', re-randomised group only reported.

‡ adalimumab versus placebo; and adalimumab versus methotrexate

3.3.1.2 PGA

The PGA rating was a secondary outcome in the four included RCTs. This measure uses either a 6- or 7-point scale rating the psoriasis from severe to clear. In each of the included trials outcomes were reported either for the proportion achieving a rating of 'clear' or 'almost clear' (in two trials, M02-528⁸⁻¹³ and M02-538^{14,15}) or the proportion achieving a rating of 'clear' or 'minimal' (two trials, REVEAL¹⁶⁻¹⁹ and CHAMPION²⁰⁻²⁴).

Significantly more participants in the adalimumab arms achieved a ‘clear’ or ‘almost clear/minimal’ score compared to placebo in the M02-538 trial^{14,15} at 12 weeks (adalimumab 54.4% (37/68); placebo 39.7% (27/68), $p=0.069$); the CHAMPION trial²⁰⁻²⁴ at 16 weeks (adalimumab 73.1%; placebo 11.3%, $p<0.001$); and period A of the REVEAL trial¹⁶⁻¹⁹ at 16 weeks (adalimumab 506 (62.2%); placebo 17 (4.3%), $p < 0.001$). At 12 weeks in the M02-528 trial⁸⁻¹³ the proportion achieving a PGA of ‘clear’ or ‘almost clear’ were 49% in the adalimumab 40mg eow treatment group compared to 2% in the placebo group. No p-value was reported in the MS [REDACTED]. In period C of the REVEAL trial¹⁶⁻¹⁹ after 19 weeks there was also a statistically significant benefit of adalimumab as measured by the PGA ‘clear’ or ‘minimal’ compared to placebo ($p<0.001$). The data points were not presented in the MS but were available in the CSR [REDACTED]. Caution is however necessary when interpreting these particular data as participants were from a selected group having responded to previous treatment with adalimumab. In the CHAMPION trial at 16 weeks the adalimumab participants achieving a PGA of ‘clear or minimal’ was also statistically significantly higher than those in the methotrexate group (adalimumab 73.1%; methotrexate 30.0%, $p<0.001$).

3.3.1.3 Quality of life – DLQI

The DLQI was reported in three of the included RCTs (M02-528;⁸⁻¹³ REVEAL;¹⁶⁻¹⁹ and CHAMPION²⁰⁻²⁴). The DLQI score was validated for patients with psoriasis and the score ranges from 0 to 30 with lower scores corresponding to better quality of life (QoL). The data in the MS and the trials were presented as change from baseline scores and is reported using negative values to indicate an improvement in score.

In the three trials adalimumab treatment led to statistically significant improvements in DLQI score compared to placebo scores. In each of these trials an improvement on DLQI was demonstrated in the placebo treated participants (not tested statistically) but treatment with adalimumab was statistically significantly greater. In the CHAMPION trial there was also a statistically significant difference between treatment with adalimumab and methotrexate. Both treatments led to improvements on the DLQI but treatment with adalimumab was better.

Table 6 DLQI change from baseline

Study	Adalimumab 40mg eow	Placebo	Methotrexate	P-Value vs. placebo
M02-528 ⁸⁻¹³ (12 weeks)	-10.8 (95% CI -13.1, -8.5)	-1.3 (95% CI -3.3, 0.7)	n/a	$p<0.001$
REVEAL ¹⁶⁻¹⁹ (16 weeks)	-8.2 (Standard error)	-1.7 (SE 0.32)	n/a	$p<0.001$

weeks) Period A	[SE] 0.22)			
CHAMPION ²⁰⁻²⁴ (16 weeks)	-9.0 (SD 6.68)	-3.1 (SD 6.00)	-5.4 (SD 5.29)	p<0.001‡

‡ p<0.001 adalimumab vs. methotrexate and placebo

Data were also presented for the CHAMPION²⁰⁻²⁴ and REVEAL¹⁶⁻¹⁹ trials in terms of the percentages of patients achieving a DLQI score of 0 (i.e. no dermatology impairment on quality of life). In the CHAMPION trial the proportions achieving a score of zero were 33.3% in the adalimumab treatment arm compared to 5.7% in the placebo arm (p<0.001). In period A of the REVEAL trial the proportions of those achieving a DLQI score of 0 were statistically significantly higher in the adalimumab group compared to placebo; p<0.001 (data points not presented in the MS [REDACTED]). Similarly in period C of the REVEAL trial a statistically significantly higher proportion achieved a DLQI score of 0 in the adalimumab group than the placebo group, p=0.001. [REDACTED] This group had previously received adalimumab and were selected for the randomised comparison as they were categorised as responders.

The MS does not report whether there was a statistically significant difference in the proportions achieving a DLQI of 0 between the adalimumab treatment group (33.3%) and the methotrexate treatment group (21.8%).

3.3.1.4 Quality of life – EQ-5D

The MS reports data on the EQ-5D from two of the included trials, M02-528⁸⁻¹³ and CHAMPION.²⁰⁻²⁴ The EQ-5D was presented as a Visual Analogue Scale (VAS) from 0-100 which assesses quality of life at a particular point in time, where higher scores correspond to the best health (the MS incorrectly notes that lower scores correspond to best health on page 53). The EQ-5D was also presented as an index score; this comprised of five dimensions of health and scores range from 0.0 (death) to 1.0 (perfect health).

On the EQ-5D index the mean change from baseline score was statistically significantly better in the adalimumab treated participants than in the placebo treated participants in both trials. Similarly on the EQ-5D VAS score the mean change from baseline was statistically significantly better in the adalimumab treated participants than the placebo participants in both trials. In the CHAMPION trials both measures were also statistically significantly better in the adalimumab arm when compared to the methotrexate arm.

Table 7 EQ-5D index mean change from baseline

Study	Adalimumab 40mg eow	Placebo	Methotrexate	P-Value vs. placebo
M02-528 ⁸⁻¹³ (12 weeks) †	0.21 (95% CI: 0.11, 0.31)	0.01 (95% CI: -0.07, 0.10).	n/a	p<0.001
CHAMPION ²⁰⁻²⁴ (16 weeks) ‡	0.21 ██████████	0.11 ██████████	0.10 ██████████	p=0.02*

† data for 95% CI were identified in the trial publication but not presented in the MS.

‡ trials report median change from baseline in EQ-5D index scores, mean scores presented therefore change from baseline scores estimated by ERG. ██████████

* p=0.004 adalimumab vs. methotrexate

Table 8 EQ-5D visual analogue score mean change from baseline

Study	Adalimumab 40mg eow	Placebo	Methotrexate	P-Value vs. placebo
M02-528 ⁸⁻¹³ (12 weeks) †	17.9 (95% CI: 10.5, 25.2)	0.5 (95% CI: -5.7, 6.8).	n/a	p<0.001
CHAMPION ²⁰⁻²⁴ (16 weeks) ‡	20.7	4.7	10.6	p<0.001*

† data for 95% CI were identified in the trial publication but not presented in the MS.

‡ mean endpoint scores not presented in the MS but presented in trial publication therefore change from baseline scores estimated by ERG.

* p=0.004 adalimumab vs. methotrexate

3.3.1.5 Quality of life – SF-36

Quality of life was measured using the SF-36 general quality of life score in two of the included trials (M02-528⁸⁻¹³ and REVEAL¹⁶⁻¹⁹). This scale produces two summary scores; one for overall mental health, the Mental Component Summary score (MCS) and one for physical health, the Physical Component Summary (PCS) score; and eight domain scores. SF-36 QoL scores are presented in the MS as mean improvement from baseline and the MCS and PCS scores are reproduced here. Higher scores represent better quality of life. On this measure participants treated with adalimumab showed statistically significantly better QoL than participants treated with placebo. The data were not presented in the MS or in the trial publications for many of the endpoint values but the p-values were presented (and the data were presented in the CSRs).

Table 9 SF-36 change from baseline

Study	Adalimumab 40mg eow	Placebo	P-Value vs. placebo
MCS			
M02-528 ⁸⁻¹³ (12 weeks)	7.8 ██████████ †	-0.1 ██████████ †	p<0.001
REVEAL ¹⁶⁻¹⁹ (16 weeks) Period A ‡	██████████	██████████	p<0.001
REVEAL ¹⁶⁻¹⁹ (19 weeks) Period C ‡*	██████████	██████████	██████████
PCS			

REVEAL ¹⁶⁻¹⁹ (16 weeks) Period A	██████████	██████████	p<0.001
REVEAL ¹⁶⁻¹⁹ (19 weeks) Period C†*	██████████	██████████	p=0.002

†mean scores not presented in the MS only p-value (CIC in REVEAL period C), mean change scores presented in CSR and reproduced here

*all patients previously given adalimumab for 32 weeks and classed as 'responders', re-randomised group only reported.

3.3.1.6 Results of the mixed treatment comparison

The MS Table 5.6.2 (MS p83) reports the results of the mixed treatment comparison in terms of the probability of achieving a PASI 50 response, a PASI 75 response, and a PASI 90 response for each drug and dose under consideration. Relative risks are also presented in this table with the estimates of the relative risk of a PASI 75 response also depicted in figure 5.6.2 (MS p84).

The mixed treatment comparison result for treatment with adalimumab 40mg every other week was a mean probability of achieving a PASI 75 response treatment of 67% (2.5%-97.5% credible interval 57-74%) in comparison to supportive care where the mean probability of achieving PASI 75 was 5% (2.5%-97.5% credible interval 4-6%). The mixed treatment comparison results for PASI 50 and PASI 90 were also in favour of adalimumab over supportive care.

The MS provides little in the way of narrative summary regarding the results of the mixed treatment comparison. The MS states that the probability of a PASI response was greater for either infliximab 5 mg/kg/day or adalimumab in comparison to both doses of etanercept by a statistically significant margin (no p-value reported), and that both doses of etanercept gave higher probabilities of PASI response compared to efalizumab and the non-biologic systemic therapies. The MS does not discuss any of the potential limitations of the analysis e.g. only two trials available contributing data to the outcomes on methotrexate, and this analysis does not incorporate adverse effects of treatments.

The pooled outcome data presented for most of the included treatments are broadly similar to those published in the Woolacott and colleagues TAR² both in terms of magnitude and direction of the response. An exception is the result for methotrexate which has a lower probability of PASI response in the MS. In the Woolacott and colleagues TAR only one trial contributed data on methotrexate. Although not discussed in the MS, the lower probability of PASI response for each of the three

PASI outcomes considered may be a consequence of the addition of the CHAMPION²⁰⁻²⁴ trial which contributes data on methotrexate to this outcome.

3.3.1.7 Adverse events

The MS provides data on adverse events which are ‘pooled’ from the included studies in two different ways. Firstly a ‘placebo-controlled study set’ pooled data from trials M02-528, ⁸⁻¹³ CHAMPION²⁰⁻²⁴ and period A of REVEAL¹⁶⁻¹⁹ for both placebo and adalimumab eow arms. Data from period C REVEAL and M02-538 were not included as participants in the placebo arms had previously received adalimumab. Alternatively an ‘all adalimumab treatment set’ pooled data from all participants receiving adalimumab, of any regimen, in any of the included studies (including the extension studies which the ERG has not included). The ERG consider here only the ‘placebo-controlled study set’ data.

The MS presents data for the three trials on incidence of adverse events and serious adverse events; discontinuations due to adverse events; non-serious infections and serious infections; incidence of non-melanoma skin cancers; injection site reactions; and other events such as congestive heart failure, malignancies and tuberculosis. Much of the data presented in the MS are marked as CIC and are presented predominantly in a descriptive manner (i.e., no actual data presented). This is particularly the case for data from the placebo arms of the trials. The MS (p86) reports that adalimumab was generally safe and well-tolerated and the incidence of any adverse events were consistent with the current safety profile (as observed in those receiving adalimumab for other indications) and do not represent new safety findings.

Data for the three trials on any adverse event, serious adverse events and discontinuations due to adverse events were extracted by the ERG from the trial publications. These data can be seen in Tables 10 to 12 below. These data are comparable with the information reported in the MS. The rates of any adverse events were similar in treatment and placebo arms; serious adverse events were comparable; and discontinuations due to adverse events were low and comparable between groups. The MS reports that the incidence of adverse events at least possibly related to study drug was statistically significantly higher in the adalimumab treatment group than the placebo groups. Data on the incidence of adverse events that were related to study drug were not presented in the publications of the three trials.

Table 10 Any adverse event

Study	Adalimumab 40mg eow	Placebo
MO2-528 ⁸⁻¹³ (12 weeks)	28/45 (62.2%)	35/52 (67.3%)
MO3-656 REVEAL ¹⁶⁻¹⁹ (Period A)	506/814 (62.2%)	221/398 (55.5%)
MO4-716 CHAMPION ²⁰⁻²⁴	79/108 (74%)	42/53 (79%)

As can be seen by the data presented in Table 10, 62-74% of participants in the adalimumab arms of these trials were likely to have any adverse event, and 55-79% of participants in the placebo arms were likely to have any adverse event. These rates appear to be similar although this is not based on any statistical analysis of the data.

Table 11 Any serious adverse event

Study	Adalimumab 40mg eow	Placebo
MO2-528 ⁸⁻¹³ (12 weeks)	1/45 (2.2%)	0/52
MO3-656 REVEAL ¹⁶⁻¹⁹ (Period A)	15/814 (1.8%)	7/389 (1.8%)
MO4-716 CHAMPION ²⁰⁻²⁴	2/108 (2%)	1/53 (2%)

On observation of the data from the three trials it would appear that the proportion of participants experiencing a serious adverse event is similar in the adalimumab treatment groups and the placebo treatment groups.

Table 12 Discontinuations due to adverse events

Study	Adalimumab 40mg eow	Placebo
MO2-528 ⁸⁻¹³ (12 weeks)	2/45 (4.4%)	1/52 (1.9%)
MO3-656 REVEAL ¹⁶⁻¹⁹ (Period A)†	14/814 (1.7%)	8/398 (2.0%)
MO4-716 CHAMPION ²⁰⁻²⁴	1/108 (1%)	1/53 (2%)

†Data in Table 2 of the publication by Menter et al¹⁸ suggests rates 10 and 4 for adalimumab and placebo groups respectively, but data in Table 3 suggests as presented above (as does Table 2 in Menter et al¹⁷).

Discontinuations due to adverse events is observably similar between the treatment arms and the placebo arms of the three trials.

The MS also presents safety data from one of adalimumab's other indications (rheumatoid arthritis) and data from an open-label study of adalimumab in participants with severe psoriasis and psoriatic arthritis which has not been checked by the ERG.

No data on adverse events are presented from the trials used in the mixed treatment comparison. The ERG is therefore unable to comment on the comparative safety with these other treatments for moderate-to-severe psoriasis.

3.4 Summary

Overall the MS contains an unbiased estimate of treatment efficacy for adalimumab based on the results of placebo-controlled comparisons. A standard pair-wise meta-analysis was not carried out, therefore the only indication of the overall efficacy of the intervention comes from the results of the mixed treatment comparison. The MS provides a very general statement that adalimumab has demonstrated clear efficacy in the treatment of moderate to severe psoriasis in section 5.9 (MS p90).

The population and intervention stated in the decision problem were defined in relation to the proposed licensed indication. The appropriateness of the evidence discussed in the MS to the stated decision problem is therefore dependent on the final wording of the licensed indication for treatment with adalimumab. At the time of assessment (October to November 2007) adalimumab had not received its licence and during the ERG assessment a change was made to the proposed licensed indication.

The interpretation of clinical evidence (MS section 5.9, p90) highlights a number of areas for consideration regarding the relevance of the evidence base for the decision problem and issues relating to current clinical practice:

Severity of psoriasis

The MS states that adalimumab is highly efficacious in the most severe group of psoriasis patients (BSA >20% in the CHAMPION trial). This is related to a subgroup analysis undertaken by the manufacturer. The MS states that trial participants in the two pivotal phase III trials, M03-656 REVEAL and M04-716 CHAMPION were comparable to patients with severe psoriasis in England and Wales.

Prior treatment history

The MS notes that there is limited published evidence that response rates vary for treatments according to prior treatment exposure, and state that the limited available data indicate that there is no difference in efficacy according to whether patients have received prior systemic therapy or not. The ERG would reiterate concerns about whether trial populations were comparable in terms of previous treatment.

Intermittent vs. continuous therapy

The MS has included continuous use of etanercept as a treatment option in the economic model to better accurately reflect current management of psoriasis in the UK.

Relative efficacy of adalimumab versus systemic therapy, Methotrexate dosing in CHAMPION study and High placebo response in M04-716 (CHAMPION)

The MS reports that M04-716, the CHAMPION trial, is the first to provide head to head RCT evidence that adalimumab is more efficacious than methotrexate and suggests that this adds weight to the evidence for the effectiveness of adalimumab. The ERG notes that participants in this trial differed from those in the other adalimumab trials because they were required to be naïve to methotrexate treatment. The dose of methotrexate used in the CHAMPION study started at 7.5mg per week rising by increments of 2.5mg at week 2, and 5mgs at week 4, with further 5 mg increments at weeks eight and 12 in those subjects with a sub-therapeutic response (and no safety concerns). The ERG suggest that the methotrexate dosing in this study is broadly in line with that stated in BAD guidelines²⁶ which suggest a small test dose of 5mg, followed by increases in 2.5 to 5mg steps according to clinical response and any toxicity. The BAD guidelines state that most patients would be adequately controlled on doses of 7.5-15mg weekly, and few patients require more than 20mg. The MS states that they followed the BAD guidelines recommendation that folic acid supplementation be provided to psoriasis patients receiving methotrexate treatment to prevent some of the adverse effects associated with methotrexate treatment. Therefore, to maintain blinding, all patients in the CHAMPION study received folates. The MS speculates that the high placebo response rates (19% of placebo patients achieving PASI 75% at week 16) may be due to the effects of providing folate.

[REDACTED]

[REDACTED]

[REDACTED]

The relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in clinical practice

The MS has highlighted the observed relationship between PASI response and EQ-5D scores and states that the correlation between these measures indicates that the main clinical outcomes assessed in the MS are useful in estimating the clinical benefits experienced by patients.

Long-term efficacy data for adalimumab and adalimumab dosing

The MS stresses that much of the data from the key trials contributing to the evidence base on efficacy relate to the 40mg eow dose. This is the anticipated dose in the licensed indication for adalimumab for the treatment of psoriasis. The MS highlights the difficulty of obtaining long-term efficacy data in comparison to placebo in an RCT setting. Long term data from the open-label extension trials are as yet few (120 weeks, n=49) but the MS states that the results show that patients can sustain a clinical response for two years. The ERG would suggest that longer term head to head randomised comparisons of active treatments are desirable.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission includes:

- A systematic review of the economic literature. The review aimed to identify published economic evaluations of therapies used for psoriasis excluding topical treatments. Six studies were identified. These included the appraisal of etanercept and efalizumab for psoriasis commissioned by NICE.² This will be extensively referred to in this report as either the York report or the York Model. All six studies identified are described in the MS, with a brief critical appraisal.
- A report of the economic model carried out by Abbott Laboratories as part of the STA process. The MS includes an economic model of treatments for psoriasis including biological therapies (adalimumab, efalizumab, etanercept, infliximab) and also two systemic treatments (ciclosporin and methotrexate), detailed in section 6.2.3 of the MS. The decision problem was stated as being the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA, MS section 1.3, p4. The model includes a series of one-way sensitivity analyses,

a probabilistic sensitivity analysis and also an expected value of perfect information analysis.

4.2 Cost-effectiveness analysis methods

The model assumes individuals have a short period of therapy during which their response to treatment is assessed, this is referred to in the report as the trial period. Individuals will continue treatment if they have a sufficiently good response at the end of this trial period. Those who respond adequately progress to treatment for a maximum of ten years. The expected length of time that individuals would spend receiving treatment after the trial period was stated as having been estimated through a Markov type process using a discount rate of 3.5%. Treatment effectiveness is defined in terms of the number of individuals who achieve defined responses from baseline PASI score. These changes were combined with estimates of the quality of life improvements associated with a reduction in PASI score. The direct costs associated with each therapy and also costs associated with being a non-responder to treatment are included in the model. The analysis is based closely upon the York Model.

4.2.1 Natural history

The modelling of disease progression closely follows that used in the York model. Individuals are assumed to be in one of two health states, responders or non-responders. These categories are based upon response to treatment in an initial trial period. Response to treatment is defined in terms of change in PASI scores from baseline and the response category corresponding to different changes in PASI score are presented in Table 13. The analysis assumes that the disease is non-progressive once severe. Individuals who respond to treatment remain at the same PASI response level for as long as they remain responders. Non-responders remain at the same PASI response category they achieved at the end of the trial period. There is no mortality assumed in the model.

Table 13 Definition of responders and non-responders used in the economic model

Change in PASI score	Response Category
<50%	Non-Responder
≥50% and <75%	Non-Responder
≥75% and <90%	Responder
≥90%	Responder

4.2.2 Treatment effectiveness

Treatment effectiveness is defined in terms of a change in PASI score from baseline, achieved at the end of the trial period. No other indicator of effectiveness is used in the model. Evidence was synthesised from a variety of trials by including direct and indirect treatment comparisons in a mixed treatment comparison to obtain response rates for all therapies considered in the model. Non-responders are assumed to have PASI response rates equivalent to supportive care.

4.2.3 Health related quality-of-life

Patients' health related quality of life in the model was assumed to be related to changes in PASI score. A change in quality of life was assigned to each of the PASI responses used in the model. Quality of life changes associated with PASI responses were estimated from data obtained from two of the RCTs (MO4-716 (Champion), and MO2-528), see ERG report, section 3.1.2.1, for further details of these studies. Quality of life values associated with each PASI response were multiplied by the proportions of individuals achieving each of these responses as indicated by the evidence synthesis presented in the MS Table 5.6.2 (MS p83). These values were then multiplied by the length of time individuals spent on the therapies in the trial and treatment periods to generate estimated QALYs for each of the therapies and for supportive care.

4.2.4 Resources and costs

Resources included in the model were: acquisition cost of therapies; blood tests and monitoring; outpatient visits; and inpatient care for individuals on supportive care. Part of the cost of systemic therapies were offset by savings made by reducing the number of individuals on supportive care.

4.2.5 Discounting

Both costs and health benefits were stated as being discounted at 3.5%

4.2.6 Sensitivity analyses

A series of one-way sensitivity analyses were carried out and these are presented in the MS, Tables 6.3.3.1 to 6.3.3.3 (MS p127-9). Also presented in the MS are the results of a probabilistic sensitivity analysis (PSA) and an expected value of perfect information analysis.

4.2.7 Model validation

The model was validated by comparison to the York model. In addition, models were developed using two computer packages and results were compared.

4.2.8 Results

Results are presented as ICERs (Table 14, from MS Table 6.3.1.1, page 118), 95% confidence interval contour plots, cost-effectiveness acceptability curves (CEACs), and annual expected value of perfect information. These are all obtained from a probabilistic model. In addition the MS presents results as a cost-effective ordering of therapies with increasing value of the cost-effectiveness threshold, i.e. with a given value of a QALY which therapy is the most likely to be cost-effective, which is the next most likely and so on. In addition, a series of one-way sensitivity analyses are presented, both in terms of ICERs, and also incremental cost and incremental effects. The MS reports results for biological therapies and systemic therapies (methotrexate and ciclosporin) compared to supportive care. The MS also presents results for ciclosporin and methotrexate, however as the proposed license indication is for individuals who were not candidates for systemic therapies_(see ERG report, section 2.3.1 for more details) the results in Table 14 include only supportive care and biological therapies. If the situation was amended to include patients who were eligible for systemic therapy then the comparator for biological therapy would be the best performing systemic agent. Using the values given in the MS, Table 6.3.1.1 the ICER for adalimumab compared to methotrexate would be approximately £250,000 per QALY and hence it appears unlikely that biological therapies would be cost-effective in patients eligible for systemic therapy.

Table 14 Results of base case scenario (annualised) for supportive care and biological treatments, taken from MS Table 6.3.1.1

	Mean QALY (95% CI)	Mean Cost (£) (95% CI)	ICER	ICER vs. Supportive Care
Supportive Care	0 (0 - 0)	0 (0 - 0)	-	-
Etanercept Intermittent [†]	0.110 (0.070 - 0.153)	4,114 (2,862 - 5,335)	Extended Domination**	37,284
Etanercept High Intermittent [†]	0.123 (0.081 - 0.166)	4,699 (3,532 - 5,865)	Extended Domination**	38,358
Efalizumab	0.124 (0.077 - 0.173)	4,942 (3,855 - 6,002)	Extended Dominated**	39,948
Adalimumab	0.164 (0.110 - 0.219)	4,993 (3,806 - 6,157)	30,538	30,538
Etanercept	0.134 (0.085 - 0.186)	5,058 (3,928 - 6,169)	Dominated*	37,676

Infliximab	0.182 (0.126 - 0.240)	7,736 (6,515 - 8,945)	147,906	42,492
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[†] Denotes intermittent use – where use is stopped upon remission and restarted upon relapse

* A treatment is dominated if an alternative has lower costs and higher effectiveness

** Extended domination refers to cases where the ICER is higher than that of another drug even though one of either costs or QALYs is more favourable

4.3 Critical appraisal of the manufacturer's submitted economic evaluation

4.3.1 Critical appraisal of economic evaluation methods

The ERG has considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 15 below, drawn from common checklists for economic evaluation methods (e.g. Drummond et al 1997²⁷).

Table 15 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	The decision problem is described in the MS on page 7. The MS estimates the cost-effectiveness of treatment with adalimumab for adults with moderate to severe chronic plaque psoriasis.
Is there a clear description of alternatives?	Yes	The MS specified the alternative treatments for psoriasis in the decision problem (MS p7) and in section 6.2.3 (MS p100) specifies comparators associated dosages. These are: <ul style="list-style-type: none"> ▪ Etanercept – 25mg twice weekly (BIW) ▪ Etanercept High – 50mg BIW ▪ Efalizumab – 1mg/kg per week ▪ Infliximab – 5mg/kg weeks 0,2, and 6, and every 8 weeks thereafter ▪ Adalimumab – 40 mg every other week
Has the correct patient group / population of interest been clearly stated?	Yes?	The base case analysis is for those with DLQI > 10 who have failed systemic therapy or for patients for whom systemic therapy is contraindicated or inappropriate. It was unclear as whether this represented a severe group or a moderate/severe group as the base line PASI score of was not indicated.
Is the correct comparator used?	Yes	All alternative treatments shown above are compared to supportive care. In addition, incremental analysis is shown in some cases comparing one biological therapy with another. The MS puts most emphasis on results of biological therapies and supportive care, see ERG report section 4.4.1.2 for more discussion on this. Intermittent etanercept was included as a comparator although the clinical expert consulted by the ERG stated that continuous etanercept is more representative of routine clinical practice.
Is the study type reasonable?	Yes	Cost-utility analysis is reasonable, as the major effects of biologics would be improvement in quality of life.
Is the perspective of the analysis clearly	Yes	The MS section 6.2.4, p101. Perspective is in accordance with the NICE framework.

stated?		
Is the perspective employed appropriate?	Yes	Perspective is that of the NHS with direct costs and benefits to the NHS only. The MS also included a sensitivity analysis that included the productivity costs for non-responders who are hospitalised.
Is effectiveness of the intervention established?	Yes?	A mixed treatment comparison evidence synthesis was run to determine the comparative efficacy of the various treatments, in terms of PASI response. See section 3.1.5 for ERG critique of this analysis. The effectiveness, in terms of quality of life, was taken from two adalimumab trials.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes?	The time horizon was 10 years in common with the York model. This was only justified to the extent that it was used in the York model
Are the costs and consequences consistent with the perspective employed?	Yes	Only uses NHS costs
Is differential timing considered?	No	The York report uses discounting to reduce the time on treatment for responders but the MS does not include discounting.
Is incremental analysis performed?	Yes	Given in the MS Table 6.3.1.1 (MS p118) for base case and Table 6.3.3.1 for sensitivity analysis (MS p127)
Is sensitivity analysis undertaken and presented clearly?	Yes	One way sensitivity analyses presented in Table 6.3.3.1 of the MS. Probabilistic Sensitivity Analysis results also presented in the form of CEACs (MS Figure 6.3.1.4, p122) and 95% confidence interval contour plots (MS Figure 6.3.1.2, p120). Also presented is an EVPI (MS, Figure 6.3.1.5, p123).

* The MS notes that greater than 3mg/kg per day was determined to be related to high toxicities (personal communication to the MS authors by S Feldman, MD)

NICE reference case

Table 16 NICE reference case requirements

NICE reference case requirements (see detail in NICE report):	Included in Submission
Decision problem: As per the scope developed by NICE Comparator: Alternative therapies routinely used in the UK NHS Perspective on costs: NHS and PSS Perspective on outcomes: All health effects on individuals Type of economic evaluation: Cost-effectiveness analysis Synthesis of evidence on outcomes: Based on a systematic review Measure of health benefits: QALYs Description of health states for QALY calculations: Use of a standardised and validated generic instrument Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale) Source of preference data: Representative sample of the public Discount rate: 3.5% pa for costs and health effects	Yes? ^a Yes Yes ^b Yes? ^c Yes Yes Yes ^d Yes ^e Yes No

- Base case includes individuals with DLQI>10. Scope calls for moderate to severe
- Costs are for NHS only
- Only those health effects associated with reductions in PASI score
- EQ-5D

- e. It was not clear from the MS what scoring method was used to assign preferences to the EQ-5D health states. Clarification was sought from the manufacturer who confirmed that the UK scoring system (based on the TTO) had been used for all EQ-5D data (ERG report, appendix 1, section B3).

4.4 Modelling methods

An outline critical review of modelling methods has been undertaken by the ERG. The review has used the framework for good practice in modelling presented by Philips and Colleagues (2004)²⁸ as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty.

4.4.1 Modelling approach / Model Structure

The MS presents a clinical pathway for the model in Figure 6.2.6.1 (MS p102), however this clinical pathway does not appear to represent the model structure. The diagram suggests patients switch between treatments if they do not respond to a particular treatment which the model does not. Furthermore the MS does not provide a clear explanation of the model, i.e. no equations are given relating to key calculations such as the derivation of costs and utilities.

The model comprises two periods, a trial and a treatment period. The model estimates the cost and utility benefit for each of these periods for each of the treatments and compares them with supportive care. The trial period lasts for between 12 and 16 weeks (16 weeks for adalimumab) and all patients in each group receive the intervention being evaluated. Patients in the trial period are assigned a probability of achieving a PASI response as determined by the mixed treatment comparison, as detailed in the MS Table 5.6.2 (MS p83). The QALY gains achieved in the trial period are calculated by multiplying the probability of being in any particular PASI response state by the quality of life benefit provided by that PASI response, detailed in the MS section 6.2.7.3 (MS p105 to 108). The costs of each therapy for this period are detailed in the MS section 6.2.9.1 (MS p111-2). Those who respond to treatment in the trial period (defined as PASI ≥ 75 or PASI ≥ 90) continue with treatment during the treatment period and are assumed to stay at this level of improvement for a period of time and then become a non-responder. The average duration of treatment is estimated using an annual drop out rate of 20%. The average treatment duration was calculated as 186 weeks. Those who respond to treatment incur both the drug treatment cost and the QALY benefit for this 186 week period. Those who do not respond to treatment receive non-responder supportive care, again for this same time period. The model estimates the total costs and benefits for

all the treatments and these are compared to supportive care for the same time period equivalent to the trial and treatment period.

4.4.1.1 Structural Assumptions

The structure of the model is based upon that used in the York report². From analysis of the spreadsheet model and the MS report the ERG considers that the structure of the model is reasonable and reflects the disease under evaluation.

The MS provides a list of assumptions and justification for each of these assumptions.

- i) It is assumed that once severe, the disease is not progressive and the chances of obtaining clear, controlled skin remain possible.
- ii) It is assumed that the treatment effect for each treatment is independent of order. Furthermore, it is assumed that failure of a particular treatment does not preclude the use of any other subsequent treatments.
- iii) The benefits from treatments are determined by examination of their impact on disease severity, specifically their impact on PASI response. It is assumed that the PASI response discriminates all the benefits of treatment. In other words a PASI 75 responder will have the same improvement in utility regardless of the treatment received.
- iv) The model excludes adverse effects of treatment from the calculation of costs and QALYs.

As noted by the MS, these assumptions have previously been employed in the York model, on which the manufacturer's model is based, and the ERG considers these assumptions to be reasonable.

In the base case model, all those with a PASI response above 75% continue treatment. This is in line with BAD guidelines⁴ for the use of biological interventions in psoriasis and NICE final guidance TA103 of efalizumab and etanercept.¹ However patients with a PASI response of 50% and a five point reduction in DLQI from when treatment started are also candidates for biologic treatments according to this guidance. Therefore a proportion of these patients may, in practice, receive further treatment. The MS has investigated the effect on subgroups of patients with <75% PASI response in the sensitivity analysis.

In order to estimate the treatment period, the model uses a cycle length of 12 months, a 10 year time horizon, and assumes that 20% of patients will drop out from treatment each year. With this drop out rate, the time horizon is reasonable, as after 10 years only about 10% of patients would still be receiving treatment. In addition, the MS also assumes that response to treatment is constant over time, i.e. drop out rates calculated over the short term can be applied to the full ten year span of the model. The model assumes that for an individual on treatment the transition from treatment to supportive care is costless, i.e. it is not associated with any inpatient or outpatient care. This was also felt to be reasonable by the ERG clinical expert.

The MS states that costs and health benefits occurring in future years were discounted at 3.5% but the ERG was unable to find evidence of this. The York report only uses discounting to estimate the length of the treatment period. The undiscounted treatment period in the MS is 186 weeks. If discounted at 3.5% the duration of treatment for measuring both costs and benefits would have been 169 weeks. The treatment period is slightly longer in the MS than it would be if discounting had been used but this appears to have little effect on the results presented.

The MS differs from the York model in its treatment of health gains for intermittent etanercept. In the York model individuals spend a period of time on treatment, then treatment is discontinued until a disease flare up. Treatment is then re-started. According to the MS, patients are likely to experience a reduction in utility upon the occurrence of each flare up while they wait for the treatment to take effect as the recommencement of treatment and the effect of treatment are not instantaneous. The ERG considers that this is not consistent with the current structure of the model as the model assumes an instantaneous benefit of the treatment during the trial period.

4.4.1.2 Data Inputs

Patient Group

It is stated in the MS section 6.2.2.1 (MS p100) that the base case considered the treatment of moderate to severe psoriasis in patients who have failed systemic therapy or for patients for whom systemic therapy is contraindicated or inappropriate, but the ERG found it difficult to determine if this was the case. Severe psoriasis can be defined as PASI ≥ 10 AND DLQI $> 10^4$ but it was not clear whether the evidence used by the MS fell within or outside this category. There were two pieces of evidence used in the model to determine outcomes for which the ERG expected

severity to have an effect. These are the PASI response rates to treatment and the quality of life change associated with PASI response rates.

Evidence on PASI response rates were obtained from a mixed treatment comparison (MS Table 5.6.2, p83). This included studies that had a range of severity-related inclusion criteria, see ERG report, section 3.1.2 for details regarding the adalimumab evidence. Fewer details were given relating to evidence used in the mixed treatment comparison for other treatments, see ERG section 3.1.5 for more details. Therefore it is not clear what proportion of the individuals from these trials would fall into a severe, or a moderate severity group. It is also not clear if similar or different effectiveness results would have been obtained if only severe, or moderate to severe individuals had been included.

The utility gains associated with different PASI response rates were obtained for groups of individuals divided on the basis of DLQI scores. These were $DLQI > 10$, $DLQI \leq 10$, and an all patient group, with $DLQI > 10$ being defined as the base case. It is not clear what PASI scores the individuals who provided these utility data had at baseline. They were drawn from two RCTs: MO4-716 (Champion) had an inclusion criterion of $PASI \geq 10$ (MS p41) but MO2-528 had an entry criterion of $\geq 5\%$ BSA involvement at screening and baseline (MS p38). So it is not clear how many individuals in the $DLQI > 10$ group also had $PASI \geq 10$. Clarification regarding this was sought from the manufacturer. The mean PASI scores for trial MO2-528 were 13.7 and 17.3 for $DLQI \leq 10$ and $DLQI > 10$ respectively. For trial MO4-716 the corresponding figures were 18.8 and 19.9. Because of this it was not possible to say that this group had severe rather than moderate to severe psoriasis. However, it seems likely that the majority of individuals used for the utility estimates in the group whose DLQI was > 10 would have been categorised as severe rather than moderate to severe, especially as MO4-716 is the larger trial.

One sensitivity analysis included individuals who had a $DLQI \leq 10$, see ERG report Table 21. With this group it is possible to categorise the degree of severity by the definition given above; this group would be categorised as moderate.

The MS states that the anticipated indication for psoriasis covers the following population (MS p4):

- Treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate or PUVA

This patient group can be analysed with respect to the comparator used in the economic evaluation. For this group systemic therapies are not appropriate therefore adalimumab can be compared to supportive care or other biological therapies.

Clinical Effectiveness

Psoriasis was assumed not to be progressive. Outcomes in the model were linked to changes in PASI scores as indicated by the mixed treatment comparison model as given in Table 5.6.2 (MS p83). The ERG critique of these methods is given in this document, section 3.1.5 p34. The key concern related to how closely patients in the comparator trials matched those eligible for adalimumab treatment. The data presented in Table 5.6.2. of the MS indicate that infliximab appears to be the most effective drug followed by adalimumab. Those individuals who achieved PASI response rates of 75% or better were classified as responders and assumed to proceed with treatment. All individuals were assumed to remain in the states achieved at the end of the trial period for as long as they remain a responder.

No adverse events associated with any treatment were included in the model (MS section 6.2.7.4, p109). The MS reports that there is no clear evidence on the existence of adverse events and their frequency. The evidence for this was taken from Pearce and colleagues²⁹ who provide evidence on 181 individuals treated with methotrexate, 16 with ciclosporin and 29 with biologics. For methotrexate 50% of patients had adverse event and 34% had significant adverse events. For ciclosporin 75% had adverse events and 63% had significant adverse events. For biologics 10% had adverse events and 0% had significant adverse events. However this is a very small study with respect to ciclosporin and biologics, in addition no rates are given for a no treatment or control group. The MS states that excluding adverse events will overstate the benefits of systemic medications and understate their cost but does not believe this will significantly affect the results. However, no comment is made on the effect this might have on results for biologics. Compared to supportive care including adverse events for biologics should (provided these are greater than supportive care) increase the cost and decrease the QALY gain of biological therapies but the ERG

have no view on the magnitude of these effects. Adverse events in the trials are discussed in more detail in ERG report section 3.3.1.7 (p45).

Patient outcomes

The quality of life benefits associated with changes in PASI were estimated in the following way. There were 395 patients from two adalimumab RCTs (MO2-528 and MO4-716 Champion) for which data on reduction in both PASI scores and EQ-5D values were available. The MS stated that a mixed model with repeated measures of analysis of covariance was used to assess the relationship between changes in EQ-5D and clinical response (MS, page 106). However, the ERG felt that insufficient details were given in the MS to fully understand the methods used though it appeared to be based on individual patient data analyses. Data from this analysis were used to infer the relationship between PASI response and QALY for three patient sub-groups, $DLQI > 10$, $DLQI \leq 10$ and all patients. The PASI responses produced by the different drugs from the mixed treatment comparison model were then combined with these quality of life differences to infer the quality of life improvement associated with drug treatment.

Health states were measured by means of a generic instrument (EQ-5D). This was obtained at different times depending upon the trial used. One trial assessed at 0 and 12 weeks. The other assessed at 0, 12, and 16 weeks. In both cases changes in PASI responses were related to changes in EQ-5D by means of a mathematical model. It was not clear to the ERG as to which method was used to score the EQ-5D health states. Clarification was sought from the manufacturer who confirmed that UK values were used in all cases. Health states associated with adverse events were specifically excluded.

Values are presented for the four response categories set out in Table 13. However, in the MS values are amalgamated for the 50% to 75% and the 75% to 90% response categories. These values are given in the MS in Figure 6.2.7.1, page 107, where it can be seen that the amalgamated value is higher than the estimate for the 75-90% group. Because of the assumption of the base case model those who have a response of 50-75% are not considered responders and do not continue on treatment. The effect of the amalgamation is therefore to slightly increase the estimate of the QALY gains associated with response to treatment. This causes a small increase in the estimated ICERs, see ERG report section 4.4.1.4 (Scenario Analysis) for more details.

This overall approach taken in the MS appears to be consistent with the NICE reference case. It also appears to be an improvement on the method used in the York report, whose authors did not have access to direct trial data linking PASI response rates to changes in EQ-5D.

Resource use

The following resource categories were included: drug costs; monitoring costs; administration costs; outpatient costs and inpatient costs (for non-responders only). Productivity costs associated with time off work were included in a sensitivity analysis.

The drug doses required for the trial and treatment periods are given in Table 17. This replicates information given in the MS (Table 6.2.9.2, MS p112). The ERG has a number of comments relating to the assumptions used to estimate resource use.

Table 17 Drug doses for the trial and treatment periods

Drug	Trial period (weeks)	Doses in trial period	Treatment period doses per year
Adalimumab	16	10	26
Etanercept intermittent	12	24	91
Etanercept 50mg intermittent	12	18	48
Etanercept continuous	12	24	104
Efalizumab	12	13	52
Ciclosporin	12	84	161

For therapies where the dose is body weight dependent a value of 80 Kg was assumed, this affects infliximab and efalizumab. For etanercept 25 mg the trial period drug use is the same for continuous and intermittent therapies. This equates to 24 doses in a 12 week trial period. For the treatment period, continuous etanercept 25mg is assumed to require 104 doses per year. Intermittent etanercept is assumed to require a percentage (88%) of 104 doses. The percentage value of 88% is taken from analysis of Integrated Healthcare Information Services (IHCIS) data given in the

MS Section 9.4, (MS Appendix 4 p148). However, this contrasts with the assumptions made in the MS in Figure 6.2.7.3 relating to how the utility gain from intermittent etanercept is calculated. Figure 6.2.7.3 calculates utility on the basis that individuals would spend 84 days on treatment then 39.6 days off treatment. This equates to spending 68% of the time on drug treatment. It seems inconsistent to calculate the costs based on spending a percentage (88%) of the time on etanercept and the utility gains assuming that a different percentage (68%) of the time is spent on etanercept. For etanercept 50mg, the assumption is made that 18 doses would be needed for the trial period and 48 per year for the treatment period (this assumes an intermittent dose is a percentage [46%] of the full dose). It was unclear from the report why therapy would be intermittent in the trial period and why the given percentage value of 46% was used in the treatment period.

Finally, infliximab usage was calculated based on four infusions in the trial period and 6.5 infusions per year subsequently. The four trial period doses are given in weeks 0, 2, 6, and 14. It is unclear why the fourth infusion was incurred in the trial period. Consultation with the clinical expert indicated that it would be likely that the individual would be assessed at week 14 before the decision to give the fourth infusion. The ERG estimated that a trial period plus one year of therapy would require three infusions in the trial period and 6.5 infusions in the treatment period. The method used in the MS would assume four and 6.5 and hence appears to overstate the requirement for infusions.

Monitoring, drug administration and outpatient costs

The analysis does not include tests or visits necessary to determine suitability for treatment. The reason given in the MS (p112) was lack of evidence. However these tests are likely to be associated with low resource implications and so would have a limited effect on the model. All strategies are assumed to require some degree of routine monitoring or use of blood tests. The schedule of routine monitoring required is taken directly from the York Report. As well as laboratory costs these would be associated with staff time required to carry out tests and discuss the test results. However, tests are assumed to be carried out during routine outpatient visits so additional staff time would not be included. It was not clear from the MS how trial period monitoring costs were calculated. Adalimumab costs are the same in the trial and treatment periods. Etanercept and efalizumab are assumed to require two thirds of the annual monitoring resource use and infliximab is assumed to require 50%.

However, the costs of these resources were extremely small in comparison to total costs and hence unlikely to significantly alter results.

Resources are also associated with the administration of some of the treatments considered. For adalimumab, etanercept, and efalizumab there are three 1-hour sessions with a nurse to receive training in self injection. These occur in the trial period only, and there are no administration resource implications in the treatment period for these drugs. Infliximab requires an infusion given in an outpatient setting, the MS assumes that four visits are required in the trial period and 6.5 visits are required per year in the treatment period.

Each treatment strategy is also associated with a requirement for outpatient visits, Table 18. The values shown in Table 18 are based upon the number of visits needed to generate the costs shown in the MS Table 6.2.9.7 (MS p114). For infliximab some of this care is assumed to be received in infusion visits. Only those visits that are additional to infusion visits are counted as extra outpatient visits, i.e. total outpatient visits in the trial period are five, four of these are infusion visits and so only one extra outpatient visit is included for resource use.

Table 18 Outpatient visit requirements

(Based on MS Table 6.2.9.7 & information derived from the MS spreadsheet model)

Outpatient only	Total trial	Total treatment
Supportive care	0	2
Adalimumab	4	4
Etanercept 25mg intermittent	3	4
Etanercept 50mg intermittent	3	4
Etanercept continuous	3	4
Efalizumab	3	4
Infliximab	5	7.5

Inpatient stays

The York model uses 21 days as an annual requirement for inpatient care. The MS also presents evidence from a review of studies showing a range of lengths of stay from 16 to 39 days (MS Table 6.2.9.8, p114). The MS used the value of 21 days and this was justified on the basis that it used evidence from UK based data (MS p114). The MS gives the source of this data as a combination of data from the Department of Health Hospital Episode Statistics (HES, 2002/3) and evidence from audit of two hospitals (MS p114). Evidence was also provided from a German study that

suggested that only 40% of individuals would need an annual inpatient stay, however if a stay was required the necessary length would be 49 days.³⁰ This was used as a sensitivity analysis by the MS but the ERG consider the resource implications of this would be similar to that of the base case (40% of 49 days would be 19.6 days). The ERG considers that there are no clear data pointing to the use of any particular value and that there is considerable uncertainty here. Furthermore the ERG was unsure whether every non responder would have an inpatient stay each year and the effect of only 40% of non responders having an inpatient stay each year was explored in the ERG scenario analyses.

Costs

Unit costs for drugs were obtained from the BNF 53.³¹ All prices in Table 6.2.9.1 (MS p112) were checked against BNF 53 and were correct. However, for efalizumab there was an error in the calculation of the price per mg presented in the MS which should be £1.35 rather than £0.35. The cost used in the MS model appeared to be correct. Costs were checked for trial and treatment period and mostly matched values obtained by the ERG. For etanercept 50mg the MS reports that 18 doses would be need in the trial period and 48 in the treatment period associated with costs of £3,166 and £8,607 respectively. The ERG found small discrepancies with these figures, presumably from rounding errors. Other total annual costs appeared correct.

Administration costs during the trial period for adalimumab, etanercept, and efalizumab were £105, or £35 per session for injection training. Two different outpatient visit costs are used in the MS. Both are derived from NHS reference costs health resource group (HRG) codes for outpatients³². For infliximab there is a value of £322 in the trial period. This corresponds to four £80 outpatient visits (with rounding error). This cost was derived from NHS reference costs and used code J09op (major dermatological conditions: other attendance with other investigation or procedure). In the treatment period there is an annual cost of £523. This equates to six and a half £80 outpatient visits per year. The use of this cost for an outpatient visit rather than a standard one (HRG code J10op) seems reasonable as part of the care required is a 1-2 hour infusion. In addition to the costs given above for infliximab there is one non-infusion outpatient visit assumed in both the trial and the treatment periods. For non-infusion outpatient visits a health care resource group (HRG) cost of £58 is used corresponding to outpatient code J10op (Major dermatological conditions; other attendance without other investigation or procedure). This cost is also used for the cost of outpatient visits for all other treatment strategies. For both

costs NHS reference costs data is used from an earlier year and updated. However, the year of the original data and the methods used to update are not given.

The MS presents costs for the components of the strategies as outlined above (MS p112-114). However, no total is given for trial and annual treatment costs in the text. The total trial and annual treatment costs for each strategy are presented in Table 19. In addition, the ERG estimated the total trial cost for infliximab if three infusions rather than four are given (£5,350). It should be noted that the annual cost for the treatment period for supportive care is given in the spreadsheet model in the parameters sheet but it did not appear to be used in the equation to derive total cost for each strategy, i.e. an estimate is made in the MS spreadsheet model, for each drug strategy, of the avoided supportive care costs. These are given as the cost of hospitalisations multiplied by the expected use of hospitalisations in the supportive care group (this is the probability of non-response with supportive care). This calculation included the cost of hospitalisation but not outpatient visits.

Table 19 Estimated Total Trial and Total Annual Treatment Costs

	MS	
	Total cost, Trial period	Total annual cost, Treatment period
Supportive care	£0	£117
Adalimumab	£3,925	£9,540
Etanercept 25mg intermittent	£2,433	£8,406
Etanercept 50mg intermittent	£3,454	£8,852
Etanercept continuous	£2,433	£9,540
Efalizumab	£2,496	£9,056
Infliximab	£7,102	£11,508

4.4.1.3 Consistency

Internal consistency

Random checking of the Excel model has been carried out for some of the key equations in the model. The ERG has not undertaken a comprehensive check of all cells in the model. The model is fully executable but has not been set up to run deterministic analyses, rather it is run as a probabilistic sensitivity analysis with multiple simulations. The manufacturer's model is reasonably presented and user friendly. The model is run from the 'Strategy' worksheet by choosing an appropriate scenario and clicking on the 'Run scenario' button. The scenarios are those shown in Table 6.2.11.1 (MS p116) for the univariate sensitivity analyses. The ERG found that running the model with 10,000 simulations, as suggested, took almost an hour and

so, for the purposes of checking internal consistency, ran the model with 1000 simulations instead. The model includes a worksheet that summarises the model inputs (clinical effect parameters, cost and utilities) on the 'Inputs' worksheet. These parameters can be changed to run different analyses than those presented in the MS. The ERG views the model as a reasonable approach to modelling the cost-effectiveness of adalimumab and from random checking the 'wiring' of the model appears to be accurate. Furthermore, model checking showed that the results were in the expected directions and had expected magnitudes. The ERG checked the results from the model using the equations from the York report and found that the results were similar.

All results are presented as incremental to supportive care, i.e. the costs and QALYs generated by supportive care were zero and the costs and QALYs of all other strategies were compared to supportive care. The ERG found this less transparent than presenting the total costs and QALYs generated of all strategies and calculating incremental costs from this. In addition, the MS calculated an annual cost and QALY by dividing the total incremental cost of each strategy by the length of the trial period plus the length of time on treatment (this was calculated by multiplying the total time on treatment by the response rate for each treatment). The ICERs for all drug treatment compared to supportive care were the same for this annual cost as they were for the total costs (compared to supportive care) given in the MS. However, the ERG found a difference in the ICERs between drug treatments depending upon which method was used, total or annual incremental values. For example, in the base case the ICER for infliximab compared to adalimumab was approximately £150,000 per QALY with annual equivalent values and approximately £80,000 with total incremental values.

External consistency

The MS states, section 6.2.13, page 117, that the model has been tested for validity 'in terms of replicating the results of the previously published York model' and the details of this validation are provided in the MS Appendix 9.5. The appendix shows replication of the York results using the manufacturer's model together with the inputs from the York report. The ICERs generated in the replication were within 1-2% of the original York results.

Furthermore, the manufacturer stated that the model had been validated through development of two alternative software formats (Microsoft Excel and R) although the

ERG received only one of these (Microsoft Excel), section 6.2.13, page 117. The MS stated that through building these models they were able to eradicate errors as the model results for the two formats were the same.

The ERG was uncertain whether the data estimates in the mixed treatment comparison were correct. The ERG ran the model using data from the largest trial for adalimumab versus placebo (REVEAL¹⁶⁻¹⁹) and found that these results were similar to those presented in the MS.

4.4.1.4 Assessment of Uncertainty

One-way sensitivity analyses

The MS presents a series of univariate sensitivity analyses on key model parameters. However the ERG considers these to be scenario analyses and these are discussed in the next section. The MS does not explore the sensitivity of the model results to changes in the input parameter values, except for the length of inpatient stays for non-responders.

ERG sensitivity analysis

The ERG presents sensitivity analyses in Table 20. These show the effect of varying parameter values on the ICER for adalimumab compared to supportive care. Where indicated, the ERG used the confidence intervals for the parameters as ranges in the sensitivity analyses. If these were unavailable an arbitrary range was chosen, i.e. +/- 20%. Generally the results were robust to changes in the model parameters. Based on these analyses, the results were most sensitive to changes in the cost of adalimumab, cost of inpatient stay and the annual length of inpatient stays for non-responders.

Table 20 ERG One-way Sensitivity Analyses on the effect of changing parameter values on ICER for adalimumab compared to supportive care (SC)

Variable	Base case	Inputs		ICER ratios vs SC, £		Range, £
		low	high	Low input	High input	
Utility gain, e.g. PASI \geq 90% [†]	0.31	0.256	0.36	30,526	30,098	428
Annual drop out rates	20%	10%	30%	28,747	32,414	3667
Treatment response rate, e.g. PASI \geq 90% ^{†*}	37%	28%	45%	32,293	29,312	2981
Inpatient stay for non-responders, days/yr	21	16	25	37,421	24,622	12,799
Cost of inpatient stay (+/- 20%)	£256	£204	£307	36,283	24,338	11,945
Cost of adalimumab per vial (+/- 20%)	£358	£286	£429	18,276	42,346	24,070

[†] Ranges for sensitivity taken from lower and upper 95% confidence limits for all response categories.

* Treatment response rate varied for both placebo and adalimumab together

Scenario Analysis

The MS presented a number of scenario analyses on 'key model parameters across a range of plausible values and assumptions', reproduced in Table 21 (MS Table 6.3.3.1, p127). The MS provided no rationale for the choice of variables included (or excluded) in the scenario analyses. The MS model included different assumptions on flare-ups with intermittent etanercept, and patient sub-groups for moderate to severe psoriasis in comparison to the York model. The MS presented scenario analysis to reflect these different assumptions.

The model was most sensitive to the disease severity subgroups. Patients with less severe impairment at baseline (DLQI \leq 10) had ICERs of between £80,124 and £116,073 for the different drug treatments. The MS used a disutility during flare-up for patients taking intermittent etanercept. The MS investigated changing these assumptions in the scenario analyses. Using the etanercept dose used in the York report reduces the ICER from £37,285 to £27,585 for intermittent etanercept. As mentioned in this document (section 4.4.1.1), the MS base case assumptions for intermittent etanercept do not seem appropriate. The ERG suggests that the dose for intermittent etanercept would be the same dose as for the York report.

Table 21 ICERs from scenario analyses changing key parameters

(Values presented are £ per QALY compared to supportive care)

	Etanercept intermittent 25mg	Efalizumab	Adalimumab	Etanercept 25mg continuous	Infliximab
Base Case*	37,284	39,948	30,538	37,676	42,492
No disutility on intermittent therapy	30,660	39,948	30,538	37,676	42,492
Etanercept dose = 74% of continuous (York values)	27,585	39,948	30,538	37,676	42,492
Alternative Utility values (York report)	41,844	43,264	38,679	42,304	57,946
PASI Response assessed using PASI 50	42,308	43,103	35,243	42,838	46,836
Utility values of patients with DLQI≤10	91,389	95,920	80,124	92,387	116,073
Utility values of all patients	52,770	56,209	44,005	53,330	61,911
Include lost productivity while hospitalised	24,736	29,223	21,540	27,356	34,211
Only 40% of non-responders hospitalised (49 days in hospital)	40,119	42,362	32,562	40,000	44,355
Adalimumab phase II trial excluded	37,671	39,856	29,399	37,970	42,644

± Breakdown of costs and QALYs can be found in tables 6.3.3.2 and 6.3.3.3

* Base case parameters: hospitalisation = 21 days, intermittent etanercept dose is a percentage 88% of continuous dose, PASI response assessed using PASI 75

ERG scenario analysis

The ERG also ran a number of scenario analyses to test certain assumptions in the model. Table 22 shows the results for running the model with the same dosage for intermittent etanercept as for the York report. This demonstrates that the ICER for intermittent etanercept compared to supportive care is reduced. The ICER for adalimumab compared to intermittent etanercept is £36,671.

The ERG also reduced the cost of intermittent etanercept in line with the length of the treatment periods (i.e. 68% of the time) and this reduced the estimate of cost-effectiveness of intermittent etanercept to £22,689 versus supportive care. For this case, the ICER for adalimumab compared to intermittent etanercept was £46,122. The ERG also considered a scenario where only three infusions for infliximab would be required in the trial period. This reduced total infliximab costs for the trial period to £5352 (compared to £7102) and reduced the ICER of infliximab compared to supportive care to £39,228. The ERG changed the length of inpatient stays for non-

responders to 40% of 21 days, i.e. 8.4 days. This increased the cost-effectiveness for all biological therapies, e.g. the ICER for adalimumab was £48,229. The ERG also explored the effect of using the individual point estimates for the utility gain associated with PASI responses for the base case model (DLQI >10). This involved using values of 0.167 for the PASI 75-90 group and 0.189 for the PASI 50-75 group instead of a value of 0.178 for both groups. The effect of this was comparatively small changing the ICER for adalimumab compared to supportive care from £30,311 to £31,291.

Table 22 ERG scenario analysis: Dosage for etanercept intermittent is the same as used in the York report.

	Incremental Cost	Incremental QALY	ICER compared to Supportive care	ICER
Supportive Care	£0.00	0.000	-	
Etanercept 25mg BIW	£3,033	0.111	£27,256	£27,256
Efalizumab 1mg/kg	£4,936	0.125	£39,612	Extended dominance **
Adalimumab 40mg EOW	£4,993	0.165	£30,311	£36,671
Etanercept 25 mg Continuous	£5,051	0.135	£37,304	Extended dominance
Infliximab 5mg/kg	£7,737	0.183	£42,245	£149,037
Etanercept 50mg BIW	£9,910	0.123	£80,288	Dominated *

* A treatment is dominated if an alternative has lower costs and higher effectiveness

** Extended domination refers to cases where the ICER is higher than that of another drug even though one of either costs or QALYs is more favourable

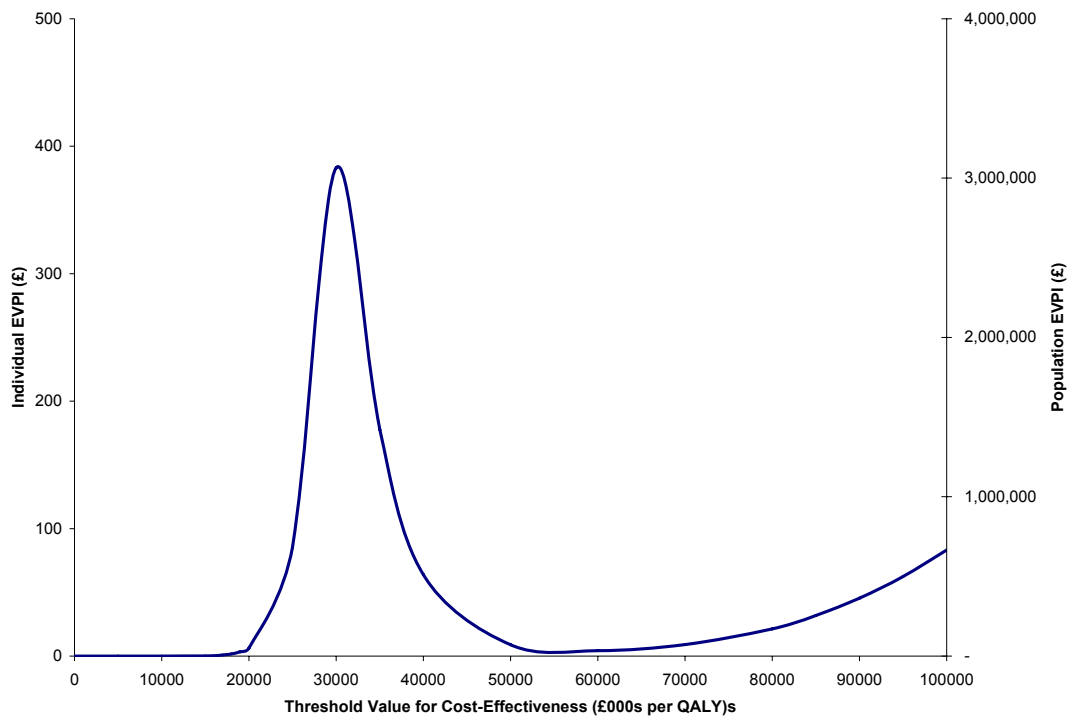
Probabilistic Sensitivity Analysis

The MS contains a probabilistic sensitivity analysis (PSA). The results of the base case PSA are presented in Table 6.3.1.1 (MS p118) and have been shown earlier in the ERG report in Table 14. The MS also reports 95% confidence interval contour plots (Figures 6.3.1.1 and 6.3.1.2, p119-120) and a cost-effectiveness acceptability curve (CEAC) (Figure 6.3.1.4 p122). According to the PSA, adalimumab had a 46% probability of being cost effective with a willingness to pay threshold of £30,000 per QALY gained. The MS reports that adalimumab is the most cost effective when compared to supportive care. Although infliximab was estimated to produce more QALYs the higher cost of the drug means that the ICER for infliximab compared to supportive care is higher. Additionally, the ICER for infliximab compared to adalimumab is £149,037.

The PSA includes uncertainty around some of the main variables in the model, but provides no rationale for which variables to include and no justification for the distributions used in the PSA. Nevertheless the choice of variables included in the

PSA appears reasonable and distributions chosen are generally appropriate. The MS did not include uncertainty in the cost of adalimumab or hospital costs. The manufacturer's model has used a normal distribution for the length of hospital stay for non-responders (mean = 25, SE = 2.55). However the MS suggest limits of 16 to 39 days which do not correspond to the distribution chosen. A normal distribution was also used for utilities. An alternative would have been the beta distribution which does not produce values >1 . It is unclear which distribution was used for the probability of PASI response. The PSA does not sample a new value each time from a probability distribution in the model for PASI response. Instead the model includes sheets of 10,000 values of the probability of PASI response for PASI 50, PASI 75 and PASI 90. These are taken directly from the mixed treatment model used to estimate effectiveness.

As part of the PSA the MS presents an expected value of perfect information (EVPI) analysis that demonstrates a low expected value of perfect information. However, this analysis is based on comparing all biological treatments with each other but not with supportive care. The ERG was unsure why supportive care was not used as a comparator. Comparing the biological therapies with supportive care gives a small increase in population EVPI (Figure 1) with a new peak of approximately £3 Million at a value of a QALY of approximately £30,000. This compares with the figure given in the MS (Figure 6.3.1.5, p123) where the expected value of perfect information peaks at around £1 Million at a willingness to pay of approximately £17,000 per QALY.

Figure 1 EVPI including supportive care

4.4.1.5 ERG probabilistic sensitivity analysis

The ERG ran a PSA using different assumptions to those used in the MS. These different assumptions were firstly, that only three infusions for infliximab were required in the trial period, and secondly, that the cost of intermittent etanercept took the same value as used in the York report (74% of the continuous etanercept costs). This was run using 10,000 simulations as per the MS approach. These results are given in Table 23 and Figure 2. For clarity, only strategies where the probability of being cost-effective is greater than 0.1% for any part of the range used are included in Figure 2. From these, it can be seen that the results are altered, with the probability that adalimumab is the most cost-effective strategy at £30,000 per QALY reducing from 46% to 16%.

Figure 2 Cost-effectiveness acceptability curve for ERG PSA

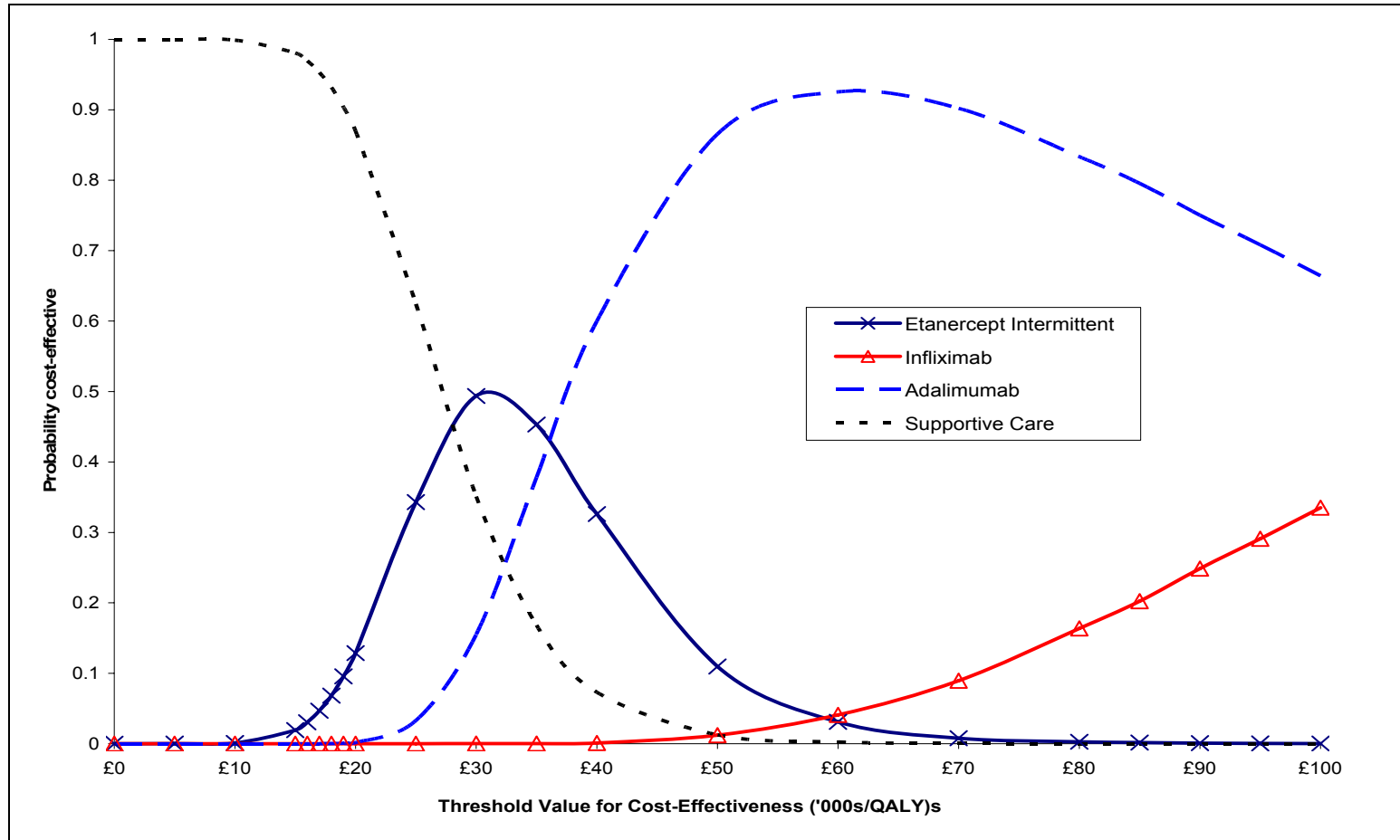


Table 23 Results for ERG PSA

Drug	Mean QALY	Mean Cost	ICER	ICER vs Supportive Care
Supportive Care	0.000	£0.00	0	-
Etanercept 25mg BIW	0.111	£3,042.56	£27,450	£27,450
Efalizumab 1mg/kg	0.124	£4,941.15	Extended Dominated **	£39,757.09
Adalimumab 40mg EOW	0.164	£4,991.39	£36,770	£30,373.81
Etanercept 25 mg Continuous	0.135	£5,056.84	Dominated *	£37,492.97
Infliximab 5mg/kg	0.183	£7,177.66	£115,067	£39,268.48
Etanercept 50mg BIW	0.123	£9,912.53	Dominated	£80,527.60

* A treatment is dominated if an alternative has lower costs and higher effectiveness

** Extended domination refers to cases where the ICER is higher than that of another drug even though one of either costs or QALYs is more favourable

4.4.2 Comment on validity of results presented with reference to methodology used

In general the approach used seemed reasonable, given the caveats outlined above.

4.4.3 Summary of uncertainties and issues

There are a number of important issues relating to the uncertainty surrounding parameters in the model. These are detailed below.

- The characteristics of the population receiving treatment. The base case analysis includes individuals whose DLQI is greater than 10. Depending on the baseline PASI scores this group is likely to be categorised as severe. It can be seen from the scenario analysis that changes in the DLQI group used have large effects on the cost-effectiveness estimates, for example if the DLQI < 10 group is used then cost per QALY gained for adalimumab increases to over £80,000 per QALY. Therefore the characteristics of the patients who receive care are very important in determining results.
- The requirement for inpatient stays (and the cost) in the supportive care group. In the model some of the costs of biological treatment are offset by reductions in supportive care costs. There seems to be a paucity of reliable data for this, it is not clear what value should be used. Changes in this value have large effects on the cost-effectiveness estimates for biological drugs.
- Long term cost-effectiveness. The data used to estimate effectiveness and also drop-out from treatment has been drawn mainly from short term trials. It is therefore unclear as to what would happen over the longer term.
- The treatment of comparators, particularly intermittent etanercept. Assumptions made regarding the cost of intermittent etanercept, relating to the proportion of continuous cost incurred by intermittent therapy, affect the comparative cost of intermittent etanercept compared to adalimumab. In the

MS base case, intermittent etanercept can be eliminated by extended dominance. If the York model assumption on the proportion of costs borne is used then this is no longer the case and the ICER of adalimumab compared to intermittent etanercept is £36,671.

- Treatment effectiveness. The model relies on results derived from the mixed treatment comparison of alternatives (MS Table 5.9.1.1, p90-1). Uncertainty around the mixed treatment comparison model used to derive these estimates, such as the processes used to determine which studies to include and uncertainty about the characteristics of the patients included in the comparator trials, will also feed into the cost-effectiveness model.

5 Discussion

5.1 Summary of clinical-effectiveness issues

- The clinical evidence on efficacy of adalimumab comes from three randomised controlled trials (RCT) comparing adalimumab with placebo. One of these three RCTs also compares adalimumab with methotrexate. One further RCT contributes evidence on efficacy and time to relapse. The main results focus on the efficacy of adalimumab after either 12 weeks (two trials) or 16 weeks (two trials) of treatment. Other data are presented for longer treatment periods (19 weeks, 48 weeks, 120 weeks) but the majority does not come from treatment-placebo comparisons.
- Only one RCT compared adalimumab directly to methotrexate and there was no other RCT evidence comparing adalimumab to the other comparator drugs specified in the scope. Therefore the manufacturer conducted a mixed-treatment comparison which included 18 studies with evidence on six comparators (Etanercept low dose, etanercept high dose, efalizumab, infliximab, ciclosporin and methotrexate). A systematic review for the comparator trials was not included in the MS and limited data on these trials were presented.
- A standard meta-analysis was not presented and as the MS does not discuss the issue of possible heterogeneity between trials the ERG is uncertain as to how appropriate it was to conduct the mixed-treatment comparison.

5.2 Summary of cost-effectiveness issues

- The model submitted is based upon a previously published model ²
- The ERG consider the model a reasonable approach to the modelling of biological therapies for psoriasis

- The comparator chosen is important in determining the ICER. If patients are assumed to be ineligible for systemic therapy then the appropriate comparators are supportive care and other biological therapies.
- The estimates of cost-effectiveness obtained depend upon the values chosen for a number of key parameters including:
 - The base line severity of individuals receiving treatment as determined by their DLQI with those whose DLQI is > 10 having much more favourable cost-effectiveness ratios than those for whom the base line DLQI was ≤ 10.
 - The assumptions made regarding the parameters of other biological therapies was important, particularly those of intermittent etanercept
 - The assumptions made relating to the need for inpatient stays for non responders are important, the longer the inpatient care needed the more cost-effective biologicals appear compared to supportive care.

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7 Appendices

Appendix 1: Manufacturer's response to clarification queries

Abbott Laboratories response to clarification questions asked by the Evidence Review Group (ERG), received 12th October 2007

- **Section A: Clinical evidence**

A1. Please provide details of how inclusion and exclusion criteria were applied, how data extraction was undertaken, and how the quality of trials was assessed.

The selection of studies according to the inclusion and exclusion criteria was conducted by one researcher. Verification of selected studies in line with the inclusion and exclusion criteria was validated by another researcher. This same process was conducted for the extraction of data from study reports and published literature. The quality of trials was assessed by one researcher to provide responses to the questions posed for the critical appraisal in section 5.3.6 of Abbott's submission. For the key adalimumab studies included in the mixed treatment comparison, the Jadad scoring tool was used to assess the quality of the trials.

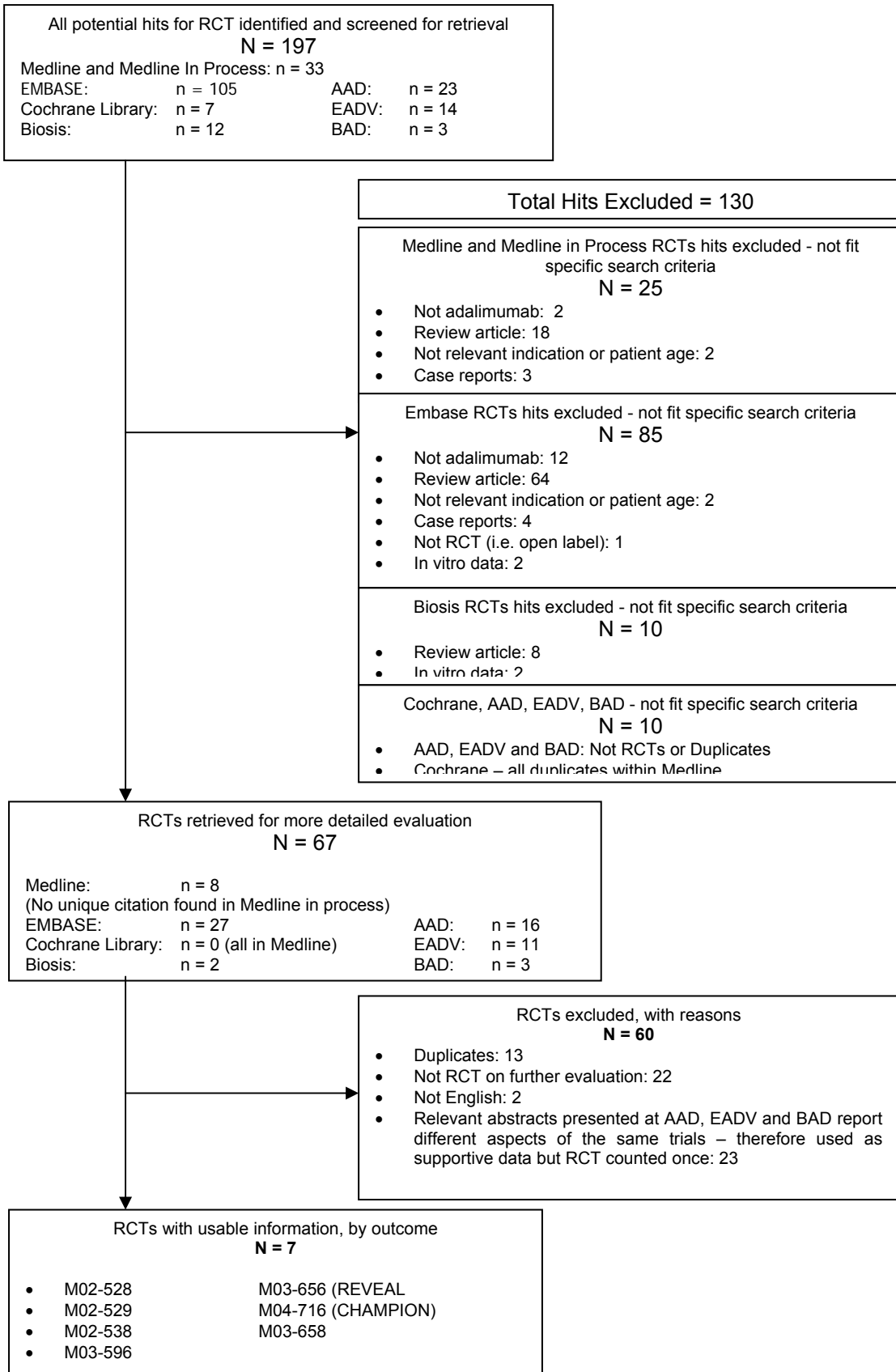
A2. Only one of the literature flow charts (5.6.1, page 78) lists the reasons for study exclusion and how many studies were excluded for each reason. The literature flow chart 5.2.6 on page 29 does list reasons for exclusion but does not indicate how many references were excluded for each reason. Please supply these figures. Please also supply a list of the excluded studies.

Abbott has replicated the literature search that was performed on 8 August 2007 as accurately as possible; however there may be some small discrepancies in the flow chart presented below (Figure A2.1) compared to the literature flow chart in Section 5.6.1 of the submission due to the different dates the searches were performed on. The replicated literature search was undertaken on 18th October 2007. Abbott deliberately conducted a wide search to ensure all potentially relevant RCTs would be captured, and is confident that all the relevant RCTs have been identified in the literature search.

Figure A2.1 provides an updated version of Figure 5.2.6 – the flow diagram of numbers of studies included and excluded at each stage as per the Quorum statement. More detailed reasons for exclusion and the number of references excluded for each reason have been provided in this figure. Please note that a number of the excluded studies found in the literature search (i.e. abstracts and posters) present different outcomes of the same trials and as such have been excluded if the RCT has already been counted once. For example, for M02-528, there are 10 references pertaining to this one study, all of which are relevant.

Figure A2.1: A flow diagram of numbers of studies included and excluded at each stage as per the QUORUM statement

Appendix 1 contains a list of the excluded studies detailed in the flow chart below.



A3. Please explain the difference between the trial populations described as having “stable plaque psoriasis” such as those in M03-656 Reveal study (page 40) and those described as having “active psoriasis” such as those in M04-716 Champion study (page 41). Please also explain how stable and active psoriasis were defined.

In both the pivotal phase III trials, M03-656 (REVEAL) and M04-716, the inclusion criteria specified that subjects had stable plaque psoriasis. Psoriasis can change from stable plaques to an unstable form, typified by eruptive inflammatory lesions that can be easily irritated by topical treatment – erythrodermic psoriasis or pustular psoriasis are forms of unstable plaque psoriasis. Stable plaques are well delineated from surrounding normal skin and are red or salmon pink in colour, covered by white or silvery scales; whereas, unstable plaques are not clearly defined, are characterised by periodic, widespread, fiery redness of the skin and tend to spread or increase in size. Chronic stable plaque psoriasis accounts for 80-90% of all cases of psoriasis^{1,2}. In the adalimumab clinical trial programme subjects had stable plaque psoriasis for at least 2 months before Screening and at Baseline.

The adalimumab clinical trial programme also lists ‘active plaque psoriasis’ in the inclusion criteria, this means active stable plaque psoriasis – i.e. the plaques persist with no improvement despite treatment with topical therapies and as such, are by definition active. There is no difference between subjects having stable plaque psoriasis and active plaque psoriasis, to avoid confusion the inclusion criteria should be read as active stable plaque psoriasis – i.e. not unstable and not responding to topical therapies. In other words, trial populations described as having stable plaque psoriasis or active psoriasis should be read interchangeably.

A4. Please provide details of the extent to which trial populations meet the anticipated indication for treatment as proposed in the draft SmPC and the criteria listed on page 5 (paragraph 1.10 ‘What is the setting for the use of the technology’). The three areas we particularly seek clarification on are as follows:

- *Trial participants with moderate to severe chronic plaque psoriasis: The inclusion criteria within the participants table 5.3.2 (pages 38-45) are stated as moderate to severe chronic plaque psoriasis with this defined differently between trials. For trial M02-528, however, the reported percentages of participants in each group with severe, or moderate to severe psoriasis (Baseline demographics and disease characteristics of trials) suggests that only about half the participants were defined by the PGA as having severe or moderate to severe psoriasis. Please confirm how many of the trial participants had severe, or moderate-to-severe psoriasis.*

There are multiple means by which psoriasis severity can be categorised – the predominant three physician reported outcomes being PASI, PGA and percentage of body surface area (BSA) affected. Table A4.1 below shows the baseline psoriasis severity for patients enrolled in M02-528, as assessed by the assigned PGA score, the proportion of patients with a PASI score ≥ 12 , and the proportion of patients with $\geq 10\%$ BSA affected at baseline. The EMEA define moderate-to severe psoriasis as a BSA involvement $>10\%$ or PASI 10 to 20³. Table A4.1 highlights the proportion of patients in M02-528 with a baseline disease severity of at least moderate-to-severe psoriasis as categorised by the EMEA. As can be seen in the table, a much higher proportion of patients have a percentage BSA of ≥ 10 and a baseline PASI score of ≥ 12 compared to the proportion of patients with moderate-to-severe or severe psoriasis as assessed by the PGA scoring system. It can be assumed therefore that determining disease severity by any one outcome is a difficult prospect. Indeed, the impact of psoriasis on a patient is more likely to be related to the area affected and the attitudes of the patient and the degree of psychological and social disability that accompanies psoriasis can be underestimated⁴. There is a movement to argue that quality of life (QoL) would be a better method of determining the severity of Ps.

It is also important to note that M02-528 is a dose-finding phase II study and not one of the pivotal phase III trials.

Table A4.1: Baseline PGA scores, PASI \geq 12 and % BSA \geq 10 at baseline for subjects enrolled in Study M02-528

	Placebo N=52	Adalimumab	
		40mg eow N=45	40mg weekly N=50
% BSA \geq 10, n (%)			
PASI \geq 12 n (%)			
PGA, n (%)			
Severe			
Moderate to severe			
Moderate			
Mild to moderate			
Mild			
Almost clear			
Clear			

It is clear from the data presented in this table that some of the patients enrolled in M02-528 would not have qualified under the BAD guidelines to receive biologic therapy for psoriasis. This is why Gordon et al conducted a sub-analysis on those patients who met some of the BAD guideline criteria for biologic therapy (i.e. baseline PASI \geq 10 and baseline DLQI $>$ 10). This sub-analysis was presented in the Abbott submission on Page 67⁵. Further to this sub-analysis, Table A4.2 shows the proportions of subjects within M02-528 achieving at least a 75% improvement in their baseline PASI score by the following subgroups: BSA $<$ 10% and BSA \geq 10%, PASI $<$ 12, PASI 12-20, and PASI $>$ 20.

Table A4.2: \geq PASI 75 Responses at Week 12 by Subgroup

		Placebo N=52	Adalimumab	
			40mg eow N=45	40mg weekly N=50
Subgroup	Category	Responders/ total number of subjects in the subgroup (%)		
BSA	$<$ 10%			
	$>$ 10%			
PASI Score	$<$ 12			
	12-20			
	$>$ 20			

Data presented in this table demonstrate that the efficacy of adalimumab for patients with 'severe' psoriasis is similar to the efficacy demonstrated by all enrolled patients; and that regardless of the definition of severity employed – which is certainly subject to debate (the EMEA state that there is still no consensus or widely accepted definition of what represents mild, moderate or severe plaque psoriasis³), higher percentages of adalimumab-treated patients achieved treatment success than those receiving placebo.

- *Trial participants who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy: Please clarify how many of the trial participants in each of the included trials had failed to respond to a prior systemic therapy.*

This question is seeking to determine to what extent the trial populations meet the anticipated indication for treatment as proposed in the draft SmPC. The proposed indication in the draft SmPC is for the treatment of moderate to severe chronic plaque psoriasis in adult patients who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA. Most patients who have a history of use of systemic therapy, but who subsequently discontinued and enrolled in the adalimumab clinical trials, can be inferred to have failed to respond, developed a contraindication, or acquired an intolerance to the agent they had been using. Tables A4.3 – A4.6 show how many of the trial participants in each of the trials had received prior systemic therapy as specified in the proposed wording of the licence. Studies M02-529, M03-596 and M03-658 have not been included because they are continuation or extension trials; and as such prior systemic treatment failure will already have been documented in the studies that preceded these continuation trials (M02-528, M02-538, M03-656 and M04-716 – tabulated below). In the two phase II studies M02-528 and M02-538, previous psoriasis treatment was

not collected from more than 12 months prior to study entry, therefore data are only available for those that received systemic treatment within 12 months of study entry.

PASI 50, 75, 90 and 100 responses have also been presented for the placebo-controlled trials (M02-528, M03-656 and M04-716) to show that the benefit achieved with adalimumab is consistent, irrespective of the type of prior therapy and that there is no significant difference in PASI response by prior treatment exposure. This finding is consistent with the evidence for etanercept and infliximab.

Table A4.3: Proportion of subjects enrolled in M02-528 who had received prior systemic therapy within the last 12 months prior to study entry and the PASI 50, 75, 90 and 100 responses at Week 12 stratified by previous psoriasis treatment

	Placebo N=52		Adalimumab			
	Received any prior systemic therapy ⁺	Did not receive any prior systemic therapy	40mg eow N=45		40mg weekly N=50	
			Received any prior systemic therapy	Did not receive any prior systemic therapy	Received any prior systemic therapy	Did not receive any prior systemic therapy
N (%)	████	████	████	████	████	████
PASI 50						
Responder (response rate %)	████	████	████	████	████	████
Non-responder	█	█	█	█	█	█
Missing	█	█	█	█	█	█
Between group p value*	████		████		████	
PASI 75						
Responder (response rate %)	████	████	████	████	████	████
Non-responder	█	█	█	█	█	█
Missing	█	█	█	█	█	█
Between group p value*	████		████		████	
PASI 90						
Responder (response rate %)	████	████	████	████	█	█
Non-responder	█	█	█	█	█	█
Missing	█	█	█	█	█	█
Between group p value*	█		████		████	
PASI 100						
Responder (response rate %)	████	████	████	████	████	████
Non-responder	█	█	█	█	█	█
Missing	█	█	█	█	█	█
Between group p value*	█		████		████	

+ systemic therapy includes PUVA

* P-value for differences between groups from Fisher's Exact test.

Non-responder imputation: subjects with missing PASI responses were counted as non-responders for the between group comparisons.

Note: data for previous systemic therapy for M02-528 can only be derived from the 12 months preceding study entry as data were not collected for any longer than this time period.

The analyses were performed based on raw data reported by the investigators, and according to the same conventions as used for the CSE.

Table A4.4: Proportion of subjects enrolled in M03-656 who had received prior systemic therapy at any timepoint prior to study entry and the PASI 50, 75, 90 and 100 responses at Week 16 stratified by previous psoriasis treatment

	Placebo N=398		Adalimumab 40mg eow N=814	
	Received any prior systemic therapy ⁺	Did not receive any prior systemic therapy	Received any prior systemic therapy	Did not receive any prior systemic therapy
N (%)	██████	██████	██████	██████
PASI 50				
Responder, n (%)	██████	██████	██████	██████
Non-responder, n (%)	██████	██████	██████	██████
Missing, n (%)	██████	██████	██████	██████
Between group p value*	██████		██████	
PASI 75				
Responder, n (%)	██████	██████	██████	██████
Non-responder, n (%)	██████	██████	██████	██████
Missing, n (%)	██████	██████	██████	██████
Between group p value*	██████		██████	
PASI 90				
Responder, n (%)	██████	██████	██████	██████
Non-responder, n (%)	██████	██████	██████	██████
Missing, n (%)	██████	██████	██████	██████
Between group p value*	██████		██████	
PASI 100				
Responder, n (%)	██████	██████	██████	██████
Non-responder, n (%)	██████	██████	██████	██████
Missing, n (%)	██████	██████	██████	██████
Between group p value*	██████		██████	

+ systemic therapy includes PUVA

* P-value for differences between groups from Fisher's Exact test.

Non-responder imputation: subjects with missing PASI responses were counted as non-responders for the between group comparisons.

Table A4.5: Proportion of subjects enrolled in M04-716 who had received prior systemic therapy at any timepoint prior to study entry and the PASI 50, 75, 90 and 100 responses at Week 16 stratified by previous psoriasis treatment

	Placebo N=53		Methotrexate N=110		Adalimumab 40mg eow N=108	
	Received any prior systemic therapy ⁺	Did not receive any prior systemic therapy	Received any prior systemic therapy	Did not receive any prior systemic therapy	Received any prior systemic therapy	Did not receive any prior systemic therapy
N (%)	████	████	████	████	████	████
PASI 50						
Responder (response rate %)	████	████	████	████	████	████
Non-responder	█	█	█	█	█	█
Missing	█	█	█	█	█	█
Between group p value*	████		████		████	
PASI 75						
Responder (response rate %)	████	████	████	████	████	████
Non-responder	█	█	█	█	█	█
Missing	█	█	█	█	█	█
Between group p value*	████		████		████	
PASI 90						
Responder (response rate %)	████	████	████	████	████	████
Non-responder	█	█	█	█	█	█
Missing	█	█	█	█	█	█
Between group p value*	████		████		████	
PASI 100						
Responder (response rate %)	████	████	████	████	████	████
Non-responder	█	█	█	█	█	█
Missing	█	█	█	█	█	█
Between group p value*	████		████		████	

+ systemic therapy includes PUVA

* P-value for differences between groups from Fisher's Exact test.

Non-responder imputation: subjects with missing PASI responses were counted as non-responders for the between group comparisons.

Table A4.6: Proportion of subjects enrolled in M02-538 who had received prior systemic therapy within the last 12 months prior to study entry, baseline values

Any systemic therapy ⁺	N=148 n, (%)
Yes	████
No	████

+ systemic therapy includes PUVA

Note: data for previous systemic therapy for M02-538 can only be derived from the 12 months preceding study entry as data were not collected for any longer than this time period.

The analyses were performed based on raw data reported by the investigators, and according to the same conventions as used for the CSE.

Table A4.7 below shows the proportion of patients from the Placebo-Controlled Set (i.e. the combined number of patients from M02-528, Period A of M03-636 [REVEAL] and M04-716 [CHAMPION] receiving adalimumab eow) who have a previous treatment history of any systemic therapy including PUVA. The PASI 75 response rates for these patients are also detailed in the table below stratified by treatment history. As can be seen from the table, a statistically significantly greater proportion of subjects receiving adalimumab had at least a 75% improvement in PASI score compared to those receiving placebo, and importantly the results for these patients with a history of systemic therapy are consistent with the results observed for the entire Placebo-Controlled Set (N=1,469).

Table A4.7: Summary of PASI 75 Response at Week 12 and Week 16 (NRI) - Subjects Who Have Received Any Prior Systemic Biologic, Systemic Non-Biologic, or PUVA Treatment (Placebo Controlled Study Set)

Visit	Treatment	N	PASI 75 Response			p-value ^a
			Responder n (%)	Non-Responder n (%)	Missing n (%)	
Week 12 ^b	Placebo	█	█	█	█	█
	Adalimumab 40mg eow	█	█	█	█	
Week 16	Placebo	█	█	█	█	█
	Adalimumab 40mg eow	█	█	█	█	

^a p-value for differences between treatment groups from Fisher's Exact Test

^b Week 12 responses are presented here as well as Week 16 responses to include subjects from the 12-week study, M02-528.

It is difficult to adequately define treatment failure, especially when there is a degree of scepticism about how reliable recollections are concerning which systemic treatments were used in a patient a number of years ago. However, sub-group analysis performed on patients in the Placebo-Controlled Study Set who are construed to have qualified for the target population specified in the licence *i.e.* have documentation of failure to respond or worsening of symptoms with systemic therapy or oral PUVA within the preceding 12 months to study entry (N=█) are presented in Table A4.8. The results show that PASI 75 response rates for the adalimumab and placebo treatment arms are comparable to the response rates seen in the entire Placebo-Controlled Study Set (N=1,469). Therefore, it can be concluded that the benefit achieved with adalimumab is consistent across both systemic therapy naïve patients and those with a previous documented failure to respond or worsening of symptoms with prior systemic therapy use.

Table A4.8: Summary of PASI 75 Response at Week 12 (NRI) - Subjects With a Failure to Respond or Worsening with prior Systemic Biologic, Systemic Non-Biologic, or Oral PUVA Treatment Within The Past 12 Months (Placebo Controlled Study Set)

Treatment	N=	PASI 75 Response			p-value ^a
		Responder n (%)	Non-Responder n (%)	Missing n (%)	
Week 12 ^b	Placebo	█	█	█	█
	Adalimumab 40mg eow	█	█	█	
Week 16	Placebo	█	█	█	█
	Adalimumab 40mg eow	█	█	█	

^a p-value for differences between treatment groups from Fisher's Exact Test

^b Week 12 response were used rather than Week 16 responses to include subjects from the 12-week study, M02-528.

[REDACTED]

This question is seeking to determine to what extent the trial populations meet the anticipated indication for treatment as proposed in the draft SmPC. However, since the submission date of 27 September 2007 and in discussion with the EMEA, the [REDACTED] [REDACTED] has been removed from the licence and the draft SmPC has been updated to reflect this. Therefore, no further data have been provided on this point.

The proposed licensed indication of adalimumab for psoriasis is now as follows: for the treatment of moderate to severe chronic plaque psoriasis in adult patients who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.

A5. The search strategies for section 5.6 are not listed in Appendix 9.2 (although we note that the results are presented in the literature flowchart 5.6.1 on page 78). Please provide these search strategies.

Provided below are the search strategies for Section 5.6:

Search A: Randomised controlled trials (RCTs) of etanercept or efalizumab in psoriasis:

- **Medline and In-Process Citations (OVID Online – <http://www.ovid.com/>)**
2004/02 wk 3 – 2006/09/19

This search retrieved 129 references:

- 1 randomized controlled trial.pt.
- 2 exp randomized controlled trials/
- 3 random allocation/
- 4 double blind method/
- 5 single blind method/
- 6 clinical trial.pt.
- 7 exp clinical trials/
- 8 controlled clinical trials/
- 9 clin\$ trial\$.ti,ab.
- 10 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
- 11 placebo\$.ti,ab.
- 12 placebos/
- 13 random\$.ti,ab.
- 14 exp evaluation studies/
- 15 follow up studies/
- 16 exp research design/
- 17 prospective studies/
- 18 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
- 19 or/1-18
- 20 animals/
- 21 human/
- 22 20 not (20 and 21)
- 23 19 not 22
- 24 exp psoriasis/
- 25 (psoria\$ or anti psoria\$ or antipsoria\$).mp.
- 26 or/24-25
- 27 etanercept.mp.
- 28 enbrel.mp.
- 29 efalizumab.mp.

30 raptiva.mp.
31 or/27-30
32 23 and 26 and 31
33 (letter or comment or editorial).pt.
34 32 not 33
35 limit 34 to ed="20040225 - 20060919"

- **Embase (OVID Online – <http://www.ovid.com/>)**
2004 wk 9 – 2006 wk 37

This search retrieved 464 references:

1 Randomized Controlled Trial/
2 randomization/ 21166
3 double blind procedure/ or single blind procedure/
4 exp clinical trial/
5 controlled study/
6 clin\$ trial\$.ti,ab.
7 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
8 placebo\$.ti,ab.
9 Placebo/
10 random\$.ti,ab.
11 evaluation/
12 follow up/
13 exp methodology/
14 prospective study/
15 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
16 or/1-15
17 (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18 exp ANIMAL/
19 Animal Experiment/
20 Nonhuman/
21 Human/
22 Human Experiment/
23 or/17-20
24 21 or 22
25 16 not (23 not (23 and 24))
26 exp psoriasis/
27 (psoria\$ or anti psoria\$ or antipsoria\$).mp.
28 or/26-27
29 etanercept/ or etanercept.mp.
30 enbrel.mp.
31 eralizumab/ or efalizumab.mp.
32 raptiva.mp.
33 or/29-32
34 25 and 28 and 33
35 (letter or note or editorial).pt.
36 34 not 35
37 limit 36 to em="200409 - 200637"

- **ISI Science and Technology Proceedings (Web of Knowledge)**
2004 – 2006

This search retrieved 185 references:

1. TS=((study or studies) SAME design*)
2. TS=((clinic*trial*) or placebo* or random* or (control* or prospectiv* or volunteer*))
3. TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
4. 1 or 2 or 3
5. TS=(psoria* or antipsoria* or anti-psoria*)
6. TS=((etanercept or efalizumab or raptiva or enbrel))

7. 4 and 5 and 6
8. TS=((animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*))
9. 7 not 8

Search B: Randomized controlled trials (RCTs) of infliximab, adalimumab or alefacept in psoriasis

- **Medline and In-Process Citations (OVID Online – <http://www.ovid.com/>)**
1966 – 2006/09/19

This search retrieved 240 references:

- 1 randomized controlled trial.pt.
- 2 exp randomized controlled trials/
- 3 random allocation/
- 4 double blind method/
- 5 single blind method/
- 6 clinical trial.pt.
- 7 exp clinical trials/
- 8 controlled clinical trials/
- 9 clin\$ trial\$.ti,ab.
- 10 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
- 11 placebo\$.ti,ab.
- 12 placebos/
- 13 random\$.ti,ab.
- 14 exp evaluation studies/
- 15 follow up studies/
- 16 exp research design/
- 17 prospective studies/
- 18 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
- 19 or/1-18
- 20 animals/
- 21 human/ 9509641
- 22 20 not (20 and 21)
- 23 19 not 22
- 24 exp psoriasis/
- 25 (psoria\$ or anti psoria\$ or antipsoria\$).mp.
- 26 or/24-25
- 27 infliximab.mp.
- 28 remicade.mp.
- 29 adalimumab.mp.
- 30 humira.mp.
- 31 alefacept.mp.
- 32 amevive.mp.
- 33 or/27-32
- 34 23 and 26 and 33
- 35 (letter or comment or editorial).pt.
- 36 34 not 35

- **Embase (OVID Online – <http://www.ovid.com/>)**
1966 – 2006/09/19

This search retrieved 752 references:

- 1 Randomized Controlled Trial/
- 2 randomization/
- 3 double blind procedure/ or single blind procedure/
- 4 exp clinical trial/
- 5 controlled study/
- 6 clin\$ trial\$.ti,ab.
- 7 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.

- 8 placebo\$.ti,ab.
- 9 Placebo/
- 10 random\$.ti,ab.
- 11 evaluation/
- 12 follow up/ 13 exp methodology/
- 14 prospective study/
- 15 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
- 16 or/1-15
- 17 (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
- 18 exp ANIMAL/
- 19 Animal Experiment/
- 20 Nonhuman/
- 21 Human/
- 22 Human Experiment/
- 23 or/17-20
- 24 21 or 22
- 25 16 not (23 not (23 and 24))
- 26 exp psoriasis/
- 27 (psoria\$ or anti psoria\$ or antipsoria\$).mp.
- 28 or/26-27
- 29 adalimumab/ or adalimumab.mp.
- 30 humira.mp.
- 31 infliximab/ or infliximab.mp.
- 32 remicade.mp. 1603
- 33 alefacept/ or alefacept.mp.
- 34 amevive.mp.
- 35 or/29-34
- 36 25 and 28 and 35
- 37 (letter or note or editorial).pt.
- 38 36 not 37

- **ISI Science and Technology Proceedings (Web of Knowledge)**
1990 – 2006

This search retrieved 295 references:

1. TS=((study or studies) SAME design*)
2. TS=((clinic*trial*) or placebo* or random* or (control* or prospectiv* or volunteer*))
3. TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
4. 1 or 2 or 3
5. TS=(psoria* or antipsoria* or anti-psoria*)
6. TS=((infliximab or remicade or adalimumab or humira or alefacept or amevive))
7. 4 and 5 and 6
8. TS=((animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*))
9. 7 not 8

Search C: Randomized controlled trials (RCTs) of all biologics together

- **Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet – <http://www.update-software.com/clibng/cliblogon.htm>)**
2006 – 3rd Quarter

This search retrieved 604 references:

1. PSORIASIS\$:me.mp.
2. (psoria\$ or anti next psoria\$ or antipsoria).mp.
3. 1 or 2
4. etanercept.mp.
5. enbrel.mp.
6. efalizumab.mp.

7. raptiva.mp.
8. infliximab.mp.
9. remicade.mp.
10. adalimumab.mp.
11. humira.mp.
12. alefacept.mp.
13. amevive.mp.
14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 3 and 14

Search D: Randomized controlled trials (RCTs) of comparator treatments in psoriasis

- **Medline and In-Process Citations (OVID Online – <http://www.ovid.com/>)**
2004/01 wk 4 – 2006/09/20

This search retrieved 252 references:

- 1 randomized controlled trial.pt.
- 2 exp randomized controlled trials/
- 3 random allocation/
- 4 double blind method/
- 5 single blind method/
- 6 clinical trial.pt.
- 7 exp clinical trials/
- 8 controlled clinical trials/
- 9 clin\$ trial\$.ti,ab. 1
- 10 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
- 11 placebo\$.ti,ab.
- 12 placebos/
- 13 random\$.ti,ab.
- 14 exp evaluation studies/
- 15 follow up studies/
- 16 exp research design/
- 17 prospective studies/
- 18 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
- 19 or/1-18
- 20 animals/
- 21 human/
- 22 20 not (20 and 21)
- 23 19 not 22
- 24 psoriasis/
- 25 (psoria\$ or anti psoria\$ or antipsoria\$).mp.
- 26 or/24-25
- 27 exp Psoralen/
- 28 psoralen\$.tw.
- 29 puva.tw.
- 30 (phototherap\$ or photo therap\$ or photochemotherap\$ or photo chemotherap\$ or photo chemo therap\$).tw.
- 31 Phototherapy/
- 32 Heliotherapy/
- 33 photochemotherapy/
- 34 ultraviolet therapy/
- 35 puva therapy/
- 36 (puva or ultraviolet A or ultra violet A or UVA or UVB or ultraviolet B or ultra violet B).tw.
- 37 (NBUVB or BBUVB).tw.
- 38 ((narrowband or narrow band) adj1 (UVB or ultraviolet B or ultra violet B)).tw.
- 39 ((broadband or broad band) adj1 (UVB or ultraviolet B or ultra violet B)).tw.
- 40 (pnbuvb or repuva).tw.
- 41 MOP.ti,ab.
- 42 methoxypsoralen\$.tw.
- 43 Acitretin/

- 44 retinoids/
- 45 etretinate/
- 46 vitamin A/
- 47 tretinoin/
- 48 (retinoid\$ or acitretin\$ or etretinate\$ or vitamin A deriv\$).tw.
- 49 (synthet\$ adj1 vitamin A).tw.
- 50 tmp.ti,ab.
- 51 trimethylpsoralen.tw.
- 52 Cyclosporins/
- 53 (cyclosporin\$ or ciclosporin\$ or csa).tw.
- 54 Hydroxyurea/
- 55 hydroxyurea\$.mp. or hydroxycarbamide\$.tw.
- 56 (fumarate\$ or fumaric acid ester\$).tw.
- 57 fumaderm.tw.
- 58 Fumarates/
- 59 (dmfae or dimethylfumar\$ or monoethylfumar\$).tw.
- 60 (mefae-ca or mefae-mg or mefae-na or mefae-zn).ti,ab.
- 61 (ohfae or octyl hydrogen fumar\$).tw.
- 62 Anthralin/
- 63 (dithranol or anthralin).tw.
- 64 (goeckerman adj1 (therap\$ or treatment\$ or method\$ or regime\$)).tw.
- 65 (ingram adj1 (therap\$ or treatment\$ or method\$ or regime\$)).tw.
- 66 Methotrexate/
- 67 methotrexate.tw.
- 68 or/27-67
- 69 23 and 26 and 68
- 70 limit 69 to ed="20040201 - 20060920"

- **Embase (OVID Online – <http://www.ovid.com/>)**
2004 wk 6 – 2006 wk 37

This search retrieved 1008 references:

- 1 randomized controlled trial/
- 2 randomizaton/
- 3 double blind procedure/ or single blind procedure/
- 4 exp clinical trial/
- 5 controlled study/
- 6 clin\$ trial\$.ti,ab.
- 7 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
- 8 placebo\$.ti,ab.
- 9 Placebo/
- 10 random\$.ti,ab.
- 11 evaluation/
- 12 follow up/
- 13 exp methodology/
- 14 prospective study/
- 15 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
- 16 or/1-15
- 17 (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
- 18 exp ANIMAL/
- 19 Animal Experiment/
- 20 Nonhuman/
- 21 Human/
- 22 Human Experiment/
- 23 or/17-20
- 24 21 or 22
- 25 23 not (23 and 24)
- 26 16 not 25
- 27 exp Psoriasis/

- 28 (psoria\$ or anti psoria\$ or antipsoria\$).mp.
- 29 or/27-28
- 30 psoralen\$.tw.
- 31 puva.tw.
- 32 (puva or ultraviolet A or ultra violet A or UVA or UVB or ultraviolet B or ultra violet B).tw.
- 33 (NBUVB or BBUVB).tw.
- 34 ((narrowband or narrow band) adj1 (UVB or ultraviolet B or ultra violet B)).tw.
- 35 ((broadband or broad band) adj1 (UVB or ultraviolet B or ultra violet B)).tw.
- 36 (pnbuvb or repuva).tw.
- 37 MOP.ti,ab.
- 38 methoxypsoralen\$.tw.
- 39 (retinoid\$ or acitretin\$ or etretinate\$ or vitamin A deriv\$).tw.
- 40 (synthet\$ adj1 vitamin A).tw.
- 41 tmp.ti,ab.
- 42 trimethylpsoralen.tw.
- 43 (cyclosporin\$ or ciclosporin\$ or csa).tw.
- 44 hydroxyurea\$.mp. or hydroxycarbamide\$.tw.
- 45 (fumarate\$ or fumaric acid ester\$).tw.
- 46 fumaderm.tw.
- 47 (dmfae or dimethylfumar\$ or monoethylfumar\$).tw.
- 48 (mefae-ca or mefae-mg or mefae-na or mefae-zn).ti,ab.
- 49 (ohfae or octyl hydrogen fumar\$).tw.
- 50 (dithranol or anthralin).tw.
- 51 (goeckerman adj1 (therap\$ or treatment\$ or method\$ or regime\$)).tw.
- 52 (ingram adj1 (therap\$ or treatment\$ or method\$ or regime\$)).tw.
- 53 methotrexate.tw.
- 54 (phototherap\$ or photo therap\$ or photochemotherap\$ or photo chemotherap\$ or photo chemo therap\$).tw.
- 55 psoralen/ or psoralen derivative/
- 56 phototherapy/ or photochemotherapy/ or puva/
- 57 ultraviolet radiation/ or ultraviolet a radiation/ or ultraviolet b radiation/
- 58 methoxsalen/ or methoxsalen derivative/
- 59 retinoid/ or etretin/ or etretinate/
- 60 retinol/ or retinol derivative/
- 61 Retinoic Acid/
- 62 Trimethylpsoralen/
- 63 Cyclosporin/
- 64 HYDROXYUREA/
- 65 fumaric acid/ or fumaric acid derivative/
- 66 fumaric acid dimethyl ester/ or fumaric acid ethyl ester/
- 67 dithranol/ or dithranol derivative/
- 68 METHOTREXATE/
- 69 antipsoriasis agent/ or 4' aminomethyl 4,5',8 trimethylpsoralen/ or fumaderm/ or psoralon/ or psorin/
- 70 or/30-69
- 71 26 and 29 and 70
- 72 limit 71 to em="200406 - 200637"

A6. The processes used and the method of the mixed treatment comparison is not described in sufficient detail for the ERG to review the approach taken and therefore the outcomes of the analysis. Please provide further details about the processes used, including the selection of studies for inclusion, and quality assessment of included studies. Please also describe whether the comparator trial populations would meet the anticipated indication for treatment with Adalimumab.

Systematic searches were undertaken with MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and ISI Science and Technology Proceedings (Web of Knowledge – <http://wos.mimas.ac.uk>) from their inception dates (terms used to search are given above). No restrictions were placed on years, publication status or language, though papers not in English were eventually excluded. The search was supplemented with hand searching after the original systematic search as well as data from unpublished trials.

Inclusion and exclusion criteria

Only randomised controlled trials of patients with moderate-to-severe psoriasis were included. Trials had to have a primary endpoint of between 8 to 16 weeks and it was necessary to have taken place in a developed country. The patients must have inadequately responded to topical treatments alone and had received prior systemic therapy or phototherapy, or were candidates for such treatment. All potential treatments for psoriasis with EMEA or FDA approval were eligible (adalimumab is included although at time of analysis it was undergoing EMEA regulatory approval). This included the biologics (adalimumab, efalizumab, etanercept, infliximab), non-biologic systemics (retinoids, methotrexate, ciclosporin) and non-systemic therapies (phototherapy, combination therapy). A link to placebo, either through direct comparison or through comparison with any other active agent compared to placebo, was necessary in order for the treatment to be included. The Psoriasis Area and Severity Index (PASI) and its derived response scores were used as the primary outcome, as it is the most consistently reported measure in RCTs.

Data Abstraction and Quality Assessment

The inclusion criteria for the analysis were applied by one researcher and verified by another. Discrepancies between the researchers were infrequent and resolved through discussion. The same process was utilised in the data abstraction process, and in the assignment of a quality rating. Study and patient characteristics, and efficacy data at the trial's primary endpoint were extracted. All data extracted comply with intention-to-treat and evidence reported in multiple publications were combined into one record and reported as one trial. The quality assessment of the included trials was performed using the Jadad scale. The Jadad scale was applied because it is widely used to measure the quality of clinical trials. The scale consists of the following 5 questions: 1) Is the study randomised? 2) Is the study double blinded? 3) Is there a description of withdrawals? 4) Is the randomisation adequately described? 5) Is the blindness adequately described?

Statistical Methods

Chi-square tests or Fisher's Exact tests were used to compare the PASI response rates of different dosages in a same treatment. Doses that were not statistically significantly different to the licensed dose in terms of PASI response rates were combined to reduce discarding potential evidence. Doses that were statistically different to licensed doses were removed. A mixed treatment comparison (MTC) evidence synthesis following from the methods developed by the York Assessment Group was run in WinBUGS version 1.4.1 to determine the comparative efficacy of the various treatments. MTC is an extension of classical meta-analytic techniques that allows indirect comparisons between treatments where no head-to-head data is available. In order to perform the analysis, all trials must be connected through a 'chain' of evidence, where every treatment can be connected to placebo either directly, or through another treatment that is connected to placebo. The PASI 50, 75 and 90 response rates from the trials are then used in a meta-analysis where the endpoints are jointly modelled using an ordered probit model. In this, where one of the PASI response rates is not reported,

the model uses the existing relationships to estimate that missing rate. For example, two of the efalizumab studies report PASI50 and PASI75, but do not report the more stringent PASI90 results.

A hierarchical Bayesian model was used, with non-informative prior distributions for each treatment. A burn in of 5000 simulations was used for convergence, followed by 10000 simulations for the estimation. The full details of methodology are described in Woolcott et al⁶. The result is a response rate for each treatment, which was estimated by using all observations and adjusting for variation in placebo response rates.

Results

Following the systematic review, 36 sources, consisting of 22 distinct trials were identified. Of these 22 trials, 20 are trials of biologics while 2 are trials of comparators. The biologic trials comprise 9704 subjects, 6566 of these received an anti-TNF or T-cell agent. The comparator trials comprise of 213 subjects, of whom 170 receive ciclosporin or methotrexate. Four trials study etanercept (n = 1965) 4 trials study infliximab (n = 1495), 3 trials study adalimumab (n = 1630), 5 trials study efalizumab (n = 3130), and 4 trials study alefacept (n = 1484). One trial studies ciclosporin versus placebo (n = 128) and 1 trial performs a direct comparison between ciclosporin and methotrexate (n = 85). Methotrexate is also the third comparator in one of the aforementioned adalimumab trials. While there were other trials studying ciclosporin, they did not meet all inclusion criteria (one did not have PASI response, another only reported 4-week results). The final analysis examined only treatments and dose regimens that are licensed and recommended for use in psoriasis patients in the UK. For example, two of the efalizumab trials administered efalizumab 1mg/kg (the licensed dose) as well as 2mg/kg (not licensed). In this case, only the 1mg/kg dose is estimated in the analysis. Alefacept was also excluded from the analysis because it is currently not licensed for use for psoriasis patients in the UK. The quality of the included trials was high, with a mean of 4.3 on the Jadad scale. Only 4 trials had a quality rating lower than 4 and no trials had a quality rating below 3.

Overall, baseline demographics did not differ widely among trials. Patients were of similar age (mean = 44 years) and disease duration (mean = 19 years) and all trials had a higher proportion of male subjects. The mean baseline characteristics for the comparator trial populations are in line with the anticipated licensed indication for adalimumab. For all these trials, the mean baseline BSA is greater than 10% and the baseline PASI is greater than 10. Efficacy results were reported at primary endpoints of between 8 and 16 weeks.

Table 5.6.1 from Abbott's submission has been updated below to include the Jadad quality score for each trial:

Table 5.6.1: Studies included in the evidence synthesis (including quality scoring)

AUTHOR (YEAR)	COMPARATOR AND DOSE	N	AGE	% MALE	PS DUR (YRS)	BSA %	BASE PASI	PASI 50	PASI 75	PASI 90	END POINT (WKS)†	Quality Rating
Papp, KA et. al. (2005) ⁷ (CONSORT)	Placebo	193	44	64%	18	20	16	9%	3%	1%	12	4
	Etanercept 25 mg BIW	196	46	65%	22	23	16.9	64%	34%	11%		
	Etanercept 50 mg BIW	194	45	67%	18	25	16.1	77%	49%	21%		
Gottlieb, AB et al. (2003) ⁸	Placebo	55	47	67%	20	34	19.5	11%	2%	0%	12	5
	Etanercept 25 mg BIW	57	48	58%	23	30	17.8	70%	30%	11%		
Leonardi, CI, et al. (2003) ⁹	Placebo	166	46	63%	18	29	18.3	14%	4%	1%	12	5
	Etanercept 25 mg OW	160	44	74%	19	28	18.2	41%	14%	3%		
	Etanercept 25 mg BIW	162	45	67%	19	29	18.5	58%	34%	12%		
	Etanercept 50 mg BIW	164	45	65%	19	30	18.4	74%	49%	22%		
Tyring, S, et al. (2006) ¹⁰	Placebo	307	46	70%	20	27	18.1	14%	5%	1%	12	5
	Etanercept 50 mg BIW	311	46	65%	20	27	18.3	74%	47%	21%		
Gottlieb, AB et al. (2004) ¹¹ (SPIRIT)	Placebo	51	45	61%	16	26	18	22%	6%	2%	10	5
	Infliximab 3mg/kg	99	45	71%	18	29	20	84%	72%	45%		
	Infliximab 5 mg/kg	99	44	74%	16	25	20	97%	88%	58%		
Reich, K et. Al. (2005) ¹² (EXPRESS I)	Placebo	77	44	79%	17	34	22.8	8%	3%	1%	10	5
	Infliximab 5 mg/kg	301	43	69%	19	34	22.9	91%	80%	57%		
Chaudhari, U, et al (2001) ^{13 *}	Placebo	11	45	73%	-	-	20.3	18%	18%	-	10	4
	Infliximab 5 mg/kg	11	51	64%	-	-	22.1	82%	82%	-		
	Infliximab 10 mg/kg	11	35	100%	-	-	26.6	91%	73%	-		
Menter, A, et al (2007) ¹⁴ (EXPRESS II)	Placebo	208	44	69%	18	28	19.8	-	2%	1%	10	5
	Infliximab 3 mg/kg	313	43	66%	18	28	20.1	-	70%	37%		
	Infliximab 5 mg/kg	314	45	65%	19	29	20.4	-	76%	45%		
Gordon, KB et al (2006) ¹⁵	Placebo	52	43	65%	19	28	16	14%	4%	0%	12	4
	Adalimumab 40 mg EOW	45	46	71%	21	29	16.7	76%	53%	24%		
	Adalimumab 40 mg OW	50	44	66%	18	25	14.5	88%	80%	48%		
Saurat, J et al. (2006) ¹⁶ (CHAMPION)	Placebo	53	41	66%	19	28	19.2	30%	19%	11%	16	5
	Adalimumab 40 mg EOW	108	43	65%	18	34	20.2	88%	80%	52%		
	Methotrexate	110	42	66%	19	32	19.4	62%	36%	14%		
Abbott (2006) ¹⁷ (REVEAL)	Placebo	398	45	65%	19	26	19.01	15%	7%	2%	16	5
	Adalimumab 40 mg EOW	814	44	67%	19	26	18.83	83%	71%	45%		
Gordon (2003) ¹⁸	Placebo	187	45	71%	19	27	19	14%	4%	1%	12	5
	Efalizumab 1 mg/kg OW	369	45	68%	19	28	19	59%	27%	5%		
Dubertret L, et al. (2006) ¹⁹ (CLEAR)	Placebo	264	45	67%	21	36	23	14%	4%	-	12	4
	Efalizumab 1 mg/kg OW	529	44	67%	19	37	23.6	54%	31%	-		
Papp, KA et. al. (2006) ²⁰	Placebo	236	46	59%	18	27	18.69	14%	3%	-	12	4

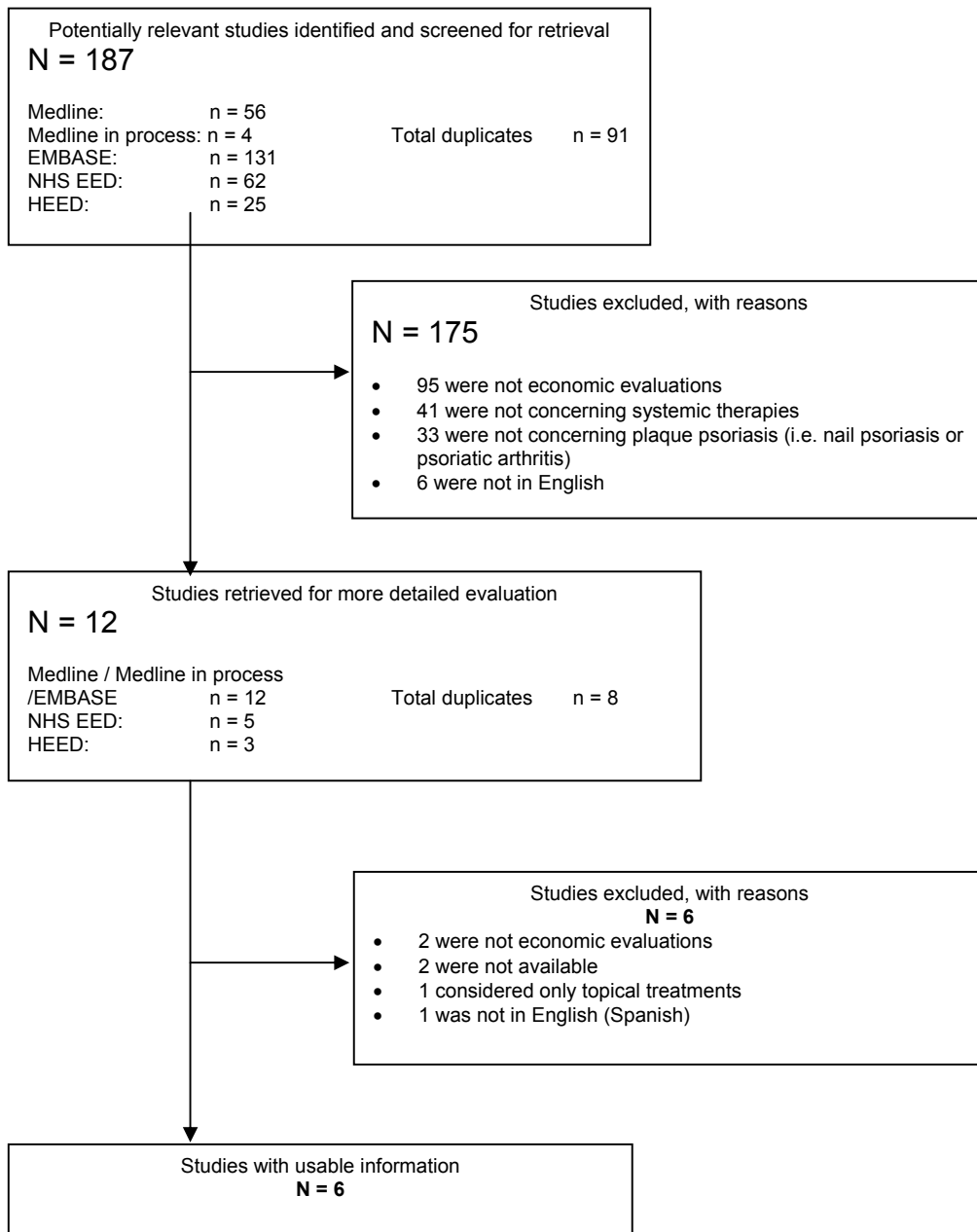
Leonardi et al. (2005) ²¹	Efalizumab 1 mg/kg OW	450	46	67%	18	28	19.14	52%	26%	-	12	3
	Placebo	170	42	73%	19	29	19	15%	2%	1%		
	Efalizumab 1 mg/kg OW	162	45	73%	19	30	18.6	61%	39%	12%		
Lebwohl et al. (2003) ²²	Efalizumab 2 mg/kg OW	166	46	71%	17	30	18.9	51%	27%	5%	12	5
	Placebo	122	-	-	-	-	-	16%	5%	1%		
	Efalizumab 1mg/kg OW	232	-	-	-	-	-	52%	22%	4%		
Meffert (1997) ²³	Efalizumab 2 mg/kg OW	243	-	-	-	-	-	57%	28%	6%	10	3
	Placebo	43	38 [†]	64 [†]	-	-	15.6	10%	5%	-		
	Ciclosporin 1.25 mg/kg/day	41	38 [†]	64 [†]	-	-	16.7	21%	10%	-		
Heydendael (2003) ²⁴	Ciclosporin 2.5mg/kg/day	44	38 [†]	64 [†]	-	-	15.1	58%	29%	-	16	3
	Methotrexate	43	41.6	65%	-	-	13.4	-	60%	40%		
	Ciclosporin 3-5 mg/kg/day	42	38.3	69%	-	-	14	-	71%	33%		

[†] Mean for the whole trial, not the specific arm

• **Section B: Cost-effectiveness**

B1. Please supply a literature flow chart and list of excluded studies with reasons for exclusion.

Appendix 2 contains a list of the excluded studies detailed in the flow chart below.



B2. For trial MO2-528 data was collected at baseline and 12 weeks for EuroQoL and it is clear that this is the time difference used for assessing the relationship between QALY change and PASI response. However, for trial MO4-716, the time periods were 0, 12 and 16 weeks. Please clarify what period was used to calculate the relationship for this trial - was it 0 to 12 weeks, 0 to 16 weeks, 12 to 16 weeks, or both 0 to 12 weeks and 12 to 16 weeks?

A mixed-model repeated-measures analysis of covariance (ANCOVA) was used to compare the mean EQ-5D utility change between DLQI groups. For the MO2-528 study, only the 12 week endpoint was used while for the MO4-716 both the 12 and the 16-week assessments were used. The analysis includes all endpoints from both trials into a single model, accounting for the correlation between repeated measures in the M04-716 study. The model included variables for baseline DLQI group and PASI category and includes a random effect for the intercept. This type of model allows for a more reliable estimate since more information is incorporated.

B3. The EQ-5D describes the health states of those individuals who complete them. These are then valued using a scoring system using values obtained from the general public. MO2-528 was carried out in the USA and Canada and MO4-716 was carried out in Europe and Canada. Please confirm whether or not the same scoring system was used for all individuals and whether all health states were assigned utility values using UK preference values.

We used the UK tariff to derive utility values for all EQ-5D health states irrespective of the country in which the trial was undertaken.

B4. Baseline utilities from the two trials that were used for the utility estimation are not provided in the submission, only the changes in utility associated with different PASI responses. It is not clear what severity of psoriasis these values are associated with. Please provide the mean baseline PASI score (and ideally, mean DLQI score) for the DLQI>10, DLQI<10 and all patient groups.

- **Table B4.1 Baseline utility and psoriasis severity values**

Baseline Variables	Trial M02-528				Trial M04-716			
	Baseline DLQI≤10 (n=62)		Baseline DLQI>10 (n=82)		Baseline DLQI≤10 (n=132)		Baseline DLQI>10 (n=119)	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
EQ-5D	0.794	0.159	0.563	0.307	0.810	0.159	0.647	0.266
PASI	13.679	6.775	17.290	7.513	18.759	6.651	19.943	7.526
DLQI	6.323	2.715	17.720	5.430	5.796	2.615	16.017	3.895

Note: Only patients who had baseline EQ-5D measures were included in the analysis

B5. It is not clear from the spreadsheet model presented how deterministic one way sensitivity analysis can be carried out. Please clarify whether one-way deterministic sensitivity analysis was carried out using the spreadsheet model and, if so, how?

Instructions for one-way sensitivity analyses are contained in the Introduction sheet of the model. Options are available in drop-down list and “run analysis” button is used to start the model. The model allows the selection of a number of one-way sensitivity analyses.

B6. Please clarify whether it is assumed that the benefit from treatment in the trial period occurs instantaneously, i.e. whether the benefit of the PASI response is gained for the whole duration of this trial period.

Following the York assessment report, we assume instantaneous benefit for all treatments. Compared to a half cycle correction approach, this seems more reasonable since many patients benefit quickly from treatment. The same assumption is used for all treatments, and therefore is unlikely to bias the estimated ICERs in favour of adalimumab. This assumption is likely to be optimistic only for methotrexate, as the onset of treatment response is somewhat slower for methotrexate in comparison to biologics.

• **Section C: Textual clarifications and additional points**

C1. Please confirm that Table 6.2.7.1 (page 106) is the all patient group (DLQI >10 and DLQI = 10 combined) as this is not clear from the title or text.

Yes, this is the “all patients” group

C2. Table 6.2.6.1 (page 103) indicates that for intermittent Etanercept 50 mg the trial period requires 74% of the continuous dose. Please explain why this is.

This assumption of 74% was obtained from our analysis of psoriasis patients in the IHCIS claims database. In this analysis, we looked at the average weekly dose (mg/week) by treatment periods of all users of etanercept. It could be argued that all patients who require high-dose etanercept would be started on 50 mg BIW (100 mg weekly) until they have been assessed for response. However, not all patients require such a high dose in order to achieve response. For the purposes of our model, we took a conservative approach and assumed that the mean weekly dose taken in the 0-90 day period of the IHCIS data (74 mg) would be representative of the highest dose needed for the patients to achieve response. Thus, the model conservatively gives patients on high dose etanercept the benefit of the efficacy from etanercept 50 mg BIW but the costs from using an average of 74 mg per week instead of the expected 100 mg per week.

Table C2.1 Average weekly dosage (mg/week) by treatment periods

Period (days)	All Users (N=497)		
	N	mean (SD)	median (Q1-Q3)
0-90	497	73.8 (26.2)	80.5 (52.4-95.9)
91-180	496	54.7 (25.5)	51.5 (38.8-66.8)
181-270	476	45.7 (23.5)	45.8 (30.9-56.1)
271-360	455	44.2 (25.6)	44.7 (27.6-56.3)
91-360	497	46.3 (22.1)	46.6 (30.7-57.6)

References

- ¹ Griffiths CEM, Barker JNWN. Psoriasis 1: Pathogenesis and clinical features of psoriasis. *The Lancet* 2007;**370**:263-271.
- ² Lebhol M. Psoriasis. Seminar: *Lancet* 2003;**361**:1197–204.
- ³ Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. EMEA. Adopted by the CHMP on 18 November 2004; date of operation June 2005. Doc. Ref. CHMP/EWP/2454/02 corr. Last accessed 21 August 2007.
<http://www.emea.europa.eu/pdfs/human/ewp/245402en.pdf>
- ⁴ British Association of Dermatologists. Psoriasis Guideline 2006.
- ⁵ Gordon K, Langley R, Leonardi C, Menter A, Okun M, McIlraith M. Efficacy and Safety of adalimumab treatment of chronic plaque psoriasis in patients who meet some criteria for biological interventions in accordance with British Association of Dermatologists guidelines. *British Journal of Dermatology* 2006;**155** (Suppl 1):21-61. Abstract No. P-28.
- ⁶ Woolacott N, Hawkins N, Mason A, et al. Etanercept and efalizumab for the treatment of psoriasis: A systematic review. *Health Technol Assess.* 2006;**10**:1-252.
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