Health Technology Assessment 2006; Vol. 10: No. 46

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November 2006

Health Technology Assessment
NHS R&D HTA Programme

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Etanercept and efalizumab for the treatment of psoriasis: a systematic review

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Declared competing interests of authors: R Riemsma is a member of the editorial board of *Health Technology Assessment* but was not involved in the editorial process for this report

Published November 2006

This report should be referenced as follows:

Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technol Assess* 2006;**10**(46).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/26/01. The protocol was agreed in January 2004. The assessment report began editorial review in November 2005 and was accepted for publication in May 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

Etanercept and efalizumab for the treatment of psoriasis: a systematic review

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Objectives: To evaluate the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and efalizumab for the treatment of moderate to severe chronic plaque psoriasis.
Data sources: Major electronic databases and several Internet resources were searched up to April 2004.
Review methods: Systematic reviews were undertaken of the efficacy, safety and economic reviews of etanercept and efalizumab. An existing systematic review of the efficacy and safety of other treatments was also updated. Economic models supplied by the manufacturers of etanercept and efalizumab were critiqued. An economic model was then developed of etanercept and efalizumab in the treatment of moderate to severe chronic plaque psoriasis.
Results: The review of the clinical evidence identified a total of 39 published and three unpublished studies: eight randomised controlled trials (RCTs) of the efficacy of etanercept (three trials) and efalizumab (five); 10 studies of the adverse effects of the interventions; and 24 RCTs of the efficacy of the other treatments for moderate to severe psoriasis. The trials of the efficacy of the interventions were all double-blind and placebo-controlled trials and generally of good quality, but three of the five efalizumab trials were poorly reported.
A total of 1347 patients were included in the etanercept trials and 2963 in the efalizumab trials. Data on the efficacy of etanercept 25 mg twice a week for 12 weeks were available from three RCTs. On average, active treatment resulted in 62% of patients achieving a Psoriasis Area and Severity Index (PASI) 50, 33% achieving a PASI 75, 11% achieving a PASI 90 and 40% were assessed as clear or almost clear. These figures are not adjusted for changes relative to placebo. Improvement in quality of life as assessed by mean percentage change in Dermatology Life Quality Index (DLQI) was around 59% with etanercept 25 mg twice a week compared with 9% with placebo, and all mean differences that could be calculated were statistically significantly in favour of etanercept. Data on the efficacy of etanercept 50 mg twice a week for 12 weeks were available from two RCTs. Across the two trials, the proportion of patients achieving PASI 50, 75 and 90 was 76, 49 and 21%, respectively; the pooled relative risks were all statistically significantly in favour of etanercept. The findings for mean PASI after treatment, mean percentage change in PASI from baseline and mean percentage change in DLQI also demonstrated the efficacy of etanercept treatment. Evidence from one RCT indicates that the response to etanercept is maintained post-treatment, at least in the medium term, and data from uncontrolled follow-up phases reflect and extend these findings. Efalizumab at a dose of 1 mg/kg once a week subcutaneously was studied in five RCTs. Across these trials, 12 weeks of active treatment resulted in an average of 55% of patients achieving PASI 50, 27% PASI 75, 4.3% PASI 90 and 27% clear or minimal psoriasis status. These figures are not adjusted for changes relative to placebo. There is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks, and long-term follow-up data relate to a range of doses and are poorly reported and so cannot be used to draw even tentative conclusions regarding the long-term efficacy of efalizumab. Uncontrolled data from trial follow-up suggest that time to relapse may be around 60 days. No data indicating the existence or absence of any rebound in psoriasis after discontinuation of efalizumab were identified. There is no evidence relating to the efficacy of efalizumab upon retreatment. A mixed

treatment comparison analysis found a higher response rate in terms of PASI 50, 75 and 90 with etanercept than with efalizumab. Injection site reactions appear to be the most common adverse effects of etanercept. Overall, etanercept appears to be well tolerated in short- and long-term use, although many of the long-term data are not from patients with psoriasis. Headache, chills and, to a lesser extent, nausea, myalgia, pain and fever are the common adverse events associated with efalizumab. Overall, withdrawal rates due to adverse events are low. Longer term data for efalizumab are not readily available for evaluation, but the adverse events data up to 3 years appear to reflect those over 12 weeks and to remain stable. Unfortunately, few data for serious infections and serious adverse events with efalizumab are available. For the primary analysis comparing etanercept, efalizumab and supportive care, the results of the York Model suggest that the biological therapies would only be cost-effective for all patients with moderate to severe psoriasis if the NHS were willing to pay over £60,000 per QALY gained. In patients with poor baseline quality of life (fourth quartile DLQI), efalizumab, etanercept 25 mg (intermittent), etanercept 25 mg (continuous) and etanercept 50 mg (intermittent) would be cost-effective as part of a treatment sequence if the NHS were willing to pay £45,000, £35,000, £45,000 and £65,000 per QALY gained, respectively. In patients who are also at high risk of inpatient hospitalisation (21 days per annum), these therapies would be cost-effective as part of a sequence as long as the NHS were willingness to pay £25,000, £20,000, £25,000 and £45,000 per QALY gained, respectively. As part of a secondary analysis including a wider range of systemic therapies as comparators, the York Model found that it would only be cost-effective to use etanercept and efalizumab in a sequence after methotrexate, ciclosporin and Fumaderm.

Conclusions: Clinical trial data indicate that both etanercept and efalizumab are efficacious in patients who are eligible for systemic therapy, but the economic evaluation demonstrates that these biological therapies are likely to be cost-effective only in patients with poor baseline QoL and who are at risk of hospitalisation. Efficacy trials conducted in the specific population for which etanercept and efalizumab are licensed are required, as are long-term comparisons of etanercept and efalizumab with other treatments for moderate to severe psoriasis. Long-term efficacy trials and safety/tolerability data for patients treated with etanercept or efalizumab are required, as are trials on the response of specific subtypes of psoriasis to different drugs. Research on the rate of inpatient hospitalisation in patients with moderate to severe psoriasis is warranted, and the effect of treatment on this rate.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Acitretin A synthetic derivative of vitamin A that is taken orally. It is indicated for severe psoriasis.

Adverse effect An abnormal or harmful effect caused by and attributable to exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.

Biological therapies (biologicals) Medical preparations derived from living organisms. In psoriasis, this category of pharmaceuticals may target the immune system.

Ciclosporin A medication originally developed to prevent the immune system from rejecting transplanted organs, which has also proved helpful in treating psoriasis.

Coal tar Tar distilled from bituminous coal applied to the skin to treat psoriasis. Often used with UV light therapy.

Confidence interval (CI) The typical ('classical' or 'frequentist') definition is the range within which the 'true' value (e.g. size of effect of an intervention) would be expected to lie if sampling could be repeated a large number of times (e.g. 95% or 99%).

Corticosteroid A synthetic hormone similar to that produced naturally by the adrenal glands that is available in pill, topical and injectable forms.

Cost–benefit analysis An economic analysis that converts the effects or consequences of interventions into the same monetary terms as the costs and compares them using a measure of net benefit or a cost–benefit ratio

Cost-effectiveness analysis An economic analysis that expresses the effects or consequences of interventions on a single dimension. This would normally be expressed in 'natural' units (e.g. cases cured, life-years gained, additional strokes prevented). The difference between interventions in terms of costs and effects is typically expressed as an incremental cost-effectiveness ratio (ICER) (e.g. the incremental cost per life-year gained).

Cost–utility analysis The same as a cost-effectiveness analysis but the effects or consequences of interventions are expressed in generic units of health gain, usually quality-adjusted life-years (QALYs).

Credible intervals Bayesian version of confidence intervals. It is the range within which the 'true' value (e.g. size of effect of an intervention) is expected to lie with a given degree of certainty (e.g. 95% or 99%).

Effect size A generic term for the estimate of effect for a study.

Emollient An agent that holds moisture in the skin, and by doing so softens or soothes it.

Erythrodermic psoriasis The least common form of psoriasis in which the skin of almost the entire body becomes red and fiery, and may cause difficulty regulating the body's temperature and heart rate. People with this type of psoriasis may require hospitalisation.

Exchangeability In the context of evidence synthesis, there is no *a priori* reason to distinguish between the studies being synthesised. In mixed treatment comparison,

continued

Glossary *continued*

the assumption is effectively that interventions could have been randomised to studies.

Fixed effect model A statistical model that stipulates that the units under analysis (e.g. people in a trial or study in a meta-analysis) are the ones of interest, and therefore constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed-effect model.

Generalised pustular psoriasis An acute generalised inflammatory form of psoriasis with many of the same problems as erythrodermic psoriasis and usually requires hospital admission.

Goeckerman regimen A psoriasis treatment consisting of crude coal tar together with UVB phototherapy, usually administered in a hospital or a psoriasis clinic.

Guttate psoriasis A type of psoriasis characterised by drop-like lesions on the trunk, limbs and scalp. Characteristically, it is triggered by a preceding streptococcal infection such as tonsillitis.

Heterogeneity In systematic reviews, heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction is sometimes made between 'statistical heterogeneity' (differences in the reported effects), 'methodological heterogeneity' (differences in study design) and 'clinical heterogeneity' (differences between studies in key characteristics of the participants, interventions or outcome measures).

Hydroxyurea One of the older anti-cancer drugs that is sometimes used in the treatment of psoriasis. When used, either in combination or alone, it requires careful blood monitoring.

Immunomodulator A substance that alters the body's immune response.

Ingram regimen Daily UVB phototherapy followed by application of dithranol (anthralin) paste to the skin. This treatment was developed for inpatient use but is now often administered in a day-case setting.

Intention-to-treat An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.

Inverse (flexural) psoriasis Psoriasis that occurs in the skin folds such as the underarm or groin area, which can cause significant discomfort when one part of the skin rubs against another. When this occurs in the genital area, it can cause sexual difficulties.

Malignant melanoma A potentially fatal form of skin cancer. Psoriasis patients who have received photochemotherapy (PUVA) should be carefully monitored for this complication, which is increased some 10-fold over the expected rate in the general population and may develop many years after completing therapy.

Methotrexate One of the oldest chemotherapy drugs used to treat cancer; used in the treatment of psoriasis.

Mixed treatment comparison Mixed treatment comparison is a form of meta-analysis used to strengthen inference concerning the relative efficacy of two treatments. It uses data based on direct comparisons (A vs B and B vs C trials) and indirect comparisons (A vs C trials) also; it facilitates simultaneous inference regarding all treatments in order to select the best treatments.

Monoclonal antibody An antibody produced in a laboratory from a single clone that recognises only one antigen.

Narrowband UVB (NBUVB) Ultraviolet light in a narrow band of 311–313 nm, thought to be faster acting, and possibly safer, than other UV light treatments.

Ordered probit model Method designed to model a discrete dependent variable that takes ordered multinomial outcomes, for example $y = 0, 1, 2, 3, \ldots$ The ordered probit model can be expressed in terms of an underlying latent variable.

PASI score Psoriasis Area and Severity Index score, a number representing the extent, redness, thickness and scaliness of a person's psoriasis.

continued

Glossary *continued*

Palmoplantar pustular psoriasis Palmoplantar pustular psoriasis or palmoplantar pustulosis is limited to the palms and soles and appears to have different genetics from psoriasis vulgaris. Only a minority of patients have psoriasis elsewhere.

Photochemotherapy (PUVA) The addition of drugs to light therapy in order to intensify its effects.

Phototherapy The use of natural or artificial UV light to treat disease.

Placebo An inactive substance or procedure administered to a patient, usually to compare its effects with those of a real drug or other intervention, but sometimes for the psychological benefit to the patient through a belief that s/he is receiving treatment.

Plaque psoriasis The most common form of psoriasis, also known as psoriasis vulgaris, recognised by red, raised lesions covered by silvery scales. About 80% of psoriasis patients have this type.

Psoralen A photosensitising drug used in combination with UVA to treat psoriasis (also known as PUVA therapy).

Psoriasis A chronic skin disease characterised by inflammation and scaling. There are several forms of the disease, of which chronic plaque psoriasis is the most common. Scaling occurs when cells in the outer layer of skin reproduce faster than normal and pile up on the skin's surface. It is understood to be a disorder of the immune system.

Psoriatic arthritis This disease is characterised by stiffness, pain and swelling in the joints, especially of the hands and feet. Early diagnosis and treatment can help inhibit the progression of joint deterioration.

Pustular psoriasis There are two important types of pustular psoriasis: generalised pustular psoriasis and palmoplantar pustular psoriasis or palmoplantar pustulosis.

PUVA Psoralen plus UVA is a psoriasis treatment that combines exposure to UVA light with psoralens. Psoralens are naturally occurring compounds that interact with UVA light; they may be taken orally or applied directly to the skin (e.g. as in bath PUVA).

Quality-adjusted life-year (QALY) An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Quality of life (QoL) A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity and also other factors which might affect their physical, mental and social well-being.

Random effects model A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Randomised controlled trial (RCT) (synonym: randomised clinical trial) An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared.

Relative risk (RR) (synonym: risk ratio) The ratio of the proportion of the intervention group experiencing an event to the proportion of the control group experiencing the event. The event can be adverse, such as developing cancer, or beneficial, such as responding to therapy. For adverse outcomes, a relative risk of less than one indicates a beneficial effect of the intervention. For beneficial outcomes, a relative risk of more than one indicates a beneficial effect of the intervention. A relative risk of one indicates no difference between intervention and control.

Remission The state of a disease being inactive or under control.

Retinoids Vitamin A derivatives often used in topical or oral psoriasis therapy.

Rheumatoid arthritis A chronic autoimmune disease characterised by pain, stiffness, inflammation, swelling and, sometimes, destruction of joints.

Sensitivity analysis An analysis used to determine how sensitive the results of a study

continued

Glossary *continued*

or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Squamous cell carcinoma A form of cancer that may affect the skin of people who have had excessive exposure to ultraviolet light, particularly PUVA.

Statistical significance An estimate of the probability of an association (effect) as large or larger than what is observed in a study occurring by chance, usually expressed as a *p*-value.

Systemic Affecting the entire body internally.

Systemic treatment A treatment given internally, usually by mouth or injection.

T cell A type of white blood cell that is part of the immune system that normally helps protect the body against infection and disease.

Tars Natural, sticky substances used to treat psoriasis, as in coal tar shampoos, topical creams and ointments.

Thrombocytopenia A disorder sometimes associated with abnormal bleeding in which the number of platelets (cells that help blood to clot) is abnormally low.

Topical agent A treatment such as a cream, salve or ointment that is applied to the surface of the skin.

Toxicity The potential of a drug or treatment to cause harmful side-effects.

Tumour necrosis factor (TNF) One of the cytokines, or messengers, known to be fundamental to the disease process that underlies psoriasis. It is believed to play a key role in the onset and the continuation of skin inflammation.

Ultraviolet (UV) light UV light (or, more correctly, UV radiation) is an important part of the energy emitted by the sun but can be produced artificially; it has a shorter wavelength than visible light and can cause profound biological effects. The shortest UV wavelengths (UVC) do not usually reach the Earth's atmosphere; UVB (290–320 nm) is responsible for acute sunburn, but when carefully controlled can be useful for treating psoriasis; long-wavelength UV (UVA: 320–400 nm) penetrates deeper into the skin than UVB and contributes to sun-induced skin ageing. Certain chemicals including psoralens (*q.v.*) interact with UVA, a property which is used in PUVA (*q.v.*) treatment of psoriasis.

UVB phototherapy Treatment involving measured doses of UV light in the UVB wavelength. Two types are broadband UVB and the increasingly used narrowband UVB. Both are used to achieve clearance of psoriasis.

Variance A measure of the variation shown by a set of observations, defined by the sum of the squares of deviations from the mean, divided by the number of degrees of freedom in the set of observations.

Visual analogue scale Direct rating where raters are asked to place a mark at a point between two anchor states appearing at either end of the line. It is used as a method of valuing health states.

Weighted mean difference (in meta-analysis) A method of meta-analysis used to combine measures on continuous scales, where the mean, standard deviation and sample size in each group are known. The weight given to each study is determined by the precision of its estimate of effect and is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.

List of abbreviations

ANA	antinuclear antibodies
BSA	body surface area
CHF	congestive heart failure
CI	confidence interval
DLQI	Dermatology Life Quality Index
DMARD	disease-modifying anti-rheumatic drugs
EMEA	European Medicines Evaluation Agency
EQ-5D	EuroQol-5D
FDA	Food and Drug Administration
HEED	Health Economic Evaluation Database
HODaR	Health Outcomes Data Repository
HRQoL	Health-related quality of life
IAGI	Investigator's Assessment of Global Improvement
ICER	incremental cost-effectiveness ratio (e.g. incremental cost per QALY gained)
ITT	intention-to-treat
MeSH	MEDLINE Thesaurus
MS	multiple sclerosis
NBUVB	narrowband ultraviolet radiation band B
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NRR	National Research Register
NS	not stated
NSAID	non-steroidal anti-inflammatory drug
OLS	ordinary least-squares
PASI	Psoriasis Area and Severity Index
PDI	Psoriasis Disability Index
PGA	physician's global assessment
PSI	Psoriasis Severity Index
PSSRU	Personal Social Services Research Unit
PUVA	photochemotherapy
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RePUVA	retinoid plus PUVA
RR	relative risk
SAPASI	Self-Administered Psoriasis Area and Severity Index
s.c.	subcutaneously
SD	standard deviation
SE	standard error
SF-36	Short Form with 36 Items
SLE	systemic lupus erythematosus
SPC	summary of product characteristics
SWB	subjective well-being scale
TB	tuberculosis

continued

List of abbreviations *continued*

TNF	tumour necrosis factor	UVB	ultraviolet radiation band B
TSS	Total Severity Score	VAS	visual analogue scale
URT	upper respiratory tract	WMD	weighted mean difference
UVA	ultraviolet radiation band A		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable amount of data that were supplied by Wyeth and Serono and which are deemed commercial in confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence data removed and replaced by the statement 'CiC removed' is available on the NICE website at www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences and tables have been removed. Readers should bear in mind that the discussion and conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Executive summary

Background

Psoriasis is a common inflammatory skin disease, with estimates of its world prevalence ranging from 0.5 to 4.6% and UK prevalence estimated at around 1.5%. Psoriasis generally occurs in adults, with males and females being equally commonly affected by the condition. Ethnic variations have been identified and Caucasians are more likely to suffer from the disease. Psoriasis is a chronic disorder that can be physically and emotionally debilitating and which can require life-long treatment. Plaque psoriasis, characterised by clearly demarcated, red, scaling plaques, is the most common form of psoriasis, occurring in more than 80% of cases. In the UK, both etanercept (Enbrel®) and efalizumab (Raptiva®) have recently been licensed for the treatment of adults with moderate to severe plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate or photochemotherapy (PUVA). Both etanercept and efalizumab are new biological agents, which target pathologic T cell activity. Other therapies available for the treatment of moderate to severe psoriasis include phototherapy and systemic agents such as ciclosporin, methotrexate and retinoids, all of which have limitations on their use due to serious long-term adverse effects.

Objective

The objective of the study was to evaluate the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and efalizumab for the treatment of moderate to severe chronic plaque psoriasis.

Methods

For the evaluation of efficacy, randomised controlled trials (RCTs) with a minimum of 20 participants were included. For the evaluation of safety, long-term experimental and observational studies of at least 24 weeks' duration and including a minimum of 100 patients were eligible for inclusion. Studies or data without an explicitly stated denominator were excluded from the review. In addition, adverse event data from the trials of efficacy of etanercept and efalizumab were included. An update of an existing systematic review of the efficacy and safety of other treatments for moderate to severe chronic plaque psoriasis was also undertaken. For the efficacy evaluation, RCTs with a minimum of 20 participants were included. Information on the adverse effects of the other treatments for moderate to severe psoriasis were summarised from tertiary reference sources.

A mixed treatment comparison analysis was then carried out to enable comparisons to be made between the efficacy of all treatments (etanercept and efalizumab and other) for moderate to severe chronic plaque psoriasis.

A systematic review was then undertaken of published economic evaluations. Studies were eligible for inclusion if they assessed both costs and benefits and compared findings with an appropriate comparator treatment. The economic models supplied by the manufacturers of etanercept and efalizumab were critiqued. An economic model was then developed of etanercept and efalizumab in the treatment of moderate to severe chronic plaque psoriasis.

For the systematic reviews, relevant studies were identified through searches of the major electronic databases. All databases were searched from their inception to the date of the search. Searches were also undertaken on several Internet resources. Searches took place over the period from January to April 2004.

The primary outcome in the review was the proportion of patients achieving a 75% reduction in the Psoriasis Area and Severity Index (PASI) score ('PASI 75'). The PASI is an assessment score, representing the extent, redness, thickness and scaliness of a person's psoriasis on a single scale, usually scored from 0 (no psoriasis) to 72.

Results

Clinical evaluation

Number and quality of studies

Our review of the clinical evidence identified a total of 39 published and three unpublished studies: eight RCTs of the efficacy of etanercept (three trials) and efalizumab (five); 10 studies of the adverse effects of the interventions; and 24 RCTs of the efficacy of the other treatments for moderate to severe psoriasis.

The trials of the efficacy of the interventions were all double-blind and placebo-controlled trials and generally of good quality, but three of the five efalizumab trials were poorly reported. A total of 1347 patients were included in the etanercept trials and 2963 in the efalizumab trials.

Efficacy of etanercept and efalizumab

Data on the efficacy of etanercept 25 mg twice a week for 12 weeks were available from three RCTs. On average, active treatment resulted in 62% of patients achieving a PASI 50, 33% achieving a PASI 75, 11% achieving a PASI 90 and 40% were assessed as clear or almost clear. These figures are not adjusted for changes relative to placebo. Improvement in quality of life as assessed by mean percentage change in Dermatology Life Quality Index (DLQI) was around 59% with etanercept 25 mg twice a week compared with 9% with placebo, and all mean differences that could be calculated were statistically significantly in favour of etanercept. Data on the efficacy of etanercept 50 mg twice a week for 12 weeks were available from two RCTs. Across the two trials, the proportion of patients achieving PASI 50, 75 and 90 was 76, 49 and 21%, respectively; the pooled relative risks were all statistically significantly in favour of etanercept. The findings for mean PASI after treatment, mean percentage change in PASI from baseline and mean percentage change in DLQI also demonstrated the efficacy of etanercept treatment.

Evidence from one RCT indicates that the response to etanercept is maintained post-treatment, at least in the medium term, and data from uncontrolled follow-up phases reflect and extend these findings. Uncontrolled data from follow-up in one trial suggest no real evidence for severe exacerbation of psoriasis after discontinuation of treatment. There is evidence from one trial that retreatment in patients who have relapsed following an earlier treatment period does not induce a poorer response than initial treatment. Overall, the trial populations may not truly reflect the difficult-to-treat patients for whom etanercept is licensed.

Efalizumab at a dose of 1 mg/kg once a week subcutaneously was studied in five RCTs. Across these trials, 12 weeks of active treatment resulted in an average of 55% of patients achieving PASI 50, 27% PASI 75, 4.3% PASI 90 and 27% clear or minimal psoriasis status. These figures are not adjusted for changes relative to placebo. There is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks, and long-term follow-up data relate to a range of doses and are poorly reported and so cannot be used to draw even tentative conclusions regarding the long-term efficacy of efalizumab. Uncontrolled data from trial follow-up suggest that time to relapse may be around 60 days. No data indicating the existence or absence of any rebound in psoriasis after discontinuation of efalizumab were identified. There is no evidence relating to the efficacy of efalizumab upon retreatment. As for etanercept, the trial populations may not truly reflect the difficult-to-treat patients for whom efalizumab is licensed.

Adverse effects of etanercept and efalizumab

Injection site reactions appear to be the most common adverse effects of etanercept. Overall, etanercept appears to be well tolerated in short- and long-term use, although many of the long-term data are not from patients with psoriasis; data derived from patients with rheumatoid arthritis may not be applicable to those with psoriasis. As identified from earlier reviews, the main areas of concern relate to uncommon but serious adverse events, but their significance is not readily discernible from the published reports of clinical trials.

Headache, chills and, to a lesser extent, nausea, myalgia, pain and fever are the common adverse events associated with efalizumab. Overall, withdrawal rates due to adverse events are low. Longer term data for efalizumab are not readily available for evaluation, but the adverse events data up to 3 years appear to reflect those over 12 weeks and to remain stable. Unfortunately, few data for serious infections and serious adverse events with efalizumab are available.

Other treatments for moderate to severe psoriasis

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the treatments available for the relief of moderate to severe psoriasis. Only infliximab and

ciclosporin have had their efficacy demonstrated in placebo-controlled RCTs, but trials are typically short term and include small numbers of patients. Although clinical experience has demonstrated excellent efficacy of PUVA and methotrexate, no placebo-controlled trials have been conducted. In clinical trials, methotrexate appears to be as effective as ciclosporin. The trials of other treatments, acitretin, RePUVA, and NBUVB, in comparison with PUVA, provide only limited evidence, demonstrating some degree of effectiveness but making it difficult to draw firm conclusions regarding relative efficacy.

Mixed treatment comparison analysis

To enable indirect comparisons to be made between all treatments for moderate to severe psoriasis, a meta-analysis of the PASI 50, 75 and 90 response rates from the RCTs was performed. The end-points were jointly modelled using an ordered probit model. The available data permitted the inclusion of etanercept (25 and 50 mg), efalizumab, infliximab, ciclosporin, methotrexate, Fumaderm and placebo in this mixed-treatment comparison that was implemented as a Bayesian hierarchical model.

In terms of mean response rate, when response is taken as PASI 75, infliximab appears the most effective, followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. As shown by the credible intervals around the mean response rates, which overlap considerably, there is uncertainty around these response rates. This is also shown in terms of the relative risks of each option (compared with placebo) and their confidence intervals. These findings for the PASI 75 level of response are mirrored in the results for the PASI 50 and PASI 90.

Cost-effectiveness

One published article examining the cost-effectiveness of biological therapy in psoriasis was identified, but its methods and US focus give it limited relevance to UK practice. Therefore, the cost-effectiveness of etanercept and efalizumab was informed by models submitted by the two manufacturers, together with a *de novo* model from the assessment team (the York Model). The company models compare only each manufacturer's product with non-systemic therapy. In contrast, the York Model compares various therapeutic strategies based on etanercept and efalizumab, and supportive care. In a secondary analysis, the York Model also includes other systemic therapies (infliximab, ciclosporin, methotrexate and Fumaderm). The York Model uses efficacy data taken directly from the mixed treatment comparison analysis. Health effects are expressed in terms of quality-adjusted life-years (QALYs), where utilities for alternative PASI response categories are derived from a 'mapping' exercise. The focus of the York Model is to establish the most cost-effective **sequence** of therapies based on alternative threshold values for cost-effectiveness.

For the primary analysis comparing etanercept, efalizumab and supportive care, the results of the York Model suggest that the biological therapies would only be cost-effective for all patients with moderate to severe psoriasis if the NHS were willing to pay over £60,000 per QALY gained. In patients with poor baseline quality of life (fourth quartile DLQI), efalizumab, etanercept 25 mg (intermittent), etanercept 25 mg (continuous) and etanercept 50 mg (intermittent) would be cost-effective as part of a treatment sequence if the NHS were willing to pay £45,000, £35,000, £45,000 and £65,000 per QALY gained, respectively. In patients who are also at high risk of inpatient hospitalisation (21 days per annum), these therapies would be cost-effective as part of a sequence as long as the NHS were willing to pay £25,000, £20,000, £25,000 and £45,000 per QALY gained, respectively.

As part of a secondary analysis including a wider range of systemic therapies as comparators, the York Model found that it would only be cost-effective to use etanercept and efalizumab in a sequence after methotrexate, ciclosporin and Fumaderm.

Conclusions

There is good evidence that etanercept is efficacious in the treatment of moderate to severe psoriasis, and that the response is maintained up to 24 weeks. The most common adverse effect of etanercept is injection site reaction. Other serious adverse events, as identified from earlier reviews, are uncommon and not readily identified from clinical trials.

There is evidence that efalizumab is efficacious in the treatment of moderate to severe psoriasis, however there is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond

12 weeks. The publicly available information for efalizumab indicates that the drug is well tolerated over a 12-week period; however, few data for any longer term treatment are available for evaluation.

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the other treatments available for the relief of moderate to severe psoriasis. All other treatments are associated with serious and possibly long-term adverse events.

In a mixed treatment comparison, including etanercept, efalizumab, ciclosporin, Fumaderm, methotrexate, infliximab and placebo, infliximab appeared the most effective, followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. The pattern is consistent across the different PASI response categories.

Overall, clinical trial data indicate that both etanercept and efalizumab are efficacious in patients who are eligible for systemic therapy, but the economic evaluation demonstrates that these biological therapies are likely to be cost-effective only in patients with poor baseline quality of life and who are at risk of hospitalisation.

Recommendations for further research

The following areas are recommended for further investigation.

- Efficacy trials conducted in the specific population for which etanercept and efalizumab are licensed, that is, patients with moderate to severe chronic plaque psoriasis in whom conventional therapy has failed or is inappropriate. Trials should assess duration of remission following treatment withdrawal.
- Long-term comparisons of etanercept and efalizumab with other treatments for moderate to severe psoriasis, particularly infliximab, methotrexate and ciclosporin.
- Long-term efficacy trials, to provide data on how etanercept and efalizumab perform as maintenance therapies.
- Long-term safety/tolerability data for patients treated with etanercept or efalizumab.
- Psoriasis is a heterogeneous group of diseases; trials to identify specific subtypes that respond better to one drug than another.
- Research on the rate of inpatient hospitalisation in patients with moderate to severe psoriasis, and the effect of treatment on this rate.

Chapter 1

Aim of the review

The objective was to evaluate the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and efalizumab for the treatment of moderate to severe chronic plaque psoriasis.

In order to achieve this aim, we undertook the following research:

- a systematic review of the efficacy and safety of etanercept and efalizumab in the treatment of moderate to severe chronic plaque psoriasis
- an update of an existing systematic review of the efficacy and safety of other treatments for moderate to severe chronic plaque psoriasis
- an analysis to enable comparisons to be made between the efficacy of all treatments (etanercept and efalizumab and other) for moderate to severe chronic plaque psoriasis
- a systematic review of existing economic evaluations of etanercept and efalizumab in the treatment of moderate to severe chronic plaque psoriasis
- a critique of the economic models supplied by the manufacturers of etanercept and efalizumab
- development of an economic model of etanercept and efalizumab in the treatment of moderate to severe chronic plaque psoriasis.

Chapter 2
Background

Description of underlying health problem

Epidemiology

Psoriasis is a common inflammatory skin disease, with estimates of its world prevalence ranging from 0.5 to 4.6%.[1] There are few data on the prevalence and incidence of psoriasis in the UK. The only nationally representative data comes from the Morbidity Statistics from General Practice,[2] which covered a 1% sample of the population in England and Wales and collected data from 60 GP practices. For 1991–2, the study reported a prevalence rate for 'psoriasis and similar disorders' of 24 per 10,000 persons (i.e. 0.24%) and an incidence rate of 48 per 10,000 years at risk. Two local surveys conducted in London (1975) and Leicestershire (1995) found prevalence point rates of 1.6%[3] and 1.48%,[4] respectively.

Psoriasis generally occurs in adults; a survey conducted in the USA reported a median age of onset of 28 years.[1] However, the same survey found that one-quarter of those affected had experienced symptoms before the age of 18 years.[1] Males and females are equally commonly affected by the condition; however, females are more likely to regard their disease as severe.[1] Ethnic variations have been identified and Caucasians are more likely to suffer from the disease.[1]

Plaque psoriasis or psoriasis vulgaris, characterised by clearly demarcated, red, scaling plaques, is the most common form of psoriasis, occurring in more than 80% of cases.[1]

Aetiology, pathology and prognosis

Psoriasis is considered a multifactorial disease in which several genetic and environmental factors interact.[1] Large-scale epidemiological studies investigating family links and studies of twins provide observational evidence for a genetic component for psoriasis.[5] A specific psoriasis gene has not yet been identified but research has identified several chromosomal locations associated with a predisposition to psoriasis. However, possession of a 'psoriatic gene' does not necessarily lead to the onset of psoriasis; it is well established that in some cases an external trigger, such as emotional stress or an infection, is responsible for initiating the disease.[5]

Psoriasis is both an epidermal and an immunological disease.[1] It was for many years considered to be primarily a disorder that involved the proliferation of keratinocytes with secondary inflammation.[6] However, the success of the immuno-suppressive agent ciclosporin in the treatment of psoriasis led to the understanding that it is a disorder of the immune system, involving the abnormal activation of T cells.[7] T cells are key surveillance elements of the immune system that proliferate during a first encounter with an infectious agent or other foreign antigen.[7] The normal activity of T cells in maintaining immunity is amplified in psoriasis patients, in whom activated T cells are pathogenic. Once the pathogenic T cells have entered the skin, they become activated and release cytokines and chemokines to attract other immune cells to perpetuate the inflammatory cascade, leading to the inflammation of the skin and excessive production of skin cells.[7]

Plaque psoriasis is characterised by well-demarcated erythematous scaling plaques.[8] Psoriatic plaques occur most often symmetrically on elbows, knees, lower back and buttocks. In addition, the scalp, nails, intertriginous areas and genitalia are often involved.[8] The extent of involvement can escalate to full body coverage in more severe cases. When only small areas are involved, lesions are often asymptomatic. Extensive body coverage with very thick or more inflamed lesions is more likely to itch, be tender or bleed.[8]

Other forms of psoriasis include inverse psoriasis, characterised by erythematous scaling plaques in flexural sites such as axillae; guttate psoriasis, which often arises after a streptococcal infection and is characterised by numerous erythematous scaling papules; palmoplantar pustular psoriasis (palmoplantar pustulosis), characterised by painful

erythema with pustules involving the palms and soles; generalised pustular psoriasis, characterised by sterile pustules covering large portions of the trunk and extremities, which in severe cases can become confluent; and erythrodermic psoriasis, where the majority of the skin surface is acutely inflamed.[1] The last two forms of psoriasis may be associated with generalised systemic symptoms, including malaise, high fever and heart failure; they may be precipitated by withdrawal of systemic corticosteroids.[1]

Psoriasis is usually classified as mild, moderate or severe, according to the proportion of the skin affected and the redness, thickness and scaling of the plaques. Assessment of psoriasis severity is not an exact science and the definition of 'severe' will inevitably differ, both amongst and between dermatologists and patients.[9] If one adheres to strict clinical criteria, then moderate psoriasis could be defined as psoriasis affecting at least 10% of skin surface area or having a Psoriasis Area and Severity Index (PASI) score of 10–20 [the PASI score is an assessment score, representing the extent, redness, thickness and scaliness of a person's psoriasis; see the section 'Outcome measures' (p. 5) for a more detailed explanation]. Severe disease could be defined as psoriasis affecting at least 20% of skin surface area or having a PASI score of at least 20. Understandably, this is an arbitrary assessment and takes no account of the effect of psoriasis on the patient's quality of life (QoL). It is important to realise that difficult-to-treat psoriasis does not necessarily equate with disease severity or extent. For instance, a patient with relatively minimal extent psoriasis may be severely psychosocially disabled by the disease and have unrealistic expectations of cure or response to treatment. Another patient with moderate disease may have failed to respond to and/or to tolerate a variety of treatments. A holistic approach may incorporate psychosocial disability and historical response to treatment in addition to clinical extent in the definition of severe psoriasis.[9]

Psoriasis is a chronic, life-long disease characterised by relapses and remissions, varying in severity even when untreated. To date, there are few treatments that induce very long-term remissions. The majority of patients with psoriasis will have limited areas of affected skin, which are amenable to topical treatment. However, many patients do require additional treatment, either because of the severity or extent of disease or because of the detrimental effect it has on their psychosocial health.

Significance in terms of ill-health

It is unclear whether psoriasis is associated directly with excess mortality,[1] but there may be an association through increased rates of smoking and alcohol consumption.[10] The health-related quality of life (HRQoL) of people with psoriasis has been shown to be significantly worse than that of healthy adults.[11,12] In a Norwegian study of adults with psoriasis, scores were statistically significantly lower than those of the general population on all dimensions of the SF-36 (see *Table 1*), after adjusting for age, gender, educational level and marital status. The largest difference between the two groups was on the 'role, emotional' scale.[13]

The extent to which psoriasis affects HRQoL is similar to that of other chronic diseases, such as depression, post-myocardial infarction, hypertension, congestive heart failure or type 2 diabetes.[14] Psoriasis has a particularly negative impact on mental health, although its physical impact appears greater than for people with hypertension or diabetes.[14] Compared with other dermatological diseases, psoriasis appears to have less impact on HRQoL than atopic dermatitis,[15,16] but more impact than acne, basal cell carcinoma or viral warts.[11]

There appears to be a broad, inverse correlation between psoriasis severity and HRQoL,[14,17] but this does not account for all or even most of the variability in HRQoL.[12] A small US study found no correlation between disease severity, measured by the PASI or Self-Administered Psoriasis Area and Severity Index (SAPASI), and QoL, as measured by the EuroQoL-5D (EQ-5D), the Short Form with 36 Items (SF-36) or the subjective well-being scale (SWB).[18] Research in the UK also found no relationship between severity and HRQoL [as measured by the EQ-5D visual analogue scale (VAS)].[19] However, these studies may have been too small to detect any true between-group differences. The impact of disease on people with psoriasis appears not to be directly related to body surface area affected or to sign scores (e.g. degree of scaling), but rather to the site affected and to patient attitudes.[20] HRQoL appears to be directly related to sufferers' ability to cope with social aspects of the disease,[21] and the anticipation of stigmatisation is an important predictor of disability.[22]

Evidence for associations between the impact of psoriasis on HRQoL and demographic factors is mixed. There is some evidence, all based on US research, that the impact of psoriasis varies with

age: the psychosocial impact of psoriasis appears greater in younger people, whereas its physical impact is greater in those over 55.[23,24] Psychosocial effects may be greater in women than in men,[15] although evidence for this is mixed.[24] One study found that gender correlated with only two of the eight scales on the SF-36, namely 'physical functioning' and 'role emotional'.[12] UK researchers used the SF-36 and the Psoriasis Disability Index to demonstrate an inverse association between social class and degree of disability.[25] However, a US study of 87 patients at a tertiary medical clinic, in which three QoL instruments were assessed, found no relationship between HRQoL and any demographic variable, including age, gender and education.[26]

The economic impact of psoriasis in terms of out-of-pocket expenses increases with severity[27] and the effect is greater in lower income groups.[23] A UK study of people with severe psoriasis found that around 60% had taken time off work in the previous year as a direct result of their condition. The average (median) time off work was 20 days, although this ranged from 1 to 100 days.[28] US research focusing on people with severe disease found that almost one-third had suffered some financial distress as a result of their psoriasis.[23] Men apparently face greater work-related stress as a result of their psoriasis, reporting a higher incidence of criticism than women for taking time off work for medical appointments.[24]

Outcome measures

Assessment of the severity of psoriasis and its response to treatment is not straightforward. In our review, we have focused on data derived using the PASI score, primarily because it is the assessment measure used in clinical trials. In clinical practice the ideal endpoint of treatment is clearance of psoriasis. Phototherapy, in particular photochemotherapy (PUVA) and narrowband ultraviolet radiation band B (NBUVB) can induce clearance of psoriasis in a majority of patients and the proportion of patients achieving clearance is therefore a reasonable measure of the relative efficacy of phototherapies. Unfortunately, phototherapy is not suitable for all types of psoriasis or for all patients and, furthermore, owing to an increased risk of skin cancer, there is a limited lifetime exposure to phototherapy. Furthermore, the systemic therapies available cannot generally be expected to induce clearance[29] and so some other lesser, but still clinically meaningful, measure of response is required.

The PASI[30] has become the most common method of assessing psoriasis activity in psoriasis trials. Although it is widely used, it is acknowledged to have many deficiencies: its constituent parameters have never been properly defined; it is insensitive to change in mild to moderate psoriasis; estimation of disease extent is notoriously inaccurate; and the complexity of the equation required to calculate the final score further increases the risk of error. It combines an extent and a severity score for each of four body areas (head, trunk, upper extremities and lower extremities). The extent score of 0–6 is allocated according to percentage skin involvement such that 0 and 6 represent no psoriasis and 90–100% involvement, respectively. The severity score of 0–12 is derived by adding scores of 0–4 for each of the symptoms of erythema (redness), induration and desquamation representative of the psoriasis within the affected area. It is probable, but usually not specified in trial reports, that most investigators take induration to mean plaque thickness without adherent scale and desquamation to mean thickness of scale rather than severity of scale shedding. The severity score for each area is multiplied by the extent score and the resultant body area scores, weighted according to the percentage of total body surface area which that body area represents (10% for head, 30% for trunk, 20% for upper extremities and 40% for lower extremities), are added together to give the PASI score. Although PASI can theoretically reach 72, scores in the upper half of the range (above 36) are uncommon even in severe psoriasis.

In clinical trials of psoriasis treatments, no definitive measure of treatment success has been identified.[31] The majority of recent trials of systemic therapy for psoriasis with drugs such as ciclosporin or oral retinoids have used a 75% reduction in baseline PASI score (PASI 75) as the primary success criterion and may also report PASI 90 (a 90% reduction in baseline PASI score), which equates to clear or minimal residual activity as reported in many phototherapy trials. More recently, the Medical Advisory Board of the National Psoriasis Foundation in the USA concluded that a 50% reduction in baseline PASI score (PASI 50) can be considered to represent a clinically significant improvement and is associated with improvements in QoL scores.[32] Also, in clinical trials PASI 50 has demonstrated discriminatory power between active treatment and placebo.[32] However, the use of PASI 50 as a primary measure of efficacy in psoriasis remains controversial and is not accepted by the European

Medicines Evaluation Agency (EMEA). Consequently, our review will take PASI 75 as the primary outcome measure but will also examine trial data using a range of success criteria derived from the PASI, including PASI 90.

This still leaves the question of what constitutes a 'good' (clinically important) level of efficacy for a given intervention: for example, should a drug be considered effective if 50% of patients achieve a PASI 50? It could be taken that any statistically significant benefit over placebo is evidence of efficacy,[31] but this is unlikely to gain general acceptance.

Whatever the problems with PASI, it does offer some degree of objective assessment of psoriasis severity. PASI does not, however, correlate with the patients' perceived QoL, which can differ among all degrees of disease severity. Assessing HRQoL in people with psoriasis is important for three main reasons. First, it encourages patient-centred care by acknowledging patients' views, conveying the physician's interest in the patient and informing consultations.[33,34] Second, HRQoL measurement can help clinicians, by informing decision-making[34] and helping to determine the effectiveness of treatments in routine practice.[11] Third, HRQoL measures can be decision tools for policy makers who need to allocate limited resources.[11,33] *Table 1* gives an overview of the generic, dermatology-specific and psoriasis-specific HRQoL measures used in international psoriasis research. Measures vary considerably in the number of items and domains included and in the assessment period used.

The Dermatology Life Quality Index (DLQI) is frequently used to measure QoL in adult psoriasis sufferers (aged 16 years and above). This questionnaire consists of 10 questions that cover six areas of the patient's life that may be affected by the disease; these include symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. QoL scores range from 0 to 30, with higher scores representing poorer QoL.[35]

Although assessment of treatment efficacy in psoriasis is difficult and complex, the outcome measures used in this review, namely PASI 50, PASI 75, PASI 90, clearance and DLQI, cover the most important aspects of the impact of psoriasis on health, and all have discriminatory ability and are generally accepted measures of efficacy.

Current service provision

There are many different treatment options for psoriasis sufferers, depending on the severity of the condition, the extent of body surface area affected and the response to prior treatment. Topical applications are generally used as a first-line approach to alleviating symptoms, especially in mild cases of psoriasis. Topical agents that are currently used in practice include emollients (for mild limited disease), corticosteroids, salicylic acid, coal tar, vitamin D analogues, retinoids and dithranol. These treatments are non-invasive and the main safety concern is skin atrophy, which is associated with the use of potent corticosteroids. When psoriasis is refractory to topical treatments or too widespread, phototherapy or systemic therapies are indicated.[1] Topical agents are commonly used as an adjunct to systemic therapy.

It has been known for much longer than psoriasis has been recognised as an entity that natural sunlight (heliotherapy) may be beneficial for skin disease. The value of natural sunlight is well recognised by psoriasis sufferers. Artificial sunlight in the form of broadband ultraviolet radiation band B (UVB)-emitting lamps has been used for over a century to treat psoriasis, often in combination with tar or dithranol, and has a good safety record. Ingram's regimen, which involves regular UVB exposure followed by application of dithranol (anthralin) paste to the skin, and Goeckerman's regimen, which involves UVB exposure followed by application of crude coal tar, were developed as inpatient therapies but are now more commonly administered in a day-case setting. Photochemotherapy, where a photosensitiser in the skin interacts with long-wave ultraviolet radiation band A (UVA), was introduced some four decades ago in an attempt to increase the efficacy of UV treatment. The most commonly used photosensitiser is a plant-derived chemical, psoralen, which can be given either as a tablet or as a topical application. Once the psoralen has penetrated the skin, the patient receives UVA irradiation from special UVA-emitting tubes (PUVA therapy). PUVA is effective at clearing psoriasis in a large proportion of treated patients and became very popular in the 1970s and 1980s. It is still widely used, but is now normally limited to no more than 200 exposures in a lifetime (approximately six to nine treatment courses) now that it is known that prolonged therapy significantly increases the risk of developing skin cancers. More recently, a modification of broadband UVB therapy has been introduced in an attempt to maximise the biological effects on

TABLE 1 *Quality of life measures used in psoriasis*

Type of instrument	Name of instrument	Acronym	Items (domains)	Assessment period	Studies
Generic	ALLTAG questionnaire on everyday life	ALLTAG	40 (6)	1 week	Augustin, 1999[16]
	EuroQol	EQ-5D	(–) 5	Current	Weiss, 2002;[18] Kernick, 2000[19]
	General Health Questionnaire	GHQ	12 (–)	Recent experience	Finlay, 1990;[36] Sampogna, 2004[37]
	Medical Outcomes Study 36-item Short Form Health Survey	SF-36	36 (8)	Typical day 4 weeks General experience	Nichol, 1996;[38] De Korte, 2002;[39] Finlay, 2003;[40] Lundberg, 1999[41]
	Nottingham Health Profile	NHP	38 (6) + impact on daily life	Current	Morgan, 1997;[15] Badia, 1999[42]
	Sickness Impact Profile	SIP	136 (12)	Current	De Korte, 2002;[39] Finlay, 1997[43]
	WHO Quality of Life Index	WHOQOL	96 (6) + 4 'general items'	Current	Mombers, 1997;[17] WHOQOL group, 1998[44]
Dermatology-specific	Adjustment to Chronic Skin Disease Questionnaire	ACS	51 (5)	1 week	Augustin, 1999;[16] Stangier, 2003[45]
	Children's Dermatology Life Quality Index	CDLQI	10 (–)	1 week	Lewis-Jones, 1995[46]
	Dermatology Life Quality Index	DLQI	10 (–)	1 week	Nichol, 1996;[38] De Korte, 2002;[39] Finlay, 1994[11]
	Dermatology Quality of Life Scales	DQOLS	41 (3)	Current/1 week	Finlay, 2003;[40] Morgan, 1997[15]
	Dermatology Specific Quality of Life Instrument	DSQL	52 (7)	4 weeks	De Korte, 2002;[39] De Tiedra, 1998[47]
	Freiburg Life Quality Assessment for Chronic Skin Disease	FLQA-d	54 (6)	Unclear	Augustin, 1999[16]
	Qualita di Vita Italiana	QUAVIDERM	11 (–)	4 weeks	De Tiedra, 1998[47]
	Skindex-29	–	29 (3)	4 weeks	De Korte, 2002;[39] De Tiedra, 1998[47]
Psoriasis-specific	Impact of Psoriasis Questionnaire	IPSO	16 (3)	Unclear	McKenna, 1997;[48] Sampogna, 2004[37]
	Psoriasis Disability Index	PDI	15 (5)	4 weeks	Koo, 2002;[33] Finlay, 1990;[36] Finlay, 1995[28] Mombers, 1997;[17] Nichol, 1996[38]
	Psoriasis Disability Scale		36 (–)	Unclear	Fleischer, 1997[49]
	Psoriasis Life Stress Inventory	PLSI	15 (–)	4 weeks	Koo, 2002;[33] Fortune, 1997;[50] Sampogna, 2004[37]
	Psoriasis Quality of Life	PQOL	41 (2)	Current	Koo, 2002[33]
	Psoriasis(-related) Stressor Scale	PRSS	20 (–)	Unclear	Fleischer, 1997[49]

psoriasis but reduce the overall energy required for clearing psoriasis; NBUVB phototherapy employs special lamps, which emit UVB in a narrow wavelength spectrum within the UVB range. It appears to have comparable efficacy to PUVA but, it is believed, will be much less likely to increase the risk of skin cancer. NBUVB is increasingly supplanting PUVA therapy in dermatology departments in the UK.

Systemic treatments that are widely used in the treatment of moderate to severe psoriasis include retinoids, methotrexate and ciclosporin. All have potential long-term side-effects including hypertension and renal toxicity with ciclosporin and liver fibrosis and cirrhosis with methotrexate.[51,52] This may limit the length of time for which they may be used in an individual patient.

Current service cost

The cost to the NHS of treating psoriasis includes direct costs, such as the cost of drugs, clinician (nurse, GP and hospital doctor) time, the cost of day-care therapies, such as phototherapy and Ingram and Goeckerman regimens and the cost of administering and monitoring drugs. Patients may also require hospital admission, with an average length of stay of around 20 days.[53]

In 2003, there were approximately 967,200 prescription items for psoriasis dispensed in the community at a cost of £27.8 million.[54] The average cost of per prescription item was £28.76, but ranged from £1.58 for salicylic acid to £79.05 for acitretin. Drugs such as ciclosporin, methotrexate and corticosteroids have multiple indications and the expenditure on these drugs for psoriasis is not reported. Moreover, data on drug expenditure in hospitals are not available. Therefore, the true cost of annual drug expenditure on psoriasis is likely to be higher than £27.8 million.

There have been a number of UK economic evaluations of treatments for psoriasis. Ashcroft and colleagues[55] compared the cost-effectiveness of topical calcipotriol (annual cost, £96) against short contact dithranol (annual cost, £31). Cockayne and colleagues[56] estimated the annual cost of hospital care, comprising labour costs (medical, domestic, porter, nurse), catering, laundry, maintenance and site overhead costs. Drug costs and costs incurred by patients were excluded from the analysis. Data were derived from an audit of a day-care centre, with matched inpatient controls and informed by a survey of eight dermatology departments in the UK.[57] The mean day-care cost per patient was £1186 [95% confidence interval (CI) £971 to £1401] and the mean inpatient care cost was reported to be £2681 (95% CI £2221 to £3141). Cork[58] estimated the annual per-patient hospital costs for PUVA (£562), methotrexate (£876) and Goeckerman regimen (£222). Davies and colleagues[57] compared the costs of ciclosporin with day-care treatment using dithranol or Goeckerman treatments. Assessing direct NHS costs, including drugs, outpatient visits, day-care costs and treatment of adverse events, they reported 8-month costs for ciclosporin (£2000) and day-care (£3500).

Patients also incur out-of-pocket expenses and may need to take time off work to attend hospital appointments [see the section 'Aetiology, pathology and prognosis' (p. 3)].

Variation in services

Around 445 dermatologists work in NHS hospitals in the UK.[59] Dermatology departments range from smaller units in a local hospital to large units, which are most often located in the large teaching hospitals. A consultant dermatologist may supervise other doctors working in a dermatology unit, such as dermatological specialists from various disciplines, doctors undergoing the specialist dermatology training and GPs with a special interest in the subject. Specialist nurses may provide certain types of intensive treatment to patients and allergy testing services.

Some centres have tertiary services for eczema and psoriasis; these take referrals from other dermatologists. The need for newer drugs is likely to be greatest in these centres.

Few UK studies have been conducted to establish variation in dermatology service provision and no survey reporting an audit of national provision for psoriasis patients was found. The British Association of Dermatologists conducted an audit of atopic eczema management in secondary care.[60] A postal survey was sent to 187 dermatology centres in England and Scotland and a response rate of 98% was achieved. Some 92% of the responding centres had trained nurses and 57% had dermatology nurses. Photochemotherapy units were present in 92% of centres, 90% reported rapid access facilities to a hospital specialist and 82% provided information sheets to

TABLE 2 *Class and therapeutic strategies for biological agents*

Generic name	Class	Target and therapeutic strategy
Etanercept	Receptor antibody fusion protein	Binds the post-secretory cytokine TNFα[a]
Efalizumab	Humanised monoclonal antibody	Anti CD11a subunit of LFA-1. Blocks T cell activation or migration

[a] TNFα is one of a number of cytokines that stimulate the dendritic cells, macrophages and keratinocytes and maintain the inflammatory state.
Adapted from Pariser (2003)[62] and Gniadecki and colleagues (2002).[61]

patients. These structural features are also relevant for the treatment of psoriasis.

Description of new intervention

Treatment for psoriasis has more recently focused on eliminating activated T cells, inhibiting activated T cells or inhibiting cytokine secretion or activity.[7] These treatments are known as biological agents as they consist of proteins created by living cells. Owing to their protein nature they cannot be given orally and are usually administered by subcutaneous, intravenous or intramuscular injection. Etanercept, one of the new biological treatments, works by binding to the post-secretory cytokine tumour necrosis factor alpha (TNFα), thereby inhibiting its action; psoriasis patients are found to have increased concentrations of this factor. Etanercept is classed as a receptor antibody fusion protein.[61,62] Efalizumab is another biological agent that has been found to inhibit inflammatory cell function by blocking T cell activation or migration.[61,62] Their agent class and therapeutic strategies are summarised in *Table 2*.

In the UK, both etanercept (Enbrel®) and efalizumab (Raptiva®) are licensed for treatment of adults with moderate to severe plaque psoriasis who have failed to respond to, or who have a contraindication to or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA. The product licence for etanercept[63] states that the recommended dose for etanercept is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly. Treatment with etanercept should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

The product licence for efalizumab[64] states that treatment should be initiated by a physician specialised in dermatology. An initial single dose of 0.7 mg/kg body weight is given followed by weekly injections of 1.0 mg/kg body weight (maximum single dose should not exceed a total of 200 mg). The duration of therapy is 12 weeks. Therapy may be continued only in patients who respond to treatment.

Anticipated costs

The total annual per-patient drug cost for etanercept (25 mg/kg twice weekly) would be £4290 if patients received two 12-week courses per year (i.e. 12 weeks on treatment followed by 12 weeks off treatment).[65] If etanercept is used continuously, this cost rises to £9296. The total annual per-patient drug cost for efalizumab (1 mg/kg once weekly) is £8798. There is no definitive estimate of the numbers of patients eligible for these treatments that would enable a total expected cost for the NHS to be calculated.

Chapter 3

Clinical evaluation: methods

In order to achieve the project's aims, we undertook the following systematic reviews:

- a systematic review of the efficacy and safety of etanercept and efalizumab in the treatment of moderate to severe chronic plaque psoriasis
- an update of an existing systematic review of the efficacy and safety of other treatments for moderate to severe chronic plaque psoriasis
- an analysis to enable comparisons to be made between the efficacy of all treatments (etanercept and efalizumab and other) for moderate to severe chronic plaque psoriasis.

Search strategy

Searches were undertaken on the following databases to identify relevant clinical literature. Full details of the search strategies are reported in Appendix 1. Searches took place over a period from January to April 2004 (see Appendix 1 for the dates of individual searches).

- MEDLINE and In-Process Citations (OVID Online)
- EMBASE (OVID Online)
- National Research Register (NRR) (CD-ROM)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet)
- CenterWatch (Internet: http://www.centerwatch.com/index.html)
- Current Controlled Trials (Internet: http://controlled-trials.com/)
- ClinicalTrials.gov (Internet: http://clinicaltrials.gov/)
- EconLit (SilverPlatter on the web)
- ISI Science and Technology Proceedings (Web of Knowledge: http://wos.mimas.ac.uk/)
- Social Science Citation Index (Web of Science: http://wos.mimas.ac.uk/)
- Science Citation Index (Web of Science: http://wos.mimas.ac.uk/).

All databases were searched from their inception to the date of the search.

Terminology

The terms for the search strategies were identified through discussion between an Information Officer and the research team, by scanning the background literature and by browsing the MEDLINE Thesaurus (MeSH). No language or other restrictions were applied.

Management of references

As several databases were searched, some degree of duplication resulted. In order to manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into Endnote bibliographic management software to remove duplicate records.

Handsearching

The bibliographies of all included studies and industry submissions made to the National Institute for Health and Clinical Excellence (NICE) were reviewed to identify further relevant studies. Handsearching continued throughout the project.

Inclusion and exclusion of studies

Study selection

Two reviewers selected the studies for the review. Discrepancies were resolved by consensus and a third reviewer was consulted when necessary. All titles and abstracts identified by the search were screened and any references that were considered relevant by either reviewer were obtained.

No language restrictions were applied to study selection. Trials reported as full publications or unpublished full reports were included in the review. Trials reported as abstracts only were to be included if adequate information was provided. All of the data submitted by Wyeth and Serono were considered in the review.

Inclusion/exclusion criteria

Efficacy of etanercept and efalizumab

The review addressed the following questions about the efficacy of etanercept and efalizumab in the treatment of moderate to severe psoriasis:

- Is the drug effective at all?
- How effective is it?
- Can the drugs be used long term?

- How long is remission and is there any rebound if active treatment is replaced with passive treatment?
- How effective is retreatment in patients who have relapsed following an earlier treatment period?

Studies were included in the review according to the inclusion criteria described below.

Intervention
Etanercept and efalizumab administered by subcutaneous injection were the interventions of interest. Comparisons with either placebo or any other active agent were eligible for inclusion.

Participants
Studies of adults with moderate to severe psoriasis were included. These patients are usually defined as having an inadequate response to topical treatments alone and either to have received prior systemic therapy or phototherapy or are candidates for such therapy.

Study design
Only randomised controlled trials (RCTs) were included in the evaluation of efficacy.

Outcomes
The outcomes of primary interest were those derived from the PASI. Data on the following outcomes were also eligible in the review of efficacy: physician's global assessment (PGA); patient-centred outcome measures; SAPASI; Psoriasis Disability Index (PDI); Total Severity Score (TSS); Investigator's Assessment of Global Improvement (IAGI); QoL; DLQI; duration of remission.

Adverse effects of etanercept and efalizumab
Adverse events data were summarised from key sources and existing reviews. These were supplemented by a systematic review of adverse events data from clinical studies. Studies were included in the systematic review according to the inclusion criteria described below. The reference details and reasons for exclusion of studies are presented in Appendix 3.

Intervention
Etanercept and efalizumab administered by subcutaneous injection were the interventions of interest. Studies with any comparator (placebo or any other active agent) or no comparator were eligible for inclusion.

Participants
Studies of adult patients receiving treatment for any of the following indications were eligible: psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and any other indication except cancer or transplantations.

Study design
Long-term experimental and observational studies of at least 24 weeks' duration and including a minimum of 100 patients were included in the review. Studies or data without an explicitly stated denominator were excluded from the review. In addition, adverse event data from the trials of efficacy of etanercept and efalizumab were included.

Outcomes
All adverse event data were considered in the review.

Other treatments for moderate to severe psoriasis
In an attempt to put into context the evidence base for the efficacy of etanercept and efalizumab, we investigated the evidence available for other treatments for moderate to severe psoriasis. Studies were included in the review according to the inclusion criteria described below.

Treatments
All of the following oral systemic agents were eligible as other treatments for moderate to severe psoriasis: ciclosporin, methotrexate, acitretin, hydroxycarbamide, Fumaderm and infliximab. It must be noted for this review we did not assume that etretinate, the ester of acitretin, was the same as acitretin; trials of etretinate were not reviewed. Photochemotherapy (PUVA), retinoid plus PUVA (RePUVA), NBUVB, acitretin plus calcipotriol, Ingram regimen [daily in-hospital phototherapy plus dithranol (anthralin)] and Goeckerman regimen (daily in-hospital phototherapy plus coal tar) were also considered relevant treatments. All of the above therapies were considered as monotherapy only, with the exception of acitretin plus calcipotriol, as this combination is recognised clinically as a single treatment. Only trials in which the control agent was placebo, etanercept, efalizumab or any of the other treatments for moderate to severe psoriasis listed above were included in the review. Trials that compared different regimens of the same treatment or compared a treatment with or without a concomitant agent were not included in the review; all such trials identified are listed under excluded studies in Appendix 3.

Participants
Studies of adults with moderate to severe plaque psoriasis were included. These patients are usually

defined as having an inadequate response to topical treatments alone and either have received prior systemic therapy or phototherapy or are candidates for such therapy.

Study design
In 2000, Griffiths and colleagues published a systematic review of RCTs of treatments for severe psoriasis.[66] The present updated review has added to some of the findings from the Griffiths review with a focus on those treatments identified as comparators for etanercept and efalizumab in clinical practice. Studies eligible for inclusion in this update were RCTs that included at least 20 patients and investigated a therapeutic dose, as advised by a clinical expert. Studies identified from the Griffiths review or from this updated review that did not meet these criteria are not discussed in this report.

Outcomes
The outcomes of primary interest were those derived from the PASI. The outcome measure PASI 75 was used where available; in its absence, an alternative PASI measure was discussed, otherwise the primary outcomes were reported.

Adverse effects
Information on the adverse effects of the other treatments for moderate to severe psoriasis were summarised from tertiary reference sources [see the section 'Search D: reports of adverse events of comparator treatments' in Appendix 1 (p. 99)].

Data extraction strategy

All data were extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus and by consultation with a third reviewer if necessary. Data were extracted on to predesigned forms. Data from studies with multiple publications were extracted and reported as from a single study. Any 'commercial-in-confidence' data taken from the company submission are clearly marked in the NICE report (underlined and followed by an indication of the relevant company name, e.g. in brackets) and removed from the subsequent submission to the HTA.

For the efficacy trials of etanercept and efalizumab, the following details were extracted from each trial:

- study details (author, year, country, type of publication, other publications/reports, funding, study design, setting, duration of trial follow-up, frequency of follow-up, sample size calculation, analyses)
- participant details (number randomised and treated, age, gender, psoriasis history, duration of psoriasis, prior systemic therapy, concurrent therapies)
- details of intervention
- results and outcomes.

For the adverse effects studies of etanercept and efalizumab, the following details were extracted:

- study details (author, year, country, type of publication, other publications/reports, funding, study design, duration of trial follow-up, study objective)
- participant details (indication, inclusion criteria, number of participants, age, gender, concurrent therapies)
- details of intervention
- adverse event results (non-infectious adverse events, infectious adverse events including any serious infections, other non-infectious serious adverse events, deaths, withdrawals due to adverse events, positive test for anti-etanercept or anti-efalizumab antibodies, other important adverse event results).

As the other treatments for moderate to severe psoriasis were not the primary focus of the review, we undertook only limited data extraction of the trials of these agents. The following details were extracted from each trial: study details (author, year, study design); participant details [psoriasis type, resistant to topicals/require systemics?, minimum body surface area (BSA) included, minimum PASI included, adult status, number of participants], details of treatment, results and outcomes.

Quality assessment strategy

Efficacy of etanercept and efalizumab

The quality of trials was assessed by one reviewer and independently checked by a second reviewer. Disagreements were resolved through consensus, consulting a third reviewer if necessary.

The efficacy trials were assessed for quality using a checklist compiled from criteria specified in CRD Report No. 4. The quality of each study was summarised as a quality rating, classifying trials as Excellent, Good, Satisfactory or Poor. The checklist and quality ratings are detailed in Appendix 2.

Adverse effects of etanercept and efalizumab

Owing to the range of study designs included in the assessment and the limitation of the review to

long-term large studies, the quality of adverse events studies was not assessed.

Other treatments for moderate to severe psoriasis

Owing to time constraints, the quality of the trials of other treatments for moderate to severe psoriasis was not assessed.

Data analysis

Efficacy of etanercept and efalizumab

Full data extraction and quality assessment were presented for each efficacy trial of etanercept and efalizumab.

Results were summarised in tables and the effect of trial quality on the efficacy findings is discussed. Relative risks (RRs) and mean differences were calculated for the primary outcomes with 95% CIs, using Revman 4.2. The primary outcome variables were PASI 50, PASI 75, PASI 90, % clear/almost clear, mean PASI, % change in mean PASI from baseline and % change in DLQI. Although the data (where available) are presented for these outcomes in this order, the primary outcome variable for this review is PASI 75.

Clinical diversity of the trials regarding adult status, minimum PASI score, BSA affected, previous treatments and concomitant medication was considered. Where the trials were not clinically diverse (heterogeneous), the data were pooled. Statistical heterogeneity was investigated using the χ^2 test; where it was statistically significant, data were not pooled. Where pooling was appropriate, pooled RRs (95% CI) or weighted mean differences (WMDs) (95% CI) were calculated using a fixed-effect model. A fixed-effect model was selected because a small number of trials were included in the meta-analysis, and a fixed-effect model is therefore considered most appropriate owing to the smaller estimation of between-study variance.[67]

Adverse effects of etanercept and efalizumab

Results were summarised in tables and the findings are discussed in a narrative synthesis. Adverse events data were grouped by duration of follow-up.

Other treatments for moderate to severe psoriasis

Data extraction was presented for each comparator trial. Results were summarised in tables and the findings are discussed. RRs and mean differences were calculated for the primary outcomes with 95% CIs; the primary outcome variables were PASI 50, PASI 75, PASI 90, % clear/almost clear, mean PASI and % change in mean PASI from baseline. PGA was used in one study in the absence of any of the above outcomes. The findings were not pooled statistically as a result of the clinical diversity of the trials and the small numbers of studies investigating the same comparison.

Mixed treatment comparison

In order to facilitate decision-making, we attempted to derive results for the relative effectiveness of etanercept and efalizumab and the other treatments reviewed. As it was expected that there would be no head-to-head trials comparing all the treatments, an analysis using the methods of mixed treatment comparisons was planned.[68] The purpose of a mixed treatment comparison analysis is to bring together the clinical evidence regarding the efficacy of all treatments for a specified indication. In general terms, this consists of identifying a 'chain of evidence' between the treatments. In the context of the present review, this would mean that, for example, although etanercept and efalizumab have not been directly compared in a trial, they can be **indirectly** compared as both have been assessed against a common comparator (placebo). Similarly, other treatments that have been compared with placebo can also be included in the analysis and compared with etanercept and efalizumab. The common comparator need not be placebo and, within a mixed treatment comparison, there can be more than one common comparator. For example, if etanercept and efalizumab and ciclosporin have all been compared with placebo but methotrexate has only been compared with ciclosporin, then methotrexate can be **indirectly** compared with etanercept and efalizumab because methotrexate can be linked into the chain of evidence. Within a mixed treatment comparison, **all** the available trials data on a treatment for the specified indication should be included.

The mixed treatment comparison used PASI 50, 75 and 90 outcomes. As the analysis was primarily for purposes of decision-making, its focus was on the generation of parameter estimates for the cost-effectiveness modelling described in Chapter 6. Exact details of the analysis are dictated by the available data and further details are given in the relevant results section [see the section 'Clinical evaluation: mixed treatment comparison analysis' (p. 39)].

Chapter 4

Clinical evaluation: results

Clinical evaluation: quantity of research available

The search strategies for efficacy, adverse events and comparator trials generated a total of 2808 references (*Figure 1*). Of these, 353 references were ordered and a total of 85 references met the inclusion criteria for the efficacy, adverse events or comparator section of the review. These references provided information on a total of 39 studies: five trials of the efficacy of the interventions of interest; 10 studies of the adverse effects of the interventions; and 24 trials of the efficacy of the other treatments for moderate to severe psoriasis. In addition, the company submissions from Wyeth[69] and Serono[70] provided details of three further trials of efficacy.

Clinical evaluation: efficacy of interventions

Efficacy of etanercept

Three RCTs were included in the review.[71–73] All three trials were double-blind and rated as Good according to the quality assessment (*Table 3*). All three trials were placebo controlled; no trial comparing etanercept with another active treatment was identified. Trial details are summarised in *Table 4* and presented in the data extraction tables [see the section 'Data extraction tables: intervention efficacy – etanercept' in Appendix 4 (p. 122)].

The trials were of adult patients, with active clinically stable plaque psoriasis involving at least 10% of the BSA, who had been previously treated with at least one systemic therapy or phototherapy or were candidates for such therapy. In two of the trials a minimum PASI score of 10 was specified in order for patients to be included.[71,72] The number of patients in the trials ranged from 112 to 652. Across all treatment groups (etanercept and placebo), the populations did not display clinically significant differences in terms of disease characteristics: mean duration of psoriasis ranged from 18.3 to 23 years; mean baseline PASI score ranged from 17.8 to 19.5; mean baseline BSA involvement ranged from 26.4 to 34%; and mean baseline DLQI score ranged from 10.1 to 13.8.

All three trials investigated etanercept at a dose of 25 mg subcutaneously twice a week. In addition, two trials examined a dose of 50 mg subcutaneously twice a week[71,72] and one trial also looked at a dose of 25 mg subcutaneously once a week.[71]

All three trials provided outcome data on the number of patients achieving PASI 50, PASI 75, PASI 90 and clear or almost clear (includes 'clear to minimal status' as reported in one trial[73]). They also provided data on mean PASI score, mean percentage change in PASI score from baseline and mean percentage change from baseline in DLQI score. All three trials assessed patient outcome after 12 weeks of treatment; one trial also assessed patient outcome at 24 weeks.[73] In addition, the three trials were continued for extended periods in which open-label and/or non-randomised designs were adopted.

Given the lack of clinical heterogeneity, the data were pooled by outcome, dose and follow-up period, unless this was prevented by the presence of statistical heterogeneity.

PASI 50

The results for PASI 50 are summarised in *Table 5*. Twelve-week data were pooled for etanercept 25 mg twice a week and etanercept 50 mg twice a week. The pooled RRs cannot be reported for reasons of confidentiality but both resultant pooled fixed effect RRs (95% CIs) were statistically significant in favour of etanercept over placebo. Although, in both cases, the Q statistic indicated a small amount of statistical heterogeneity, this was not statistically significant.

PASI 75

The results for PASI 75 are summarised in *Table 6*. All treatment differences were statistically significantly in favour of etanercept over placebo. Twelve-week data were pooled for etanercept 25 mg twice a week and etanercept 50 mg twice a week. Both resultant pooled fixed effect RRs (95% CIs) were statistically significant in favour of etanercept over placebo. In both cases, the test for heterogeneity was not statistically significant.

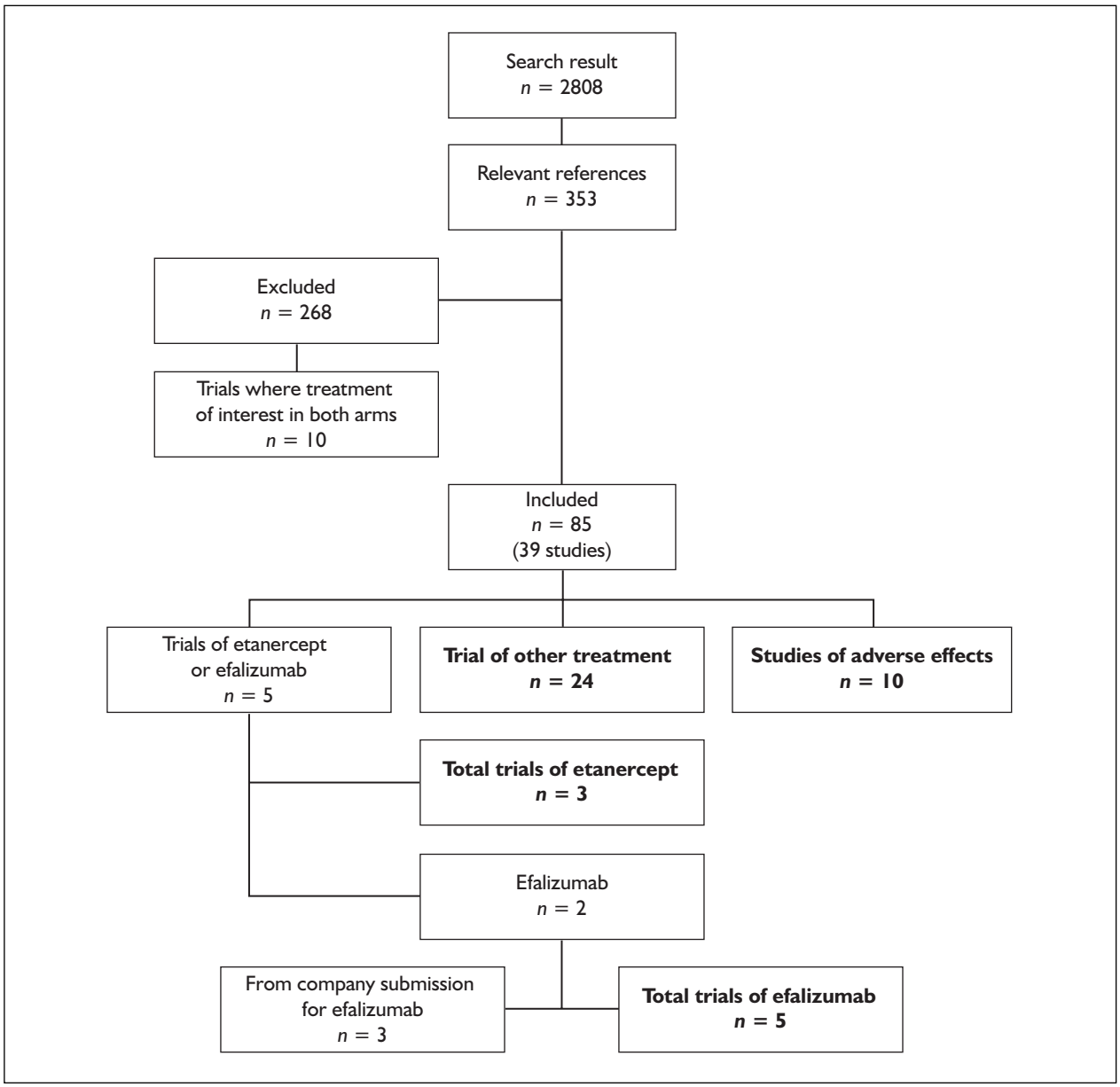

FIGURE 1 *Flow chart of study identification*

PASI 90

The PASI 90 results are summarised in *Table 7*. Twelve-week data were pooled for etanercept 25 mg twice a week and for etanercept 50 mg twice a week. Both resultant pooled fixed effect RRs (95% CIs) were statistically significant in favour of etanercept over placebo (data not shown for reasons of confidentiality). In both cases, the statistical test for heterogeneity was not statistically significant.

Clear or almost clear/clear to minimal

All three trials reported data on the number of patients rated as clear or almost clear in severity of psoriasis according to physician global assessment; the results are summarised in *Table 8*. Twelve-week data were pooled for etanercept 25 mg twice a week and etanercept 50 mg twice a week. Both resultant pooled fixed effect RRs (95% CIs) were statistically significant in favour of etanercept over placebo (data not shown for reasons of confidentiality). In both cases, the test for heterogeneity was not statistically significant.

Mean PASI score and mean percentage change in PASI score from baseline

The results for mean PASI score and mean percentage change in PASI score from baseline are summarised in *Table 9*.

TABLE 3 *Results of quality assessment for trials of etanercept*

Quality assessment criteria	Reference		
	Leonardi, 2003,[71] USA	**Elewski, 2004,[72] USA, Canada, Europe**	**Gottlieb, 2003,[73] USA**
Eligibility criteria specified?	Y	Y	Y
Power calculation?	Y	Y	Y
Adequate sample size?	Y	Y	Y
Number randomised stated?	Y	Y	Y
True randomisation?	Y	Y	Y
Double-blind?	Y	Y	Y
Allocation of treatment concealed?	Y	Y	Y
Treatment administered blind?	Y	Y	Y
Outcome assessment blind?	Y	Y	Y
Patients blind?	Y	Y	Y
Blinding successful?	NS	NS	NS
Adequate baseline details presented?	Y	Y	Y
Baseline comparability?	Y	Y	Y
Similar co-interventions?	Y	Y	Y
Compliance with treatment adequate?	Y	Y	Y
All randomised patients accounted for?	Y	Y	Y
Valid ITT analysis?	Y	Y	Y
≥80% patients in follow-up assessment?	Y	Y	Y
Quality rating	Good	Good	Good

ITT, intention to treat; N, no; NS, not stated; Y, yes.

TABLE 4 *Details of included trials of etanercept*

Reference	Participants	Duration (weeks)	Intervention	Comparison	Outcomes
Leonardi, 2003,[71] USA	*N* = 652 Adults Clinically stable plaque psoriasis; ≥10% BSA; baseline PASI ≥10	12	Etanercept 25 mg s.c. once a wk (*n* = 160) Etanercept 25 mg s.c. twice a wk (*n* = 162) Etanercept 50 mg s.c. twice a wk (*n* = 164)	Placebo (*n* = 166)	Proportion achieving PASI 50, PASI 75, PASI 90, clear or almost clear Mean PASI score, % change in PASI score, % change in DLQI score
Elewski, 2004,[72] USA, Canada, Europe	*N* = 583 Adults Clinically stable plaque psoriasis; ≥10% BSA; baseline PASI ≥10	12	Etanercept 25 mg s.c. twice a wk (*n* = 196) Etanercept 50 mg s.c. twice a wk (*n* = 194)	Placebo (*n* = 193)	Proportion achieving PASI 50, PASI 75, PASI 90, clear or almost clear Mean PASI score, % change in PASI score, % change in DLQI score
Gottlieb, 2003,[73] USA	*N* = 112 Adults Clinically stable plaque psoriasis; ≥10% BSA	24	Etanercept 25 mg s.c. twice a wk (*n* = 57)	Placebo (*n* = 55)	Proportion achieving PASI 50, PASI 75, PASI 90, clear or minimal Mean PASI score, % change in PASI score, % change in DLQI score

s.c., subcutaneously; wk, week.

TABLE 5 *Proportion of patients achieving PASI 50*

Reference	Etanercept	Placebo	RR (95% CI)
12-week follow-up, etanercept 25 mg once a week			
Leonardi, 2003[71]	65/160 (40.6%)	24/166 (14.5%)[a]	2.81 (1.87 to 4.27)
12-week follow-up, etanercept 25 mg twice a week			
Leonardi, 2003[71]	94/162 (58.0%)	24/166 (14.5%)[a]	4.01 (2.74 to 5.97)
Elewski, 2004[72]	[**Confidential information removed**]		
Gottlieb, 2003[73]	40/57 (70.2%)	6/55 (10.9%)	6.43 (3.14 to 13.99)
12-week follow-up, etanercept 50 mg twice a week			
Leonardi, 2004[71]	121/164 (73.8%)	24/166 (14.5%)[a]	5.10 (3.53 to 7.52)
Elewski, 2004[72]	[**Confidential information removed**]		
24-week follow-up, etanercept 25 mg twice a week			
Gottlieb, 2003[73]	44/57 (77.2%)	7/55 (12.7%)	6.07 (3.15 to 12.39)

[a] Where a trial had more than one intervention arm, results from the placebo arm are reported more than once.

TABLE 6 *Proportion of patients achieving PASI 75*

Reference	Etanercept	Placebo	RR (95% CI)
12-week follow-up, etanercept 25 mg once a week			
Leonardi, 2003[71]	23/160 (14.4%)	6/166 (3.6%)[a]	3.98 (1.72 to 9.32)
12-week follow-up, etanercept 25 mg twice a week			
Leonardi, 2003[71]	55/162 (34.0%)	6/166 (3.6%)[a]	9.39 (4.30 to 20.90)
Elewski, 2004[72]	67/196 (34.2%)	6/193 (3.1%)[a]	11.00 (5.04 to 24.38)
Gottlieb, 2003[73]	17/57 (29.8%)	1/55 (1.8%)	16.40 (2.98 to 95.36)
Pooled RR			10.69 (95% CI 6.15 to 18.57)
Test for heterogeneity			$Q = 0.281$ ($df = 2$), $p = 0.869$
12-week follow-up, etanercept 50 mg twice a week			
Leonardi, 2003[71]	81/164 (49.4%)	6/166 (3.6%)[a]	13.66 (6.35 to 30.04)
Elewski, 2004[72]	96/194 (49.5%)	6/193 (3.1%)[a]	15.92 (7.38 to 34.95)
Pooled RR			14.80 (95% CI 8.40 to 26.06)
Test for heterogeneity			$Q = 0.070$ ($df = 1$), $p = 0.791$
24-week follow-up, etanercept 25 mg twice a week			
Gottlieb, 2003[73]	32/57 (56.1%)	3/55 (5.5%)	10.29 (3.67 to 30.57)

df, Degrees of freedom.
[a] Where a trial had more than one intervention arm, results from the placebo arm are reported more than once.

TABLE 7 *Proportion of patients achieving PASI 90*

Reference	Etanercept	Placebo	RR (95% CI)
12-week follow-up, etanercept 25 mg once a week			
Leonardi, 2003[71]	5/160 (3.1%)	1/166 (0.6%)[a]	5.19 (0.82 to 33.31)
12-week follow-up, etanercept 25 mg twice a week			
Leonardi, 2003[71]	19/162 (11.7%)	1/166 (0.6%)[a]	19.47 (3.39 to 113.77)
Elewski, 2004[72]	[**Confidential information removed**]		
Gottlieb, 2003[73]	6/57 (10.5%)	0/55 (0%)	12.54 (1.29 to 126.64)
12-week follow-up, etanercept 50 mg twice a week			
Leonardi, 2003[71]	36/164 (22.0%)	1/166 (0.6%)[a]	36.44 (6.47 to 209.39)
Elewski, 2004[72]	[**Confidential information removed**]		
24-week follow-up, etanercept 25 mg twice a week			
Gottlieb, 2003[73]	12/57 (21.1%)	0/55 (0%)	24.12 (2.59 to 236.69)

[a] Where a trial had more than one intervention arm, results from the placebo arm are reported more than once.

TABLE 8 *Proportion of patients achieving clear or almost clear*

Reference	Etanercept	Placebo	RR (95% CI)
12-week follow-up, etanercept 25 mg once a week			
Leonardi, 2003[71]	37/160 (23.1%)	8/166 (4.8%)[a]	4.80 (2.36 to 9.89)
12-week follow-up, etanercept 25 mg twice a week			
Leonardi, 2003[71]	55/162 (34.0%)	8/166 (4.8%)[a]	7.04 (3.55 to 14.21)
Elewski, 2004[72]	[**Confidential information removed**]		
Gottlieb, 2003[73]	[**Confidential information removed**]		
12-week follow-up, etanercept 50 mg twice a week			
Leonardi, 2003[71]	81/164 (49.4%)	8/166 (4.8%)[a]	10.25 (5.26 to 20.38)
Elewski, 2004[72]	[**Confidential information removed**]		
24-week follow-up, etanercept 25 mg twice a week			
Gottlieb, 2003[73]	30/57 (52.6%)	[**Confidential information removed**]	

[a] Where a trial had more than one intervention arm, results from the placebo arm are reported more than once.

TABLE 9 *Mean PASI score and mean percentage reduction in PASI score from baseline*

Reference	Etanercept: mean (SD)		Placebo: mean (SD)		Mean difference (95% CI) for % reduction in PASI score from baseline
	Final (post-treatment) PASI score	% reduction in PASI score from baseline	Final (post-treatment) PASI score	% reduction in PASI score from baseline	
12-week follow-up, etanercept 25 mg once a week					
Leonardi, 2003[71]	[**Confidential information removed**]	40.9 (30.36) (n = 160)	[**Confidential information removed**]	14.0 (33.50)[a] (n = 166)	26.9 (19.95 to 33.85)
12-week follow-up, etanercept 25 mg twice a week					
Leonardi, 2003[71]	[**Confidential information removed**]	52.6 (34.37) (n = 162)	[**Confidential information removed**]	14 (33.50)[a] (n = 166)	38.6 (31.26 to 45.94)
Elewski, 2004[72]	[**Confidential information removed**]				
Gottlieb, 2003[73]	[**Confidential information removed**]				
12-week follow-up, etanercept 50 mg twice a week					
Leonardi, 2003[71]	6.5 (7.68)	64.2 (30.74) (n = 162)	15.8 (9.02)[a]	14 (33.50)[a] (n = 166)	50.2 (43.26 to 57.14)
Elewski, 2004[72]	[**Confidential information removed**]				
24-week follow-up, etanercept 25 mg twice a week					
Gottlieb, 2003[73]	[**Confidential information removed**]	67.0 (30.20) (n = 57)	[**Confidential information removed**]	1.6 (51.91) (n = 55)	65.4 (49.6 to 81.2)

[a] Where a trial had more than one intervention arm, results from the placebo arm are reported more than once.

Mean percentage reduction (improvement) in DLQI score from baseline

The results and calculated mean differences for the mean percentage change in DLQI score from baseline are summarised in *Table 10*.

Summary of findings from RCTs for licensed doses

Data on the efficacy of etanercept 25 mg twice a week for 12 weeks were available from three good-quality RCTs. On average, treatment resulted in 62% of patients achieving a PASI 50 and 33% achieving a PASI 75. These results were all statistically significantly better than placebo. These findings were reflected in results for mean PASI after treatment and for mean percentage change in PASI from baseline: across the respective mean changes in PASI from baseline were 58.8% and 5.1% with placebo. All mean differences calculated were statistically significant in favour of etanercept. Similarly, the mean percentage change

TABLE 10 *Percentage reduction (improvement) in DLQI score from baseline*

Reference	Etanercept: mean (SD)	Placebo: mean (SD)	Mean difference (95% CI)
12-week follow-up, etanercept 25 mg once a week			
Leonardi, 2003[71]	47.2 (36.68) (n = 160)	10.9 (61.84) (n = 166)[a]	36.3 (25.21 to 47.39)
12-week follow-up, etanercept 25 mg twice a week			
Leonardi, 2003[71]	50.8 (48.37) (n = 162)	10.9 (61.84)[a] (n = 166)[a]	39.9 (27.87 to 51.93)
Elewski, 2004[72]	[**Confidential information removed**]		
Gottlieb, 2003[73]	61.2 [**Confidential information removed**] (n = 57)	10 [**Confidential information removed**] (n = 55)	51.2 [**Confidential information removed**]
12-week follow-up, etanercept 50 mg twice a week			
Leonardi, 2003[71]	61 (55.07) (n = 162)	10.9 (61.84)[a] (n = 166)[a]	50.1 (37.46 to 62.74)
Elewski, 2004[72]	[**Confidential information removed**]		
24-week follow-up, etanercept 25 mg twice a week			
Gottlieb, 2003[73]	64.3 (37.75)	7.2 (59.33) (n = 55)	57.1 (38.75 to 75.45)

[a] Where a trial had more than one intervention arm, results from the placebo arm are reported more than once.

in DLQI was around 59% with etanercept 25 mg twice a week compared with 9% with placebo and again all mean differences that could be calculated were statistically significantly in favour of etanercept.

Longer term, 24-week data for etanercept 25 mg twice a week were only available from one small RCT, but the results do reflect the 12-week data.

Data on the efficacy of etanercept 50 mg twice a week for 12 weeks were available from two good-quality placebo-controlled RCTs. Across the two trials the proportion of patients achieving PASI 50, 75 and 90 was 76, 49 and 21%, respectively, and the pooled RRs were all statistically significant in favour of etanercept. The findings for mean PASI after treatment and for mean percentage change in PASI from baseline also demonstrated the efficacy of etanercept treatment. Similarly, the mean change in DLQI was around 66% with etanercept 50 mg twice a week compared with 9% with placebo. The mean differences indicated a statistically significant treatment benefit with etanercept 50 mg twice a week.

The findings of good-quality, but short-term, clinical trials demonstrate that etanercept at its licensed dose of 25 mg twice per week is clinically and statistically significantly more effective than placebo in the treatment of moderate to severe psoriasis. Etanercept 50 mg twice a week has also demonstrated its efficacy, and is possibly more efficacious than the lower dose. This is discussed further in the mixed treatment comparison analysis [see the section 'Clinical evaluation – mixed treatment comparison analysis' (p. 39)].

Etanercept long-term follow-up data from RCTs

Follow-up on open-label treatment

One trial provided long-term follow-up after the RCT phase of the trial during which all patients were treated in an open-label fashion with etanercept 25 mg/kg twice a week, giving a total study duration of 36 weeks.[72] Thus half of the patients received etanercept at a dose of 25 mg/kg twice a week for the whole 36-week study and half received 50 mg/kg twice a week for 12 weeks and then had the dose halved for the remaining 24 weeks. After 24 weeks on etanercept 25 mg, 46% of patients had a PASI 75. At the same follow-up point, 55% of those who had received 50 mg twice a week for the first 12 weeks recorded a PASI 75. Data for patients who were in the placebo group during the RCT phase are not reported here as their response to etanercept was not established under RCT conditions and the duration of etanercept treatment for these patients was shorter.

Patients who remained on the 25 mg/kg dose of etanercept throughout the study had an improvement in mean PASI score of 2.0. Those who had received the 50 mg/kg dose up to week 12 showed on average a slight deterioration in mean PASI score of –0.1.[72]

The results at 36 weeks do not indicate any lessening of response to etanercept over time: at least 45% of all patients (including those originally on placebo) recorded a PASI 75.

Follow-up after discontinuation of etanercept

Two trials followed up patients after discontinuation of etanercept (*Table 11*).[71,73] It is unclear in both trials whether the treatment

TABLE 11 *Summary of follow-up after discontinuation (RCTs only)*

Trial	Dose	Duration of treatment (weeks)	Definition of relapse	*n*	Median time to relapse (days) (75th and 25th percentiles)
Gottlieb, 2003[73]	[**Confidential information removed**]				
Leonardi, 2003[71]	25 mg twice a week	24	Loss of half the PASI improvement achieved by end of treatment	107	85 (56, 169)
	50 mg twice a week	24	Loss of half the PASI improvement achieved by end of treatment	122	91 (60, 169)

blinding of the RCT phase was continued during this discontinuation phase, i.e. did patients and investigators know from which treatment they had been discontinued?

The data from one trial cannot be described here for reasons of commercial confidentiality.[73] In the other trial,[71] a total of 409 patients who had received treatment with etanercept 25 or 50 mg twice a week for up to 24 weeks and who had achieved at least a PASI 50 had their treatment withdrawn and were followed to assess time to relapse. Data were available on 227 patients (*Table 11*) and the time to relapse was not dose related. Few patients experienced any significant exacerbation of their psoriasis: three patients relapsed to a PASI score of 125% or more of baseline score.

Retreatment after relapse

One trial provided data on the efficacy of etanercept upon retreatment after relapse.[71] Of a total of 409 patients who had received treatment with etanercept 25 mg once or twice a week or 50 mg twice a week for up to 24 weeks and who had achieved at least a PASI 50 and had their treatment withdrawn, 297 were retreated with etanercept (at each patient's original dose). The efficacy of retreatment was assessed as the difference in the PASI score at week 12 of retreatment with the PASI score at week 12 of initial treatment. Across all doses the mean difference was –0.5 [standard error (SE) 0.3] (95% CI –1.1 to 0.0), with no indication of a poorer treatment response upon retreatment.

Summary of efficacy of etanercept in the treatment of moderate to severe psoriasis

- There is evidence from three good-quality double-blind, placebo-controlled trials that etanercept is efficacious in the treatment of moderate to severe psoriasis.
- The evidence demonstrates that the level of efficacy to be achieved with etanercept 25 mg twice a week is good, with a clinically significant proportion of patients achieving PASI 75 or clear/almost clear status after 12 weeks of therapy. The efficacy of a higher dose of etanercept (50 mg twice a week) may be greater.
- Evidence from one good-quality double-blind, placebo-controlled trial indicates that the response to etanercept is maintained, at least in the medium term. Conclusions to be drawn are limited by the small sample size of this trial and the limited duration of follow-up (24 weeks). Data from uncontrolled follow-up phases reflect and extend these findings. However, such data may be unreliable.
- There are no data from RCTs to inform the duration of remission. Uncontrolled data from follow-up in one trial suggest that the median duration is around 90 days. Little evidence of severe exacerbation of psoriasis after discontinuation of treatment was reported.
- There is evidence from one trial that retreatment of patients who have relapsed following an earlier treatment period does not induce a poorer response than the initial treatment.
- The trial populations may not truly reflect the difficult-to-treat patients for whom etanercept is licensed.

Efficacy of efalizumab

Five RCTs were included in the review.[74–78]

The results of the quality assessment of the two published trials of efalizumab are reported in *Table 12*; one was rated as Good[75] and the other as Satisfactory.[74] Three further trials were presented in the industry submission only: only very limited details were reported and most of these were deemed commercial-in-confidence. These three trials received a quality rating of Poor, reflecting the very limited reporting rather than the trial

TABLE 12 *Results of quality assessment for trials of efalizumab*

Quality assessment criteria	Reference	
	Lebwohl, 2003[74]	Gordon, 2003[75]
Eligibility criteria specified?	Y	Y
Power calculation?	Y	Y
Adequate sample size?	Y	Y
Number randomised stated?	Y	Y
True randomisation?	Y	Y
Double-blind?	Y	Y
Allocation of treatment concealed?	NS	Y
Treatment administered blind?	NS	Y
Outcome assessment blind?	NS	Y
Patients blind?	Y	Y
Blinding successful?	NS	NS
Adequate baseline details presented?	N	Y
Baseline comparability?	Y	Y
Similar co-interventions?	NS	Y
Compliance with treatment adequate?	Y	Y
All randomised patients accounted for?	Y	Y
Valid ITT analysis?	Y	Y
≥80% patients in follow-up assessment?	Y	Y
Quality rating	Satisfactory	Good

ITT, intention-to-treat; N, no; NS, not stated; Y, yes.

quality.[76–78] Of the two studies reported in publications, one received a quality rating of Good[75] and The other of satisfactory[74] (*Table 12*).

All five trials were placebo controlled; no trials comparing efalizumab with another active treatment were identified. One additional randomised placebo-controlled trial examined the effects of a different formulation of efalizumab: delivered intravenously at 0.1 and 0.3 mg/kg once a week.[79] This trial is not considered here. Trial details are presented in *Table 13* and full details are given in the data extraction tables [see the section 'Data extraction tables: intervention efficacy – efalizumab' in Appendix 4 (p. 134)].

The trials were of adult patients with clinically stable moderate to severe plaque psoriasis affecting at least 10% of the BSA and with a minimum PASI score of 12, who had received prior systemic therapy or were candidates for such therapy. The number of patients in the trials ranged from 145 to 793. In the two trials reporting such details,[74,75] mean duration of psoriasis was 19 years and mean baseline PASI scores were 20[74] and 19.[75]

All five trials assessed patient outcome after 12 weeks of treatment. Two trials were continued for extended periods in which open-label and/or non-randomised designs were adopted.[74,76]

All five trials investigated efalizumab at a dose of 1 mg/kg body weight administered subcutaneously once a week. In addition, one trial examined a higher dose of 2 mg/kg body weight administered subcutaneously once a week.[74]

Overall, the trials provided data on the proportion of patients achieving PASI 50, PASI 75, PASI 90 and proportion of patients rated as minimal or clear, mean percentage change from baseline in PASI score and mean percentage change from baseline in total DLQI score. Other outcomes reported included proportion of patients rated excellent or cleared, mean percentage change from baseline in PSA frequency, PSA severity and itching scores; these data are presented in the data extraction tables [see the section 'Data extraction tables: intervention efficacy – efalizumab' in Appendix 4 (p. 134)].

The trial populations were not considered to be clinically heterogeneous and data were pooled according to outcome, dose and follow-up duration, unless prevented by statistical heterogeneity.

PASI 50

The results for patients achieving PASI 50 are summarised in *Table 14*. Data for efalizumab 1 mg/kg once a week were pooled from all five trials. The resultant pooled fixed-effect RR (95% CI) was statistically significant in favour of

TABLE 13 *Details of included trials of efalizumab*

Reference	Participants	Duration (weeks)	Intervention	Comparison	Outcomes
Lebwohl, 2003,[74] USA	*N* = 597 Adults Clinically stable moderate to severe plaque psoriasis; ≥ 10% BSA; baseline PASI ≥ 12	12	Efalizumab 1 mg/kg s.c. once a wk (*n* = 232) Efalizumab 2 mg/kg s.c. once a wk (*n* = 243)	Placebo (*n* = 122)	Proportion achieving PASI 50; PASI 75; PASI 90 Mean % change in PSA frequency, PSA severity, itching score, DLQI score, PASI score
Gordon, 2003,[75] USA	*N* = 556 Adults Clinically stable moderate to severe plaque psoriasis; ≥ 10% BSA; baseline PASI ≥ 12	12	Efalizumab 1 mg/kg s.c. once a wk (*n* = 369)	Placebo (*n* = 187)	Proportion achieving PASI 50; PASI 75; clear or minimal; excellent or clear physician rating Mean % change in PSA frequency, PSA severity, itching score, DLQI score
ACD2058g, 2004[76]	*N* = 332 Adults Clinically stable moderate to severe plaque psoriasis; ≥ 10% BSA; baseline PASI ≥ 12	12	Efalizumab 1 mg/kg s.c. once a wk (*n* = 162)	Placebo (*n* = 170)	Proportion achieving PASI 50 Mean % change in PSA frequency, PSA severity, itching score, DLQI score
ACD2600g, 2004[77]	*N* = 686 Adults Clinically stable moderate to severe plaque psoriasis	12	Efalizumab 1 mg/kg s.c. once a wk (*n* = 450)	Placebo (*n* = 236)	Proportion achieving PASI 50
IMP24011, 2004[78]	*N* = 793 Adults Clinically stable moderate to severe plaque psoriasis	12	Efalizumab 1 mg/kg s.c. once a wk (*n* = 529)	Placebo (*n* = 264)	Proportion achieving PASI 50; PASI 75

TABLE 14 *Proportion of patients achieving PASI 50*

Reference	Efalizumab	Placebo	RR (95% CI)
12-week follow-up, efalizumab 1 mg/kg once a week			
Lebwohl, 2003,[74] USA	120/232 (51.7%)	19/122 (15.6%)[a]	3.32 (2.20 to 5.15)
Gordon, 2003,[75] USA	216/369 (58.5%)	26/187 (13.9%)	4.21 (2.95 to 6.11)
ACD2058g, 2004[76]	99/162 (61.1%)	25/170 (14.7%)	4.16 (2.87 to 6.12)
ACD2600g, 2004[77]	234/450 (52.0%)	33/263 (12.5%)	4.14 (3.00 to 5.80)
IMP24011, 2004[78]	[**Confidential information removed**]		
12-week follow-up, efalizumab 2 mg/kg once a week			
Lebwohl, 2003[74] USA	138/243 (59.0%)	19/122 (15.6%)[a]	3.65 (2.42 to 5.64)

[a] Where a trial had more than one intervention arm, results from the placebo arm are reported more than once.

TABLE 15 *Proportion of patients achieving PASI 75*

Reference	Efalizumab	Placebo	RR (95% CI)
12-week follow-up, efalizumab 1 mg/kg once a week			
Lebwohl, 2003,[74] USA	52/232 (22.4%)	6/122 (4.9%)[a]	4.56 (2.02 to 10.31)
Gordon, 2003,[75] USA	98/369 (26.6%)	8/187 (4.3%)	6.21 (3.09 to 12.49)
IMP24011, 2004[78]	163/529 (31.0%)	11/264 (4%)	7.40 (4.09 to 13.37)
Pooled RR			6.34 (95% CI 4.27 to 9.42)
Test for heterogeneity			$Q = 0.89$ ($df = 2$), $p = 0.64$
12-week follow-up, efalizumab 2 mg/kg once a week			
Lebwohl, 2003,[74] USA	69/243 (28.4%)	6/122 (4.9%)[a]	5.77 (2.68 to 12.78)

[a] Where a trial had more than one intervention arm, results from the placebo arm are reported more than once.

TABLE 16 *Proportion of patients achieving PASI 90*

Reference	Efalizumab	Placebo	RR (95% CI)
12-week follow-up, efalizumab 1 mg/kg once a week			
Lebwohl, 2003,[74] USA	10/232 (4.3%)	1/122 (0.8%)[a]	5.26 (0.89 to 31.74)
12-week follow-up, efalizumab 2 mg/kg once a week			
Lebwohl, 2003,[74] USA	15/243 (6.2%)	1/122 (0.8%)[a]	7.53 (1.30 to 44.48)

[a] Where a trial had more than one intervention arm, results from the placebo arm are reported more than once.

TABLE 17 *Proportion of patients achieving clear or minimal status*[a]

Reference	Efalizumab	Placebo	RR (95% CI)
12-week follow-up, efalizumab 1 mg/kg once a week			
Gordon, 2003,[75] USA	98/369 (26.6%)	8/187 (4.3%)	8.19 (3.78 to 18.08)

[a] This trial only provided data rounded to the nearest percentage of patients who were clear or minimal for each arm. The corresponding numbers of patients were calculated for each arm from this data, assuming the highest possible number to have achieved the outcome. These were the numbers from which the RR (95% CI) was calculated.

efalizumab.The statistical test for heterogeneity was not significant.

PASI 75

Three trials reported data on the number of patients achieving PASI 75 (*Table 15*). All treatment differences were statistically significant in favour of efalizumab over placebo. Data for efalizumab 1 mg/kg once a week were pooled from both trials and the pooled fixed effect was statistically significant in favour of efalizumab. There was no significant statistical heterogeneity.

PASI 90

One trial reported data on the number of patients achieving PASI 90 (*Table 16*). The RR in favour of efalizumab over placebo was statistically significant for the high (2 mg/kg) dose of efalizumab but not for the 1 mg/kg dose.

Clear or minimal

One trial of reported data on the proportion of patients rated as clear or minimal according to the Overall, Lesion Severity Scale as assessed by the physician (*Table 17*). The RR (95% CI) was statistically significant in favour of efalizumab over placebo.

Mean percentage change in PASI score from baseline

One trial reported data on mean percentage change in PASI score from baseline (*Table 18*). The mean difference could not be calculated for this trial and outcome because no measure of variance had been reported.

TABLE 18 *Mean percentage change in PASI score from baseline*

Reference	Efalizumab	Placebo
12-week follow-up, efalizumab 1 mg/kg once a week		
Gordon, 2003,[75] USA	52%[a]	19%[a]
[a] Standard deviation not reported or calculable.		

TABLE 19 *Mean percentage change in DLQI score from baseline*

Reference	Efalizumab	Placebo
12-week follow-up, efalizumab 1 mg/kg once a week		
Lebwohl, 2003,[74] USA	45.4%[a]	12.3%[a]
Gordon, 2003,[75] USA	47.0%[a]	14.0%[a]
ACD2058g, 2004,[76]	47.0%[a]	16.1%[a]
IMP24011, 2004,[78]	[**Confidential information removed**]	
[a] Standard deviation not reported or calculable.		

Mean percentage change in DLQI score from baseline

Four trials reported data on mean percentage change in DLQI score from baseline (*Table 19*). The mean differences could not be calculated for this outcome in these trials because no measure of variance had been reported.

Summary of findings from RCTs for licensed dose

Efalizumab at a dose of 1 mg/kg once a week subcutaneously has been studied in five RCTs. Across these trials, 12 weeks of treatment resulted in an average of 55% of patients achieving PASI 50, 27% PASI 75 and 4% PASI 90. Only one trial reported mean change from baseline in PASI score; it was 56% for efalizumab-treated patients compared with 19% for placebo-treated patients. The proportion of patients achieving clear or minimal status as reported in a single trial was 26.6% compared with 4.3% with placebo [RR 8.19 (95% CI 3.78 to 18.08)]. Mean change from baseline in DLQI score averaged across four trials was higher for efalizumab-treated patients than for placebo-treated patients.

Data on a higher dose of efalizumab (2 mg/kg once a week) were reported from a single trial. They reflected those of the 1 mg/kg dose.

The licensed dose of efalizumab of 1 mg/kg once a week has been demonstrated to be clinically and statistically significantly more effective than placebo in the treatment of moderate to severe psoriasis over a 12-week treatment period. Although efalizumab appears to be similarly effective at 2 mg/kg once a week, evidence was limited to one placebo-controlled trial.

Efalizumab long-term follow-up data from RCTs

Efficacy with open-label therapy

From the company submission,[70] it appears there were three RCTs which had open-label follow-up.[74–76] Unfortunately, details for only one of these trial extensions[74] have been identified; this study had a total duration of 24 weeks.

Following a 12-week double-blind placebo-controlled phase in which patients received 1 mg/kg efalizumab once a week or 2 mg/kg efalizumab once a week or placebo, patients were re-randomised to treatment according to their response to treatment and then treated for a second 12-week period.[74] The doses in this second 12-week period were 2 mg every 2 weeks, 2 mg every week and 4 mg every week. Thus, although some patients will have received continuous efalizumab therapy for 24 weeks in a randomised controlled fashion, the doses under which these results were achieved are unclear and the results for this analysis (*Table 20*) are therefore unreliable.

In summary, there are few long-term RCT-based data for efalizumab, and those extensions of RCTs that have been performed have been poorly reported, making it impossible to assess the efficacy of more than 12 weeks of treatment with the recommended dose of efalizumab (1 mg/kg/week). No RCT-based efalizumab data were available for any period longer than 24 weeks.

TABLE 20 *Treatment response at 24 weeks*

	Efalizumab 1 mg/kg/wk	Efalizumab 2 mg/kg/wk	Efalizumab 4 mg/kg/wk
Patients with PASI 75 at wk 12			
PASI 75	30/39 (77%)	31/40 (78%)	
PASI 50	35/39 (90%)	38/40 (95%)	
PASI 90	12/39 (31%)	13/40 (32%)	
Patients with PASI 50–74 at wk 12			
PASI 75	25/47 (53%)	13/45 (29%)	
PASI 50	35/47 (74%)	30/45 (67%)	
PASI 90	1/47 (2%)	3/45 (7%)	
Patients with PASI <50 at wk 12			
PASI 75	–	–	15/118 (13%)
PASI 50	–	–	47/118 (40%)
PASI 90	–	–	5/118 (4%)

Discontinuation of treatment

Two RCTs followed up patients after discontinuation of therapy.[74,76]

In one RCT,[74] prior to treatment discontinuation, patients had been treated with a range of doses of efalizumab: 2 mg every 2 weeks, 2 mg every week and 4 mg every week. Across all doses, mean time to relapse (loss of more than 50% of improvement achieved in PASI score at week 24) in those who had achieved ≥PASI 50 was 84 days. At week 36 (end of follow-up), approximately one-third of patients who had received continuous efalizumab had not relapsed.

In the other trial, the 12-week period in which patients had been treated with either 1 mg/kg efalizumab once a week (149 patients) or 2 mg/kg efalizumab once a week (145 patients) was followed by either continued treatment or retreatment following relapse. Unfortunately, further details of this trial were not available and the number of patients followed after discontinuation or the time to relapse is unknown.

The company submission[70] states that for the two trials together the median time to relapse (defined as loss of 50% of PASI improvement achieved by end of treatment) was 59 days. Given that the dose that patients were taking up to discontinuation in the first trial was not the licensed dose and is unknown for the second trial, and that the number of patients followed is unknown, this result cannot be considered reliable or informative.

In summary, the limited data available do not permit conclusions to be drawn regarding the duration of response following discontinuation of efalizumab.

Retreatment after relapse

No data on retreatment with efalizumab from RCTs or follow-up extensions of RCTs were identified.

Summary of efficacy of efalizumab in the treatment of moderate to severe psoriasis

- There is evidence from five double-blind, placebo-controlled trials that efalizumab is efficacious in the treatment of moderate to severe psoriasis.
- The evidence demonstrates that the level of efficacy to be achieved with efalizumab 1 mg/kg once a week is good with around one-quarter of patients achieving PASI 75 after 12 weeks of treatment. However, evidence relating to the potential of efalizumab to induce clearance or near clearance of psoriasis is weak.
- There is no randomised evidence that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks. Long-term follow-up data relate to a range of doses and are poorly reported and so cannot be used to draw even tentative conclusions regarding the long-term efficacy of efalizumab.
- There are no data from RCTs to inform the duration of remission following treatment withdrawal. Uncontrolled data from trial follow-up suggest that time to relapse may be around 60 days, but this may not be reliable. No data indicating the existence or absence of any rebound in psoriasis after discontinuation of efalizumab were identified.
- There is no evidence relating to the efficacy of efalizumab upon retreatment.

Clinical evaluation: adverse events for etanercept and efalizumab

Adverse effects of etanercept

Information from standard reference texts

A list of adverse effects of etanercept summarised from standard reference sources[63,65,80,81] was generated [see the section 'Information from standard reference texts' in Appendix 6 (p. 163)]. This list of adverse effects appears very comprehensive but provides only limited information on the significance of individual events.

Information from existing reviews of etanercept

In addition to the standard reference texts, there are a large number of published articles and reviews on the adverse effects of etanercept.[82–91] Most of the clinical experience and trial and study data drawn upon for these reviews involved patients with rheumatoid arthritis, with a smaller body of evidence from patients with psoriasis and psoriatic arthritis. To date, the main areas of concern relate to the potential of etanercept to increase the risk of infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease. Further details are presented in the section 'Information from existing reviews of etanercept' in Appendix 6 (p. 163).

Adverse events for etanercept: data from included studies

From the selection of trials for inclusion in the efficacy evaluation of etanercept, three RCTs of etanercept in psoriasis provided data on the adverse effects of etanercept in psoriasis.[71–73] Although these trials do not meet the selection criteria for studies to be included in the adverse effects part of the review (because of their short trial duration), they are included in order that the data on both the harms and the benefits reported in the trials of efficacy are considered in this review.

In addition to the RCTs of efficacy, nine clinical studies that provided data on the adverse events of etanercept were identified.[92–100] Details of all studies are presented in the data extraction tables [see the section 'Data extraction tables: intervention adverse events – etanercept' in Appendix 5 (p. 148)]. Each of these nine studies had included at least 100 patients and provided at least 24 weeks' data. Five of these studies were of patients treated with etanercept for rheumatoid arthritis; one was of patients with psoriasis, one was of patients with psoriatic arthritis, one study was of patients with ankylosing spondylitis and the last was of patients with either rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Overall, there are data available on the adverse effects of etanercept over 12 weeks, 24 weeks (6 months), 1 year and 2 years or more. These data are summarised in the section 'Adverse events for etanercept: data from included studies' in Appendix 6 (p. 165).

Two RCTs of etanercept in psoriasis[71,72] provided data on the adverse effects of etanercept over a 12-week period. Note that because one of the selection criteria for studies to be included in the evaluation of adverse effects was that trials should be at least 24 weeks long, only the data from the trials of efficacy in psoriasis are included in this summary of 12-week data. Both trials compared etanercept 25 mg twice weekly and etanercept 50 mg twice weekly with placebo. The number of patients studied was 358 for etanercept 25 mg, 358 for etanercept 50 mg and 359 for placebo.

The most commonly reported adverse events are summarised in *Table 21*. Unfortunately, many of the data are commercial-in-confidence and cannot be presented. Across both trials, the rate of reported adverse events was high: the proportion of patients that reported any non-infectious adverse event was similar in both etanercept dose groups and in the placebo group and the reported

TABLE 21 *Adverse events reported most frequently during 12 or 24 weeks of treatment with etanercept*

Treatment period (weeks)	Adverse event
12[a]	Any non-infectious Injection site reaction Headache Any infection URT infection Serious adverse event[c] Withdrawals due to adverse event
24[b]	Any non-infectious Injection site reaction Headache Any infection URT infection Serious adverse event[c] Withdrawals due to adverse event

URT, upper respiratory tract.
[a] All RCT data.
[b] Some data uncontrolled.
[c] Serious adverse event including serious infection, cancer, death and any other non-infectious adverse event.

rate of infections was up to 30% in all treatment groups with no difference between active and placebo treatment. Withdrawals due to adverse events were low and not different from those on placebo.

In both trials, the most commonly occurring non-infectious adverse event was injection site reaction; this occurred at a rate of around 15% in patients receiving etanercept with no discernible difference between the two doses, and 6.5% in placebo patients. No other common adverse event occurred more frequently in etanercept-treated patients than in placebo-treated patients. Data on serious infections and serious adverse events cannot be presented owing to commercial confidentiality.

Treatment for 24 weeks with etanercept 25 mg twice weekly was also associated with a high rate of adverse events, but again this rate was not demonstrably higher than that seen in placebo-treated patients (*Table 21*). Withdrawals across the trials were not consistently higher than on placebo. The highest withdrawal rate over 24 weeks of treatment was 5.6%, reported in an uncontrolled study in rheumatoid arthritis.[100] Only injection site reactions (including ecchymosis, bruising or bleeding at the injection site) and possibly an increase in respiratory tract infections are clearly linked to etanercept. The overall rate of infections with etanercept is high but not necessarily higher than that on placebo. Serious infections have been reported and represent a concern with etanercept therapy. In clinical trials, the rate of withdrawals due to adverse events was no higher than with placebo, indicating that generally the drug was well tolerated. Data from one study indicate that the higher dose of etanercept (50 mg twice a week) is also well tolerated.

Data regarding anti-etanercept antibodies are also scarce, with few studies reporting them. The rates reported indicated that up to 6% of patients might develop antibodies.

Most long-term data for 2 years or more for etanercept are from patients with rheumatoid arthritis. Furthermore, published long-term data are poorly reported and therefore of limited value. With longer term use, neurological adverse events are reported and haematological effects such as neutropenia appear. However, it is unclear whether such effects are treatment related.

Summary of adverse events for etanercept

Injection site reactions appear to be the most common adverse effects of etanercept. Overall, etanercept appears to be well tolerated in short- and long-term use, although much of the long-term data is not from patients with psoriasis; data derived from patients with rheumatoid arthritis may not be applicable to those with psoriasis. As identified from earlier reviews, the main areas of concern relate to uncommon but serious adverse events: the potential of etanercept to increase the risk of serious infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease. Their significance is not readily discernible from the published reports of clinical trials.

Adverse effects of efalizumab

Information from standard reference texts

No information from standard texts other than from the Summary of Product Characteristics for Raptiva[64] was available for efalizumab. In brief, the most frequent symptomatic adverse events reported during efalizumab therapy are mild to moderate dose-related acute flu-like symptoms; these are associated with the first few doses of efalizumab. Infections are common in efalizumab-treated patients, but not more so than with placebo treatment. Other adverse events very common with efalizumab are leucocytosis and lymphocytosis. Common adverse events include psoriasis, arthralgia, psoriatic arthritis (exacerbation/flare), hypersensitivity reactions, back pain, asthenia, elevation of alkaline phosphatase and elevation of alanine aminotransferase. Thrombocytopenia, urticaria and injection site reactions appear to be uncommon adverse events. Antibodies to efalizumab were detected in only 6% of patients. Experience with efalizumab has not shown evidence of risk of developing malignancy exceeding that expected in the psoriasis population. Safety data beyond 12 weeks in the target population were not yet available. Further details are given in the section 'Information from standard reference texts' in Appendix 6 (p. 176).

Information from existing reviews of efalizumab

Little has been published on the adverse effects of efalizumab. Two overviews[101,102] summarise the clinical trials data. These data are evaluated as part of the systematic review below and are therefore not discussed further here.

Adverse events for efalizumab: data from included studies

In addition to the five trials already identified for the assessment of the efficacy of efalizumab in psoriasis,[74–78] there was one long-term follow-up

TABLE 22 *Adverse events reported most frequently during 12 weeks of treatment with efalizumab*

Treatment period (weeks)	Adverse event	Efalizumab 1 mg/kg[a] (%)	Efalizumab 2 mg/kg[b] (%)	Placebo (%)
12[b]	Any adverse event	Up to 86	85	Up to 77
	Headache	Up to 35	38	Up to 30
	Chills	Up to 16	13	2 to 6
	Nausea	Up to 15	14	Up to 9
	Myalgia	Up to 10	9	[**Confidential information removed**]
	Serious non-infectious adverse event (not including cancer)	2	3	1
	Cancer[b]	0.5	–	0
	Any infection	[**Confidential information removed**]		
	Serious infection[b]	0.5	–	0.5
	Withdrawals due to adverse event	[**Confidential information removed**]	3	1–3.5

[a] From RCTs.
[b] From one RCT only.

study also in patients with psoriasis[95] that provided information on the adverse effects of subcutaneous efalizumab injection. Although the five efficacy trials do not necessarily meet the selection criteria for studies to be included in the adverse effects part of the review, they are included in order that the data on both the harms and the benefits reported in the trials of efficacy are considered in this review. In addition, one trial of an intravenous formulation of efalizumab was also found.[79] Details of all studies are presented in the data extraction tables [see the section 'Data extraction tables: intervention adverse events – efalizumab' in Appendix 5 (p. 162)]. No data for efalizumab from studies of indications other than psoriasis met the inclusion criteria.

The five trials of efalizumab at a dose of 1 mg/kg administered subcutaneously once a week were all double-blind placebo-controlled RCTs conducted in patients with plaque psoriasis. One of these trials also evaluated a higher dose of 2 mg/kg, administered once a week.[74] All five trials provided adverse events data for a 12-week treatment period, with a total of 1740 patients treated with efalizumab 1 mg/kg once a week, 243 treated with efalizumab 2 mg/kg once a week, and 979 treated with placebo. The most common adverse events reported are summarised in *Table 22* with further details in the section 'Adverse events for efalizumab: data from included studies' in Appendix 6 (p. 177). In addition, two trials[74,76] provided data for a further 12 weeks in selected patients (number not reported) and one of these trials[74] provided data for a treatment-free follow-up period of 12 weeks (171 with efalizumab and 158 with placebo). Data from these studies are summarised in the section 'Adverse events for efalizumab: data from included studies' in Appendix 6 (p. 177).

Across the trials, the proportion of patients reporting at least one adverse event during 12 weeks of treatment with efalizumab 1 mg/kg was high, but not dissimilar to the rate for patients treated with placebo. Adverse events more common on efalizumab than placebo were headache, chills, nausea, myalgia, pain and fever. No specific infection was reported more commonly with efalizumab than with placebo. Unfortunately, the rate of serious infections was not reported, so any tendency for efalizumab to increase these relatively rare events cannot be discerned from these trial data.

The rate of serious adverse events with efalizumab was low at around 2%, but again data are sparse with only two trials reporting them.[74,75] There were no deaths associated with 12 weeks of efalizumab treatment and most trials did not report cancer data. Rates of around 1–5% for patients who developed anti-efalizumab antibodies were reported.

Two trials[74,76] evaluated 24 weeks of efalizumab treatment, but unfortunately one of these trials evaluated only the higher dose of efalizumab for the second 12 weeks,[74] and in the other it is unclear which dose was studied.[76] For both, the

level of detail available from the available reports is very limited and the total number of patients treated with efalizumab was only 171 in one trial[74] and not reported in the other.[76] These limited data indicate that adverse events were similar to or less than for the initial 12-week period and one trial[74] reported that adverse events leading to withdrawal were more common in patients receiving placebo. Infection was the most common adverse event.

One long-term study provided data on 339 patients who had responded to efalizumab and who were then followed for up to 3 years.[95] These data indicate that the clinically significant adverse events were non-specific infections (mostly colds and upper respiratory tract infections), accidental injury, increased cough, rhinitis and sinusitis. Clinically significant including serious adverse events remained generally stable between each 3-month period of the whole study period. The rate of serious adverse events per 3-month period ranged from 1 to 5.5%. The average frequency of skin cancer per 3-month period ranged from 0 to 3.3%, the higher figure representing one month's atypical high rate. Withdrawals during any period of the follow-up were at a rate of 3.4% or less.

Summary of adverse events data for efalizumab

Headache, chills and, to a less extent, nausea, myalgia, pain and fever are the common adverse events associated with efalizumab. Overall, withdrawal rates due to adverse events are low. Longer term data for efalizumab are not readily available for evaluation but the adverse events periods up to 3 years appear to reflect those over 12 weeks and to remain stable. Unfortunately, few data for serious infections and serious adverse events with efalizumab are available. The available published reports of the efalizumab trials did not reveal leucocytosis and lymphocytosis as common adverse consequences of therapy. Some patients developed antibodies, but this did not appear to be associated with any increased risk of adverse events.

Overall, the publicly available information for efalizumab indicates that the drug is well tolerated over a 12-week period and in the long term; however, few data for long-term treatment are available for detailed evaluation.

Clinical evaluation: other treatments for moderate to severe psoriasis

In 2000, Griffiths and colleagues published a systematic review of treatments for severe psoriasis.[66] The present updated review has added to some of the findings from the Griffiths review with a focus on those treatments identified as comparators for etanercept and efalizumab in clinical practice. Studies eligible for inclusion in this update were RCTs that consisted of 20 or more patients and investigated a therapeutic dose, as advised by a clinical expert. The outcome measure PASI 75 has been used where available; in its absence, an alternative PASI measure has been discussed, otherwise the primary outcomes have been reported. Studies identified from the Griffiths review and this updated review that did not meet these criteria have not been discussed in this report.

Of the 24 trials that met the inclusion criteria of this review, 14 were found in the Griffiths report and an additional 10 trials were identified by this updated review. Details of each trial can be found in the data extraction tables (Appendix 7). They are summarised in *Table 23*, which presents all the available treatment comparisons of the other treatments for moderate to severe chronic plaque psoriasis.

Trials involving ciclosporin

Six trials investigated the efficacy of ciclosporin, of which four compared ciclosporin with placebo,[103–106] and two compared ciclosporin with methotrexate (*Table 24*).[107,108] A range of doses was studied, from 2.5 to 5.5 mg/kg/day. All but one trial were of at least 8 weeks' duration. The number of patients included in each study was small, with a total of only 113 patients treated with ciclosporin in placebo-controlled trials. Despite their small sample sizes, two of the four placebo-controlled trials found a statistically significant treatment effect for ciclosporin over placebo.[103,104] The other two placebo-controlled trials also indicated a beneficial effect of ciclosporin, but their ability to discriminate between treatments was hampered by their small sample sizes.[105,106] Most of the trials used doses lower than that considered to be optimal (5 mg/kg/day), and this may also have contributed to their failure to clearly demonstrate efficacy with ciclosporin.

Two trials compared ciclosporin (range 3–5 mg/kg/day) with methotrexate (range 15–35 mg/week). The Sandhu trial[107] included only very severely affected patients (minimum BSA 40%). The trials found that over 70% of patients achieved a PASI 75 with ciclosporin and that both drugs were equally efficacious. Overall, ciclosporin appears to be effective in the treatment of moderate to severe psoriasis but there is only limited evidence from RCTs.

TABLE 23 *Complete list of trials of other treatments for moderate to severe psoriasis*

Study	Placebo	Ciclosporin	Methotrexate	Acitretin	Acitretin + calcipotriol	PUVA	RePUVA	NBUVB	NBUVB + dithranol	Infliximab	Fumaderm
Ellis, 1991[103]	✓	✓									
Guenther, 1991[104]	✓	✓									
Meffert, 1997[105]	✓	✓									
van Joost, 1988[106]	✓	✓									
Sandhu, 2003[107]		✓	✓								
Heydendael, 2003[108]		✓	✓								
Goldfarb, 1988[109]	✓			✓							
Lassus, 1987[110]	✓			✓							
Caca-Biljanovska, 2002[111]				✓		✓					
Saurat, 1988[112]						✓	✓				
Sommerburg, 1993[113]						✓	✓				
Tanew, 1991[114]						✓	✓				
Dogan, 1999[115]						✓	✓				
van de Kerkhof, 1998[116]				✓	✓						
Rim, 2003[117]				✓	✓						
Van Weelden, 1990[118]						✓		✓			
Gordon, 1999[119]						✓		✓			
Markham, 2003[120]						✓		✓			
Dawe, 2003[121]						✓		✓			
Storbeck, 1993[122]								✓	✓		
Chaudhari, 2001[123]	✓									✓	
Gottlieb, 2004[124]	✓									✓	
Altmeyer, 1994[125]	✓										✓
Nugteren-Huying, 1990[126]	✓										✓

TABLE 24 *Details of trials including ciclosporin as a comparator*

Study	Comparison	Population	Dose (treatment duration)	Outcome measure	Results
Ellis, 1991[103]	Ciclosporin vs placebo	Plaque Min. BSA >25% Min. PASI not stated	3 mg/kg/day (8 wks)	Mean PASI	Ciclosporin (n = 25) 6.2 (SE range 4–7) Placebo (n = 25) 6.1 (SE range 5–7) Mean difference not calculable
				Clearance	Ciclosporin 36% (9/25) Placebo: 0% (0/25) RR 19.00 (95% CI 1.17 to 309.77)
			5 mg/kg/day (8 wks)	Mean PASI	Ciclosporin (n = 25) 6.5 (SE range 5–7) Placebo: 6.1 (SE range 5–7) Mean difference not calculable
				Clearance	Ciclosporin 65% (13/20) Placebo: 0% (0/25) RR 33.43 (95% CI 2.11 to 530.00)
Guenther, 1991[104]		Psoriasis type not stated Min. BSA not stated Min. PASI >12	2.5 mg/kg/day (10 wks)	PASI 50	Ciclosporin 12/12 Placebo 1/11 RR 11.00 (95% CI 1.70 to 71.28)
				Mean PASI	Ciclosporin (n = 12): (wk 0) mean 23, (wk 10) mean 2 Placebo (n = 11): (wk 0) mean 21, (wk 10) mean 16 Mean difference not calculable
Meffert, 1997[105]		Plaque Min. BSA not stated Min. PASI 8–25	2.5 mg/kg/day (10 wks)	PASI 75	Ciclosporin 10% (n = 41) Placebo 5% (n = 43) RR 2.10 (95% CI 0.41 to 10.84)
van Joost, 1988[106]		Plaque Min. BSA not stated Min. PASI >20	5.5 mg/kg/day (4 wks)	PASI 75	Ciclosporin 7/10 Placebo 0/10 RR 15.00 (95% CI 0.97 to 231.84)
Sandhu, 2003[107]	Ciclosporin vs methotrexate	Plaque and erythrodermic Min. BSA >40% Mean baseline PASI: treatment 29.6, control 27.6	Ciclosporin: 3–4 mg/kg/day Methotrexate: 35 mg/wk (12 wks)	PASI 75	Ciclosporin 14/15 Methotrexate 15/15 RR 0.93 (95% CI 0.82 to 1.07)
Heydendael, 2003[108]		Plaque Min. BSA not stated Min. PASI >8	Ciclosporin: 3–5 mg/kg/day Methotrexate: 15–22.5 mg/wk (16 wks)	PASI 75	Ciclosporin 30/42 Methotrexate 26/43 RR 1.18 (95% CI 0.87 to 1.61)

Trials involving methotrexate

Two trials were identified that investigated the efficacy of methotrexate; both were comparisons with ciclosporin and are discussed above. No placebo-controlled trial of methotrexate was identified. The dose of methotrexate used in two trials and particularly in the Sandhu trial[107] (35 mg/week) is much higher than that currently used in the UK for treatment of psoriasis. Furthermore, the Sandhu trial involved a very severely affected population (minimum BSA 40%). The trials are therefore of limited

utility in informing clinical practice. At the doses utilised, methotrexate appears to be effective in the treatment of moderate to severe psoriasis.

Trials involving acitretin

There were five trials that looked at the effect of acitretin (*Table 25*).[109–111,116,117] Three trials considered the drug as a monotherapy compared with placebo[109,110] or PUVA[111] and the other two trials investigated the combination of acitretin with calcipotriol compared with acitretin alone.[116,117] There are additional trials of etretinate versus placebo;[66] however, in this review we did not assume that etretinate equated with acitretin and these trials have not been included.

Of the two trials that compared acitretin with placebo,[109,110] data were extractable from only one.[110] This one trial found acitretin at 50- and 75-mg doses to be significantly more effective in terms of PGA than placebo, but acitretin at 25 mg was not.[109]

The one trial that compared acitretin (30 mg/day) with PUVA (four times a week for 6 weeks)[111] found no statistically significant difference in the reduction of mean PASI or clearance between the treatments at week 8.

Two trials compared acitretin with a combination of acitretin plus calcipotriol.[116,117] One trial found that clearance was achieved significantly more often with combination therapy than with acitretin and placebo,[116] but the other trial did not.[117]

Overall, the few data available indicate that acitretin has some efficacy in the treatment of psoriasis and this might be enhanced when use in combination with calcipotriol.

There were four trials that compared acitretin in combination with PUVA with PUVA alone; these are discussed below.

Trials involving phototherapy

Ten studies looked at the efficacy of a phototherapy regimen (*Table 26*). Four trials investigated the efficacy of PUVA compared with NBUVB,[118–121] one study compared PUVA with acitretin,[111] four trials compared PUVA plus acitretin (RePUVA) with PUVA alone[112–115] and one trial investigated the effect of NBUVB in combination with dithranol compared with NBUVB alone.[122]

Although clinical opinion would generally consider PUVA more powerful than NBUVB, only one of four trials comparing PUVA with NBUVB reported a greater rate of clearance with PUVA.[119] Thus, from the limited data available, the efficacies of the two forms of phototherapy treatment appear to be similar.

PUVA was compared with acitretin in one trial, which found no difference between the two treatments in reduction of mean PASI or clearance.[111] This study is also discussed above.

Four trials were identified that compared the efficacy of acitretin in combination with PUVA (known as RePUVA, representing the combination of a retinoid with PUVA) with PUVA alone.[112–115] These trials appear to show no marked differences in the outcomes of each treatment arm. In general, patients receiving the combination therapy appear to have a better rate of improvement in a variety of outcomes; however, the difference is not statistically significant.

In summary, PUVA has not been compared with placebo, but the available trial data indicate a degree of efficacy which is comparable to that achieved with NBUVB and with acitretin and which may be only slightly enhanced by addition of acitretin.

NBUVB in combination with dithranol was compared with NBUVB alone in one trial.[122] However, as it was not possible to extract the data from the report, no conclusions can be drawn about the relative efficacy of these treatments.

Trials involving infliximab

Two trials were identified that compared infliximab with placebo (*Table 27*).[123,124] Across the two trials infliximab was tested at doses of 3, 5 and 10 mg. At all three doses of infliximab the proportion of patients achieving PASI 75 was significantly higher than those receiving placebo.[123] Overall, there is evidence of efficacy with infliximab in the treatment of moderate to severe psoriasis.

Trials involving Fumaderm

Two studies compared Fumaderm with placebo (*Table 28*).[125,126] One study found a significant number of patients achieving clearance in the Fumaderm group at 16 weeks, although the 95% CI for the RR is wide.[125] The second trial found no significant difference in clearance between the treatment arms.[126]

TABLE 25 *Details of trials including acitretin as a comparator*

Study	Comparison	Population	Dose	Outcome measure	Results
Goldfarb, 1988[109]	Acitretin vs placebo	Psoriasis type not stated Min. BSA >10% Min. PASI not stated	25 mg	PGA (0–6) 0 = absent or clear, 6 = severe [mean (SD)]	Acitretin (n = 5): 1 (SD 0.67) Placebo (n = 12): 0.5 (SD 1.04) Mean difference: 0.5 (95% CI –0.33 to 1.33)
			50 mg (8 wks)		Acitretin (n = 11): 1.6 (SD 1.33) Placebo (n = 12): 0.5 (SD 1.04) Mean difference: 1.10 (95% CI 0.12 to 2.08)
			75 mg (8 wks)		Acitretin (n = 5): 3 (SD 1.79) Placebo (n = 12): 0.5 (SD 1.04) Mean difference: 2.50 (95% CI 0.82 to 4.18)
Lassus, 1987[110]		Plaque, erythrodermic, pustular Min. BSA not stated Min. PASI not stated	25 mg (8 wks)	Reduction in PASI	Data not extractable
			50 mg (8 wks)		Data not extractable
Caca-Biljanovska, 2002[111]	PUVA vs acitretin	Plaque Min. BSA >30 Mean baseline PASI: treatment 24.06 (SD 3.62); control 24.56 (SD 3.40)	PUVA: 4/wk for 6 wks + 2/wk for 2 wks Acitretin: 30 mg/day	Mean PASI	PUVA (n = 20): mean change from baseline 22.37 (SD 14.84) Acitretin (n = 20): mean change from baseline 23.66 (SD 8.48) Mean difference 1.29 (95% CI –6.20 to 8.78)
				Clearance	PUVA: 7/20 Acitretin: 10/20 RR 0.70 (95% CI 0.33 to 1.47)
van de Kerkhof, 1998[116]	Acitretin + calcipotriol vs acitretin	Plaque Min. BSA not stated Mean (SD) baseline PASI: treatment 17.8 (8.9); control 17.4 (8.6)	Acitretin 20–70 mg/day + calcipotriol 2/day (12 wks) Acitretin 20–70 mg/day + placebo (12 wks)	Mean PASI	Acitretin + calcipotriol (n = 76) mean reduction 13.2 Acitretin (n = 59): mean reduction 8.8 Mean difference not calculable – SDs not reported
				Clearance	Acitretin + calcipotriol: 51/76 Acitretin: 24/59 RR 1.65 (95% CI 1.17 to 2.33)
Rim, 2003[117]		Plaque Min. BSA >5% Mean baseline PASI: treatment 21.6, control 24.3	Acitretin 10–40 mg/day + calcipotriol 50 mg 2/day (12 wks) Acitretin: 10–40 mg/day (12 wks)	Clearance	Acitretin + calcipotriol: 16/40 Acitretin: 3/20 RR 2.67 (95% CI 0.88 to 8.09)

SD, standard deviation.

TABLE 26 *Details of trials including phototherapy as a comparator*

Study	Comparison	Population	Dose	Outcome measure	Results
Van Weelden, 1990[118]	PUVA vs NBUVB	Plaque Min. BSA not stated Min. PASI not stated	PUVA: 2/wk NBUVB: 2/wk (4 wks)	Overall, impression	Data not extractable
Gordon, 1999[119]		Plaque Min. BSA not stated Min. PASI not stated	PUVA: (oral) 2/wk NBUVB: 2/wk (until clearance)	Clearance	PUVA (n = 49): (after 16 treatments) 41/49 NBUVB (n = 51): (after 16 treatments) 32/51 RR 1.33 (95% CI 1.04 to 1.70)
Markham, 2003[120]		Plaque Min. BSA ≥ 8% PASI baseline range 11–19	PUVA: (oral methoxsalen) 2/wk NBUVB 3/wk (until clearance)	Clearance	PUVA (n = 29): (3 mths) 23/29 NBUVB (n = 25): (3 mths) 18/25 RR 1.10 (95% CI 0.81 to 1.50)
Dawe, 2003[121]		Plaque Min. BSA not stated Min. PASI not stated	PUVA: (bath trimethoxy-psoralen) 2/wk NBUVB: 3/wk	Reduction in PASI	PUVA (n = 28): mean 17.5 NBUVB (n = 28): mean 20 Mean difference not calculable – SDs not reported
				Clearance	PUVA: 18/28 NBUVB: 15/28 RR 1.20 (95% CI 0.77 to 1.87)
Caca-Biljanovska, 2002[111]	PUVA vs acitretin	Plaque Min. BSA >30 Mean baseline PASI: treatment 24.06 (SD 3.62); control 24.56 (SD 3.40)	PUVA: 4/wk for 6 wks + 2/wk for 2 wks Acitretin: 30 mg/day (8 wks)	Mean PASI	PUVA (n = 20): mean change from baseline 22.37 (SD 14.84) Acitretin (n = 20): mean change from baseline 23.66 (SD 8.48) Mean difference 1.29 (95% CI –6.20 to 8.78)
				Clearance	PUVA: 7/20 Acitretin: 10/20 RR 0.70 (95% CI 0.33 to 1.47)
Saurat, 1988[112]	RePUVA vs PUVA	Plaque, erythrodermic Min. BSA >20% Min. PASI not stated	Acitretin 50 mg/day + PUVA (12 wks) PUVA + placebo (12 wks)	PASI 90	17/20 16/22 RR 1.17 (95% CI 0.85 to 1.60)
				Clearance	Acitretin + PUVA: 17/18 (94%) PUVA: 16/20 (80%) RR 1.18 (95% CI 0.92 to 1.51)
Sommerburg, 1993[113]		Plaque, guttate or nummularis Min. BSA not stated Min. PASI not stated	Acitretin 25 mg/day + PUVA (8 wks) PUVA + placebo 3–5/wk (8 wks)	>75% decrease in PSI	34/44 26/44 RR 1.31 (95% CI 0.98 to 1.75)

continued

TABLE 26 *Details of trials including phototherapy as a comparator (cont'd)*

Study	Comparison	Population	Dose	Outcome measure	Results
Tanew, 1991[114]		Plaque, guttate or erythrodermic Min. BSA ≥20% Min. PASI not stated	PUVA 4/wk + acitretin 1 mg/kg a day PUVA 4/wk + placebo Both 11 wks or until complete clearance	90% clearance	22/30 20/30 RR 1.10 (95% CI 0.79 to 1.53)
Dogan, 1999[115]		Psoriasis type not stated Min. BSA ≥15% Mean baseline PASI 12	Acitretin: 50 mg/day for 15 days, 25 mg/day thereafter plus PUVA (oral psoralen) 3/wk PUVA: 3/wk Both for 3 months or until clearance	PASI 50	RePUVA: 20/20 PUVA: 29/30 RR 1.03 (95% CI 0.97 to 1.11)
				Clearance	RePUVA: 6/20 PUVA: 25/30 RR 0.36 (95% CI 0.18 to 0.72)
Storbeck, 1993[122]	NBUVB vs NBUVB + dithranol	Plaque, guttate or erythrodermic Min. BSA not stated Min. PASI not stated	NBUVB: 3–5/wk + dithranol NBUVB: 3–5/wk Both until non-compliance	PASI	Data not extractable

TABLE 27 *Details of trials including infliximab as a comparator*

Study	Comparison	Population	Dose	Outcome measure	Results
Chaudhari, 2001[123]	Infliximab vs placebo	Plaque Min. BSA >5% Mean baseline PASI: treatment 5 mg/kg 22.1; mean treatment 10 mg/kg 26.6; control 20.3	5 mg/kg (10 wks)	PASI 75	Infliximab: 9/11, 10 mg/kg: 8/11 Placebo: 2/11 RR 4.50 (95% CI 1.25 to 16.25)
			10 mg/kg (10 wks)		Infliximab: 8/11 Placebo: 2/11 RR 4.00 (95% CI 1.08 to 14.75)
Gottlieb, 2004[124]		Plaque Min. BSA ≥10% Min. PASI ≥12	3 mg/kg	PASI 75	Infliximab: 71/99 Placebo: 3/51 RR 12.19 (95% CI 4.04 to 36.80)
			5 mg/kg		Infliximab: 87/99 Placebo: 3/51 RR 14.94 (95% CI 4.97 to 44.89)

TABLE 28 *Details of trials including Fumaderm as a comparator*

Study	Comparison	Population	Dose	Outcome measure	Results
Altmeyer, 1994[125]	Fumaderm vs placebo	Plaque, guttate or erythrodermic Min. BSA >10% Min. PASI not stated	Fumaderm 105 escalating to 1290 mg/day (16 wks)	Mean PASI	Fumaderm (n = 49): 10.77 Placebo (n = 51): 23 Mean difference not calculable – SDs not reported
				Clearance	Fumaderm: 12/49 Placebo: 1/51 RR 12.49 (95% CI 1.69 to 92.47)
Nugteren-Huying, 1990[126]		Psoriasis type not stated Min. BSA >10% Min. PASI not stated	DMFAE 120 mg; MEFAE-Ca 87 mg; MEFAE-Mg 5 mg; MEFAE-Zn 3 mg. (16 wks) OHFAE 284 mg; MEFAE-Mg 5 mg; MEFAE-Zn 3 mg. (16 wks)	Clearance	DMFAE: 6/12 OHFAE: 0/10 Placebo: 0/12 DMFAE: RR 13.00 (95% CI 0.81 to 207.84) OHFAE: not estimable

DMFAE, dimethylfumaric acid ester; MEFAE-Ca, -Mg and -Zn, calcium, magnesium and zinc salts of monoethylfumaric acid ester; OHFAE, octylhydrogen fumaric acid ester.

Summary of efficacy of other treatments for moderate to severe psoriasis

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the treatments available for the relief of moderate to severe psoriasis. Only infliximab and ciclosporin have had their efficacy demonstrated in placebo-controlled RCTs, and even then these data are relatively few, with most trials having included a small number of patients and only a short treatment period.

Although clinical experience has demonstrated excellent efficacy of PUVA and methotrexate, no placebo-controlled trials have been conducted. In clinical trials methotrexate appears to be as effective as ciclosporin. The trials of other treatments, acitretin, RePUVA, and NBUVB, in comparison with PUVA provide only limited evidence, demonstrating some degree of effectiveness but making it difficult to draw firm conclusions regarding the relative efficacy.

All data provide evidence of induction of remission rather than long-term effectiveness in the treatment of psoriasis.

Adverse events of other treatments for moderate to severe psoriasis

Ciclosporin

Dose-related hypertension and renal toxicity are associated with the use of ciclosporin.[51,52] These adverse effects have been found to increase over time, resulting in discontinuation of the treatment.[52] Malignancies have also been associated with the use of ciclosporin, specifically cutaneous malignancies such as squamous and basal cell carcinoma.[51] Where ciclosporin is used as an immunosuppressant, at higher doses than used for psoriasis, such malignancies are not uncommon. In psoriasis, the risk of squamous cell carcinoma is higher in patients treated with ciclosporin and a history of PUVA therapy.[51]

Methotrexate

Myelosuppression, a potentially fatal adverse effect of methotrexate, is related to dose and occurs more frequently in the elderly.[52] Liver fibrosis and cirrhosis are serious long-term adverse events associated with the use of methotrexate.[51,52] The likelihood of these events is thought to be dose dependent, with a greater chance of development associated with increased alcohol consumption,[52] and much of the clinical experience with

methotrexate is with doses far higher than those used for the treatment of psoriasis. However, there is some evidence that patients with psoriasis may be more susceptible to liver toxicity.[127,128] Acute or chronic pneumonitis may occur with the use of methotrexate, although it is rare. Haematological toxicity can occur and is particularly associated with drug interactions, for example with drugs that inhibit folate metabolism (e.g. sulfonamides) or which increase the bioavailability of methotrexate [e.g. non-steroidal anti-inflammatory drugs (NSAIDs)].[51,52] When administered in combination with PUVA, methotrexate has been associated with an increased risk of squamous cell carcinoma.[52] An increased risk of lymphoma may also be associated with methotrexate.

Acitretin

The primary concern with acitretin and other retinoids is its teratogenicity, and acitretin must therefore not be used by pregnant women.[51] Acitretin may be metabolised partly to etretinate, which is eliminated from the body very slowly. Mucocutaneous adverse events are commonly reported when using acitretin, including cheilitis, dry skin and conjunctivitis, but these are generally mild.[51,52] An increase in serum lipids including cholesterol and triglyceride is also commonly reported.[51,52] Low-grade hepatotoxicity can occur and acute hepatitis has been reported, although its incidence is rare.[51,52] Patients taking acitretin over a long period have been reported to develop hypertrophy of bone ligaments, tendons and other tissues.[51,52]

PUVA

Serious adverse events associated with PUVA are squamous and basal cell carcinoma, and there is a possibility that malignant melanoma may also be related.[51,52] Pruritus is also associated with PUVA therapy, in addition to a sunburn-like reaction[51] and premature photoageing.[52] Cataracts can develop when UVA eyeglasses are not worn after ingesting psoralen.[51,52] Gastrointestinal effects including nausea have been experienced.[51]

NBUVB

Photoageing and an increased risk of skin cancer are associated with UVB treatment; however it has been estimated that the excess annual risk of non-melanoma skin cancer associated with UVB radiation is likely to be less than 2%.

Infliximab

Infliximab has been associated with acute infusion-related reactions, including anaphylactic shock and delayed hypersensitivity. Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions.

Other common adverse events associated with infliximab are infusion-related reactions [including fever, chills, pruritus, urticaria, chest pain, dyspnoea, flushing, headache, hypotension (dizziness/fainting)], viral infection (e.g. influenza, herpes infections), serum sickness-like reactions, lupus-like syndrome, respiratory tract allergic reactions, anaphylactic reactions, headache, vertigo/dizziness, flushing, upper respiratory tract infection (URT), lower respiratory tract infection (e.g. bronchitis, pneumonia), sinusitis, nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, rash, increased sweating, dry skin, fatigue, myalgia and elevated hepatic transaminases.[65,80,81,129]

Fumaderm

Gastrointestinal adverse effects and flushing are commonly related to treatment with Fumaderm. Eosinophillia is also associated with Fumaderm.[52] There have been reports of renal failure but as yet no link has been clearly established. Other adverse events reported by patients receiving Fumaderm include oropharyngeal irritation, taste disturbances, rash, insomnia, nausea and pruritus, potential paradoxical bronchospasm, epigastric pain, diarrhoea, constipation, faecal impaction, nephrotoxicity, reversible elevation of transaminases, reversible lymphopenia and osteomalacia.[65,130]

Calcipotriol

Skin irritation has been linked to the use of calcipotriol. Dose-related effects include hypercalcaemia and hypercalciuria.[52] Calcipotriol may also cause skin rash, atrophy of skin, folliculitis and worsening of psoriasis.[80]

Goeckerman treatment

Localised irritation is associated with the Goeckerman regimen.[52]

Ingram regimen

Localised irritation is associated with Ingram treatment.[52] Adverse effects of dithranol include staining of the skin, burning and smell.[52] Frequently occurring events associated with dithranol that require medical attention are redness and skin irritation. Allergic reactions are rare but would require medical attention if observed.[65,80,81,130]

Summary of adverse events of other treatments for moderate to severe psoriasis

Most comparator treatments are associated with risks of serious and long-term adverse events. However, much of the available information is derived from patients with illnesses other than psoriasis or from the use of higher doses than those employed in UK practice.

Clinical evaluation: mixed treatment comparison analysis

The purpose of the mixed treatment comparison analysis was to bring together the clinical evidence regarding the efficacy of etanercept, efalizumab and other treatments of moderate to severe psoriasis as identified and extracted [as detailed in the sections 'Clinical evaluation – efficacy of interventions' (p. 15) and 'Clinical evaluation – other treatments for moderate to severe psoriasis' (p. 30)]. The analysis was primarily for purposes of decision-making, so its focus is to generate parameter estimates for the cost-effectiveness modelling described in Chapter 6.

Specification of the synthesis

Changes in utility arising from treatment were estimated based on the PASI 50, 75 and 90 response data as reported. The available trials have been listed in earlier sections (*Tables 4*, *13* and *23*). The trials of etanercept and efalizumab were placebo controlled. The trials including the other systemic therapies included both placebo and a variety of active treatments as controls.

It can be seen from the tables of clinical trials (*Tables 3*, *14* and *23*) that there were no head-to-head trials comparing all the treatments.

Etanercept and efalizumab were linked to most other therapies via a placebo control. Most other therapies (i.e. those listed in *Table 23*) were also linked through a placebo control. Methotrexate had not been compared with placebo, but linked into the chain of evidence through having been compared with ciclosporin, which in turn had been investigated in placebo-controlled trials.

Treatments that could not be linked into the chain of evidence were acitretin, acitretin plus calcipotriol, PUVA, RePUVA, NBUVB and NBUVB plus dithranol. Of these six treatments, only acitretin had been compared with placebo; all the others had been compared with acitretin or each other. Unfortunately, the link to the chain of evidence through the acitretin–placebo comparison could not be made because no usable measure of response was recorded in either of the two placebo-controlled acitretin trials.[109,110]

The pattern of comparisons available for those trials that comprised the chain of evidence is shown in *Table 29*. The populations investigated in

TABLE 29 *Treatment comparisons comprising the chain of evidence*

	Study	Treatment option						
		Placebo	Ciclosporin	Fumaderm	Methotrexate	Infliximab	Etanercept	Efalizumab
Trials	Meffert, 1997[105]	■	■					
	Van Joost, 1988[106]	■	■					
	Ellis, 1991[103]	■	■					
	Guenther, 1991[104]	■	■					
	Altmeyer, 1994[125]	■		■				
	Chaudhari, 2001[123]	■				■		
	Gottlieb, 2004[124]	■				■		
	Heydendale, 2003[108]		■		■			
	Elewski, 2004[72]	■					■	
	Leonardi, 2003[71]	■					■	
	Gottlieb, 2003[73]	■					■	
	IMP24011[78]	■						■
	ACD 2058g[76]	■						■
	Lebwohl, 2003[74]	■						■
	ACD 2600g[77]	■						■
	Gordon, 2003[75]	■						■

these trials were all adults suffering from moderate to severe psoriasis as defined by having a minimum BSA of 10, a minimum baseline PASI of 10 or a mean baseline PASI of at least 10. *Table 30* summarises the data extracted from the clinical trials.

To allow indirect comparisons between all the comparators, a meta-analysis of the PASI 50, 75 and 90 response rates from the randomised trials was performed. Where the proportion of patients reported as 'clear' or 'almost clear' was given, these were assumed to be equivalent to the PASI 75 end-point. The end-points were jointly modelled using an ordered probit model.[131,132] Further details are presented in the section 'Ordered probit model' in Appendix 8 (p. 205).

The meta-analysis then provided estimates for response rates for each of the treatments based on all observed comparisons adjusting for (implicit) variation in placebo response rates on the log-odds scale. These estimates of response rates were used in the cost-effectiveness model. The meta-analysis was conducted using WinBUGS version 1.4.[133] The WinBUGS code is reproduced in the section 'Code used for mixed treatment comparison and economic modelling' in Appendix 8 (p. 206).

TABLE 30 *Summary of the response data extracted from the clinical trials and used in the mixed treatment comparison*

Trial	Ref.	Treatment	Outcome (percentage change In PASI)	Outcome code used in model	*n*
Elewski, 2004	72	Supportive care	<50	1	175
Elewski, 2004	72	Supportive care	50–75	2	12
Elewski, 2004	72	Supportive care	75–90	3	5
Elewski, 2004	72	Supportive care	≥90	4	1
Elewski, 2004	72	Etanercept 50 mg	<50	1	44
Elewski, 2004	72	Etanercept 50 mg	50–75	2	54
Elewski, 2004	72	Etanercept 50 mg	75–90	3	56
Elewski, 2004	72	Etanercept 50 mg	≥90	4	40
Elewski, 2004	72	Etanercept 25 mg	<50	1	70
Elewski, 2004	72	Etanercept 25 mg	50–75	2	59
Elewski, 2004	72	Etanercept 25 mg	75–90	3	46
Elewski, 2004	72	Etanercept 25 mg	≥90	4	21
Gottlieb, 2003	73	Supportive care	<50	1	49
Gottlieb, 2003	73	Supportive care	50–75	2	5
Gottlieb, 2003	73	Supportive care	75–90	3	1
Gottlieb, 2003	73	Supportive care	≥90	4	0
Gottlieb, 2003	73	Etanercept 25 mg	<50	1	17
Gottlieb, 2003	73	Etanercept 25 mg	50–75	2	23
Gottlieb, 2003	73	Etanercept 25 mg	75–90	3	11
Gottlieb, 2003	73	Etanercept 25 mg	≥90	4	6
Lebwohl, 2003	74	Supportive care	<50	1	103
Lebwohl, 2003	74	Supportive care	50–75	2	13
Lebwohl, 2003	74	Supportive care	75–90	3	5
Lebwohl, 2003	74	Supportive care	≥90	4	1
Lebwohl, 2003	74	Efalizumab	<50	1	112
Lebwohl, 2003	74	Efalizumab	50–75	2	68
Lebwohl, 2003	74	Efalizumab	75–90	3	42
Lebwohl, 2003	74	Efalizumab	≥90	4	10
Leonardi, 2003	71	Supportive care	<50	1	142
Leonardi, 2003	71	Supportive care	50–75	2	18
Leonardi, 2003	71	Supportive care	75–90	3	5
Leonardi, 2003	71	Supportive care	≥90	4	1
Leonardi, 2003	71	Etanercept 50 mg	<50	1	43
Leonardi, 2003	71	Etanercept 50 mg	50–75	2	40
Leonardi, 2003	71	Etanercept 50 mg	75–90	3	45
Leonardi, 2003	71	Etanercept 50 mg	≥90	4	36
Leonardi, 2003	71	Etanercept 25 mg	<50	1	68
Leonardi, 2003	71	Etanercept 25 mg	50–75	2	39
Leonardi, 2003	71	Etanercept 25 mg	75–90	3	36

continued

TABLE 30 *Summary of the response data extracted from the clinical trials and used in the mixed treatment comparison (cont'd)*

Trial	Ref.	Treatment	Outcome (percentage change In PASI)	Outcome code used in model	*n*
Leonardi, 2003	71	Etanercept 25 mg	≥90	4	19
Gordon, 2003	75	Supportive care	<50	1	161
Gordon, 2003	75	Supportive care	50–75	2	18
Gordon, 2003	75	Supportive care	≥75	5	8
Gordon, 2003	75	Efalizumab	<50	1	153
Gordon, 2003	75	Efalizumab	50–75	2	118
Gordon, 2003	75	Efalizumab	≥75	5	98
ACD2058g 2004	76	Supportive care	<50	1	145
ACD2058g 2004	76	Supportive care	≥50	6	25
ACD2058g 2004	76	Efalizumab	<50	1	63
ACD2058g 2004	76	Efalizumab	≥50	6	99
ACD2600g 2004	77	Supportive care	<50	1	230
ACD2600g 2004	77	Supportive care	≥50	6	33
ACD2600g 2004	77	Efalizumab	<50	1	216
ACD2600g 2004	77	Efalizumab	≥50	6	234
Guenther, 1991	104	Supportive care	<50	1	10
Guenther, 1991	104	Supportive care	≥50	6	1
Guenther, 1991	104	Ciclosporin	<50	1	0
Guenther, 1991	104	Ciclosporin	≥50	6	12
IMP24011 2004	78	Supportive care	<50	1	226
IMP24011 2004	78	Supportive care	≥50	6	38
IMP24011 2004	78	Efalizumab	<50	1	245
IMP24011 2004	78	Efalizumab	≥50	6	284
Altmeyer, 1994	125	Supportive care	<Clear	9	50
Altmeyer, 1994	125	Supportive care	≥Clear	5	1
Altmeyer, 1994	125	Fumaderm	<Clear	9	37
Altmeyer, 1994	125	Fumaderm	≥Clear	5	12
Chaudari, 2001	123	Supportive care	<75	9	9
Chaudari, 2001	123	Supportive care	≥75	5	2
Chaudari, 2001	123	Infliximab	<75	9	2
Chaudari, 2001	123	Infliximab	≥75	5	9
Ellis, 1991	103	Supportive care	<Clear	9	25
Ellis, 1991	103	Supportive care	≥Clear	5	0
Ellis, 1991	103	Ciclosporin	<Clear	9	9
Ellis, 1991	103	Ciclosporin	≥Clear	5	9
Ellis, 1991	103	Ciclosporin	<Clear	9	7
Ellis, 1991	103	Ciclosporin	≥Clear	5	13
Gottlieb, 2004	124	Supportive care	<75	9	48
Gottlieb, 2004	124	Supportive care	≥75	5	3
Gottlieb, 2004	124	Infliximab	<75	9	28
Gottlieb, 2004	124	Infliximab	≥75	5	71
Gottlieb, 2004	124	Infliximab	<75	9	12
Gottlieb, 2004	124	Infliximab	≥75	5	87
Heydendael, 2003	108	Methotrexate	<75	9	17
Heydendael, 2003	108	Methotrexate	≥75	5	26
Heydendael, 2003	108	Ciclosporin	<75	9	12
Heydendael, 2003	108	Ciclosporin	≥75	5	30
Meffert, 1997	105	Supportive care	<75	9	41
Meffert, 1997	105	Supportive care	≥75	5	2
Meffert, 1997	105	Ciclosporin	<75	9	37
Meffert, 1997	105	Ciclosporin	≥75	5	4
Van Joost, 1988	106	Supportive care	<75	9	10
Van Joost, 1988	106	Supportive care	≥75	5	0
Van Joost, 1988	106	Ciclosporin	<75	9	3
Van Joost, 1988	106	Ciclosporin	≥75	5	7

TABLE 31 *Results of the mixed treatment comparison*

	Probability of a response (%)			RR		
	Mean	**2.5% CI**	**97.5% CI**	**Mean**	**2.5% CI**	**97.5% CI**
Response = PASI50						
Supportive care	14	12	16	1.00	1.00	1.00
Etanercept 50 mg	76	54	92	5.61	3.87	7.12
Etanercept 25 mg	63	43	82	4.67	3.11	6.20
Efalizumab	55	38	70	4.01	2.75	5.32
Ciclosporin	80	66	92	5.92	4.62	7.24
Fumaderm	53	18	86	3.88	1.33	6.45
Infliximab	93	81	99	6.88	5.58	8.10
Methotrexate	82	50	98	6.02	3.66	7.66
Response = PASI75						
Supportive care	3	2	4	1.00	1.00	1.00
Etanercept 50 mg	50	25	74	15.69	7.79	24.67
Etanercept 25 mg	35	17	56	10.98	5.34	18.24
Efalizumab	27	14	41	8.35	4.45	13.35
Ciclosporin	55	37	75	17.30	10.74	25.38
Fumaderm	27	5	63	8.49	1.49	20.17
Infliximab	79	55	95	24.89	15.97	33.62
Methotrexate	59	23	89	18.56	7.04	30.00
Response = PASI90						
Supportive care	0	0	1	1.00	1.00	1.00
Etanercept 50 mg	22	7	43	57.00	17.65	120.70
Etanercept 25 mg	12	4	26	31.39	10.10	69.10
Efalizumab	8	3	15	20.20	7.74	40.08
Ciclosporin	25	12	45	66.13	29.66	124.90
Fumaderm	9	1	32	23.39	1.71	83.79
Infliximab	52	24	79	134.98	58.46	230.20
Methotrexate	31	6	66	79.89	15.32	183.50

Key assumptions

The estimation of response rates from the mixed treatment comparisons relies on two assumptions: first, that the treatment effects are constant across end-points on the probit scale, and second, that the treatment effects can be considered exchangeable between the trials. The randomisation process (should) ensure exchangeability between patients within a randomised trial. If the treatments had been randomised between the trials, this would ensure the exchangeability of the effect estimates within the mixed treatment comparison. However, because they are not, we cannot exclude the possibility of systematic differences between the sets of trials comparing, say, different treatments.

Results

Table 31 summarises the results of the mixed treatment comparison in terms of absolute response rates. The placebo arm was regarded as representing 'supportive care', i.e. the patient receives no systemic therapy. In terms of mean response rate, when response is taken as PASI 75, infliximab appears the most effective, followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. As shown by the credible intervals (i.e. Bayesian CIs) around the mean response rates, which overlap considerably, there is uncertainty around these response rates. This is also shown in terms of the RRs of each option (compared with placebo) and their credible intervals. These findings for the PASI 75 level of response are also reflected in the results for the PASI 50 and PASI 90.

Summary

The results of the analysis indicate that efalizumab is less effective than etanercept 25 mg, and both are less effective than infliximab, methotrexate and ciclosporin. Importantly, the 50-mg dose of etanercept appears clearly more effective than the 25-mg dose.

The quantity and quality of data included in this analysis were not equal across all treatments compared. Efalizumab and ciclosporin have been

the most investigated with five RCTs each, compared with Fumaderm and methotrexate for which only one trial each was able to contribute data.

It is important to note that this analysis is limited by the data available: it only draws conclusions regarding short-term use; relative efficacy at 12 weeks for treatment of a chronic condition is not ideal. Therefore it is unknown whether this efficacy might continue (there is some evidence of tachyphylaxis with continued use of infliximab), and whether long-term efficacy might improve with some agents and not others. However, this lack of information reflects the evidence base for all treatments, not just the new biological therapies. What is lacking with all the newer drugs compared with the older treatments is, of course, long-term clinical experience.

The mixed treatment comparison analysis also omits the adverse effects of the various treatments. From long experience with the other treatments, it is well known that they are associated with the risk of long-term serious adverse effects and how these have to be managed [see the section 'Clinical evaluation: adverse events for etanercept and efalizumab' (p. 27)]. The relative efficacy of the new biological therapies needs to be considered in the light of what is known about their safety profiles; so far, they appear well tolerated and safe, but much more experience of use with these agents is required before a clear picture emerges.

Chapter 5

Review of existing economic evaluations

Methods for review of published economic evaluations

Search strategy

Searches were undertaken on the following databases to identify relevant economic literature. Full details of the search strategies are reported in Appendix 1. Searches took place over a period from January to April 2004 (see Appendix 1 for dates of individual searches).

- MEDLINE and In-Process Citations (OVID Online)
- EMBASE (OVID Online)
- NHS Economic Evaluation Database (NHS EED) (CRD administration database)
- Health Economic Evaluation Database (HEED) (CD-ROM)
- EconLit (SilverPlatter on the web)
- ISI Science and Technology Proceedings (Web of Knowledge: http://wos.mimas.ac.uk/)
- Social Science Citation Index (Web of Science: http://wos.mimas.ac.uk/)
- Science Citation Index (Web of Science: http://wos.mimas.ac.uk/).

All databases were searched from their inception to the date of the search.

Terminology

The terms for the search strategies were identified through discussion between an Information Officer and the research team, by scanning the background literature and by browsing the MEDLINE Thesaurus (MeSH). No language or other restrictions were applied.

Management of references

As several databases were searched, some degree of duplication resulted. In order to manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into Endnote bibliographic management software to remove duplicate records.

Handsearching

The bibliographies of all included studies and industry submissions made to NICE were reviewed to identify further relevant studies. Handsearching continued throughout the project.

Inclusion and exclusion of studies

Study selection

Two reviewers selected the studies for the review (AM, YBV). Discrepancies were resolved by consensus and a third reviewer (MS) was consulted when necessary. All titles and abstracts identified by the search were screened and any references that were considered relevant by either reviewer were obtained.

No language restrictions were applied to study selection. Trials reported as full publications or unpublished full reports were included in the review. Trials reported as abstracts only were to be included if adequate information was provided.

Inclusion/exclusion criteria

Studies were eligible for inclusion if they assessed both the costs and benefits of either efalizumab or etanercept and compared findings with an appropriate comparator treatment.

Data extraction strategy

All data were extracted by one reviewer (AM) and independently checked for accuracy by a second reviewer (YBV). Disagreements were resolved through consensus, and by consulting with a third reviewer (MS) if necessary. Data were extracted into a standard template, covering the timeframe used, types of costs included and their sources, measures of benefit and methods used to derive these, modelling undertaken and key findings. Data from studies with multiple publications were extracted and reported as from a single study.

Quality assessment strategy

Data were extracted into a quality assessment template, covering selection of alternatives, treatment of costs and benefits (including any modelling undertaken), use of discounting, allowance for uncertainty and presentation of results. The checklist is an updated version of that developed by Drummond and colleagues.[134]

Data analysis

Only one economic evaluation of an intervention drug was identified. The study was not amenable to analysis because incremental data were not reported.

Systematic review of published economic evaluations: results

The search strategy (see Appendix 1) yielded 117 hits. Of these, just one study met the inclusion criteria,[135] and compared etanercept with seven alternative treatments. No economic evaluation of efalizumab was found. Details of the economic data extracted from the included study and its quality appraisal are given in Appendix 9.

Overview

The paper estimated the cost per treatment success of eight antipsoriatic therapies used to treat patients with severe psoriasis, where severe psoriasis was defined as needing phototherapy or systemic treatment. The setting for the study was managed care in the USA.

Summary of effectiveness data

Effectiveness was defined as the percentage of patients achieving a 75% improvement in their PASI score from baseline. Data on effectiveness were drawn from a review of the literature, based on a MEDLINE search for 'recent' papers reporting effectiveness data for the biological therapies and on two existing reviews. Details of the search strategy used were not reported. Head-to-head trials were not found, so the analysis was based on a comparison of findings from placebo-controlled trials. However, estimates of effectiveness for active treatments were not adjusted by the placebo estimates of effectiveness. Where different measures of effect were reported in the literature for any of the active drugs, expert consensus was used to select baseline values for the analysis. The impact of high and low estimates of effect on cost-effectiveness was explored using deterministic sensitivity analysis.

Summary of resource utilisation and cost data

All relevant direct costs were included in the analysis, including clinician time (proxied by cost/visit), laboratory tests, drug costs and hospitalisation for biopsy. The cost of liver transplantation was explicitly excluded, although the authors acknowledged that this could affect findings.

Several sources were used to derive estimates of treatment doses, treatment durations and the frequency of office visits and laboratory tests. These included published clinical guidelines, manufacturers' guidelines and expert opinion.

National Medicare fee schedules provided unit costs for provider costs, laboratory tests, intravenous infusion and UVB treatment. Local Medicare fee schedules were used to estimate day hospital costs for liver biopsy. The Drug Topics Red Book provided drug acquisition costs. Although the authors state that indirect costs were estimated, details of the methods used and estimates obtained were not reported and it is unclear whether these were included in the analysis.

Summary of cost-effectiveness

Defining cost-effectiveness as the cost per treatment success, the paper reports average (rather than incremental) cost-effectiveness ratios. A probabilistic analysis was not conducted.

The base-case analysis found UVB phototherapy to be the most cost-effective option, followed by methotrexate. Although infliximab was the most cost-effective of the three biological therapies considered, it was still less cost-effective than any non-biological therapy. Alefacept (given intravenously) was the least cost-effective therapy overall, and remained so when sensitivity analysis was used to explore the impact of different effectiveness estimates. However, a probabilistic sensitivity analysis was not undertaken and so the uncertainty around estimates of cost-effectiveness was not taken into account.

Comments

The authors highlight many limitations to their economic evaluation and advise caution in interpreting the findings. Problems include the absence of head-to-head effectiveness data and of long-term data for both effectiveness and safety. The chosen time frame of 12 months is acknowledged to be inadequate for modelling the treatment of a chronic disease, but this reflects the availability of long-term data. The shortcomings of the PASI 75 are discussed and the authors acknowledge that QoL, compliance and patient satisfaction have not been addressed.

The comparators chosen reflect the availability of treatments in the USA. The type and frequency of laboratory tests also reflect US clinical practice. For the purposes of NHS decision-making, the study therefore has several limitations: it does not report health gain in terms of a generic measure [i.e. quality-adjusted life-years (QALYs)]; findings relate to US clinical practice and US costs; and the uncertainty in the findings was not reported.

Quality assessment of the economic evaluation

The authors clearly state their reasons for selecting the alternatives to be used in the

economic analysis, namely that these reflect clinical practice in the USA. Weaknesses in the evidence base for effectiveness estimates are stated and explored using sensitivity analysis. The costing methodology is generally explicit, although the authors' treatment of indirect costs is unclear. There is incomplete reporting of the modelling undertaken and it appears that parameter uncertainty was not explored using probabilistic sensitivity analysis.

Summary

No economic evaluation of efalizumab was identified and only one cost-effectiveness evaluation of etanercept was found.[135] The US study compared etanercept with seven alternative treatments, including three biological therapies (etanercept, infliximab and alefacept). UVB phototherapy appeared to be the most cost-effective option, followed by methotrexate. Although infliximab was the most cost-effective of the three biological therapies considered, it was still less cost-effective than any of the non-biological therapies evaluated. As the evaluation reflected US practice and costs, these findings may not be generalisable to other settings, and the absence of a generic health outcome measure and of probabilistic sensitivity analysis limit the informational value for NHS decision-making.

Review of economic evaluations supplied by manufacturers of etanercept and efalizumab (company submissions)

Two cost-effectiveness models were received from manufacturers, one for etanercept ('the Wyeth model') and one for efalizumab ('the Serono model').

Methods for reviewing company submissions

Data extraction strategy

All data were extracted by one reviewer (YBV) and independently checked for accuracy by a second reviewer (MS). Disagreements were resolved through consensus. The models were assessed using a standard template, which is reproduced in Appendix 10. The template covered key features of the models, such as the time frame and perspective adopted, the comparators assessed and the sources of data used (e.g. effectiveness, resource use, unit cost, mortality, utility data). Information on the modelling approach used, the application of sensitivity analysis and summaries of the key results were also abstracted.

Quality assessment strategy

Data were extracted into a quality assessment template, covering selection of alternatives, treatment of costs and benefits (including any modelling undertaken), use of discounting, allowance for uncertainty and presentation of results. The checklist is an updated version of that developed by Drummond and colleagues.[134] A narrative critique of the models, informed by these data, was then written.

Wyeth's cost-effectiveness model

Details of the Wyeth model are presented in Appendix 10 in terms of a data extraction table and a quality assessment.

Summary

Methods

The analysis assesses the cost-effectiveness of etanercept 25 mg (twice per week), etanercept 50 mg (twice per week) and an option of 'no systemic therapy' (i.e. topical therapy only). These three alternatives are considered over a time horizon of 12 weeks (based on follow-up in the registration trials: studies 20021632, 20021639 and 20021642). Costs are assessed from the perspective of the NHS and outcomes are expressed in terms of QALYs.

Two longer term etanercept strategies are also evaluated over a time horizon of 96 weeks: the use of continuous etanercept 25 or 50 mg; and the use of intermittent etanercept 25 mg. With continuous therapy, patients were assessed at 12-weekly intervals (eight treatment periods) in terms of their PASI response. Patients experiencing an improvement of PASI 50 or better continue treatment, otherwise therapy is stopped and they move to no active systemic therapy. At 24 weeks after treatment initiation, etanercept therapy is maintained only in patients who achieve a PASI 75. In addition, when patients move to no systemic therapy, their psoriasis can improve (i.e. spontaneous remission) following observations in the placebo arms of the registration trials.

The intermittent strategy relates to etanercept 25 mg only, which is compared with no systemic therapy. The model is similar to continuous therapy: it is based on a 96-week time horizon with response assessment at 12-week intervals. However, with intermittent therapy, therapy is stopped for all patients 12 weeks following initiation. Only patients who show a response at 12 weeks (in terms of PASI 50) are considered for re-initiation of therapy if and when efficacy wears off. The strategy follows the treatment strategy

used in study 20021639, modified to allow patients to be withdrawn from therapy if adequate response is achieved after 12 weeks.

The short-term (12-week) analysis is based on patient-level data from the trials. Resource use and costs relate to the cost of etanercept and of adverse events observed in the trials. No utility data were collected directly in the registration trials. Therefore, a 'mapping' exercise was undertaken to estimate the relationship between psoriasis-related QoL (as measured by the DLQI) and utility (using the EQ-5D). This mapping analysis was based on a survey of psoriasis patients treated at a single acute NHS hospital in Cardiff over a 2-year period. Patients were asked to complete the DLQI and the EQ-5D, and PASI data were taken from clinical notes. The regression analysis found a statistically significant association between utility and DLQI and estimated each one-point increase in the DLQI to be associated with a fall of 0.0248 in patient utility. Patients' DLQI scores at each visit were converted into utility scores using the algorithm

$$\text{EQ-5D utility score} = 0.956 - [0.0248 \times (\text{DLQI total score})]$$

QALYs were computed, for each patient, using area-under-the-curve methods based on change in utility (predicted from DLQI) between baseline and 12 and 24 weeks.

For the longer term extrapolation analyses used to evaluate strategies based on continuous and intermittent etanercept, simple Markov models were used. These were populated with cost and QALY data adapted from the 12-week analyses, and response rates at 12 and 24 weeks taken from the registration trials. Between 24 and 96 weeks (when no trial evidence existed), extrapolation was apparently based on the assumption of constant transition rates with assumptions about withdrawal of therapy.

The cost-effectiveness results were presented for patients with the mix of baseline characteristics in the three registration trials. In addition, extensive scenario analyses were presented to indicate how the cost-effectiveness of etanercept varies according to severity (in terms of PASI) and QoL (in terms of DLQI) at baseline. Little analysis was undertaken regarding parameter uncertainty in the analysis, either stochastic analysis based on patient-level data or deterministic or probabilistic sensitivity analysis on the models.

Results

The results of the short-term (12-week) analysis are shown in *Table 32*. This indicates that the cost of the etanercept itself is by far the largest cost component. Over a 12-week time horizon, the additional cost of etanercept is high relative to the QALYs gained when compared with topical therapy only. This is reflected in the magnitude of the incremental cost-effectiveness ratios (ICERs).

The results for the longer term extrapolation model for continuous etanercept therapy are shown in *Table 33*. The table shows the results for

TABLE 32 *Results of the 12-week trial analysis as part of the Wyeth submission*

	Costs (£)						
Treatment	**Drug**	**Initial visit**	**Follow-up visit**	**Adverse events**	**Total**	**QALY gain**	**ICER (£)**
No systemic therapy	0	0	55	18	72	0.011	–
Etanercept 25 mg	2,043	76	218	15	2,352	0.029	124,732
Etanercept 50 mg	4,160	76	218	9	4,474	0.031	1,255,840

TABLE 33 *Results of the long-term (96-week) extrapolation model for two dosages of continuous etanercept therapy as part of the Wyeth submission*

	All patients			Patients with PASI >20 and DLQI >15		
Treatment	**Cost (£)**	**QALY gain**	**ICER (£)**	**Cost (£)**	**QALY gain**	**ICER (£)**
No systemic therapy	578	0.084	–	578	0.139	–
Etanercept 25 mg	8,635	0.236	53,056	8,655	0.451	25,926
Etanercept 50 mg	12,175	0.264	127,464	10,867	0.415	Dominated

TABLE 34 *Results of the long-term (96-week) extrapolation model for intermittent etanercept therapy (25 mg twice per week) as part of the Wyeth submission*

	All patients			Patients with PASI >10 and DLQI >15		
Treatment	**Cost (£)**	**QALY gain**	**ICER (£)**	**Cost (£)**	**QALY gain**	**ICER (£)**
No systemic therapy	563	0.093		563	0.093	–
Etanercept 25mg	5,274	0.220	37,199	5,274	0.288	24,229

all patients and for those with relatively severe psoriasis and QoL at baseline. It can be seen that the ICER of etanercept (compared with no systemic therapy) declines markedly for the relatively severe subgroup. It is also worth noting that the higher dose therapy becomes dominated in this subgroup (the possible reasons for this are not explored in the submission).

The results for the longer term extrapolation for intermittent etanercept therapy (25 mg twice per week) are shown in *Table 34*. Note the slightly different definition of 'relatively severe' patients in this analysis compared with that for continuous therapy. The same picture emerges as for continuous therapy: the ICER falls in the relatively severe subgroup of patients.

Limitations of the Wyeth model

The Wyeth model seems generally well conducted. The availability of patient-level data from the three regulatory trials is an important strength of the analysis. The mapping exercise between the DLQI and utility is far from ideal. However, it is difficult to see an alternative way of expressing health effects in terms of QALYs given the absence of patient-level EQ-5D (or similar) data collection in any of the registration trials. There are some specific methodological weaknesses in the analysis (see detailed quality assessment in Appendix 10). Some of the more important weaknesses are discussed below.

Comparators

The Wyeth analysis compares various dosages of etanercept, using alternative strategies, with an option of no systemic therapies. Given the licence for etanercept, which suggests the use of the treatment when other (non-biological) systemic therapies have been tried, this comparison seems reasonable. It remains the case, however, that, in routine clinical practice, biological therapies may be considered before some systemic therapies, and this decision is not informed by the Wyeth analysis. More importantly, there is no comparison with efalizumab, an alternative biological therapy being considered as part of this assessment. The key decision question is (a) whether either therapy should be used in preference to no systemic therapy and (b) which should be tried first. Another limitation of the analysis is that it does not formally compare continuous and intermittent use of etanercept.

Modelling

Not surprisingly, the ICER of etanercept (compared with no systemic therapy) is relatively high over the period of follow-up in the registration trials (12 or 24 weeks). The rationale for extrapolation modelling is that it facilitates estimates of cost-effectiveness which can reflect more accurately how etanercept would be used in routine clinical practice. In particular, it can reflect the likelihood that clinicians will make assessments of how patients are responding to the drug, and withdraw or maintain therapy as appropriate. A key issue relates to the assumptions used to implement this longer-term modelling. An important assumption is the use of the PASI 50 as definition of response and as a threshold to determine whether patients remain on therapy at 12 weeks (for continuous therapy) or are considered for further therapy if necessary (for intermittent therapy). Clinical advice to the Assessment Team suggests that some clinicians would not consider PASI 50 as an adequate threshold of response. Ideally, the Wyeth analysis would have used scenario analysis to explore the implications of using a range of possible definitions of response – these are, of course, an element of defining alternative treatment strategies. A second key modelling assumption relates to the basis of extrapolation beyond the trial period for which data are available (12 or 24 weeks). It is not spelled out in detail how this extrapolation is implemented, but it seems to result in a large proportion of patients going into spontaneous remission when not on systemic therapy. Greater clarity and use of sensitivity analysis to explore alternative assumptions would have been warranted here.

Uncertainty

An important limitation of the Wyeth model (which has already been referred to above) is the

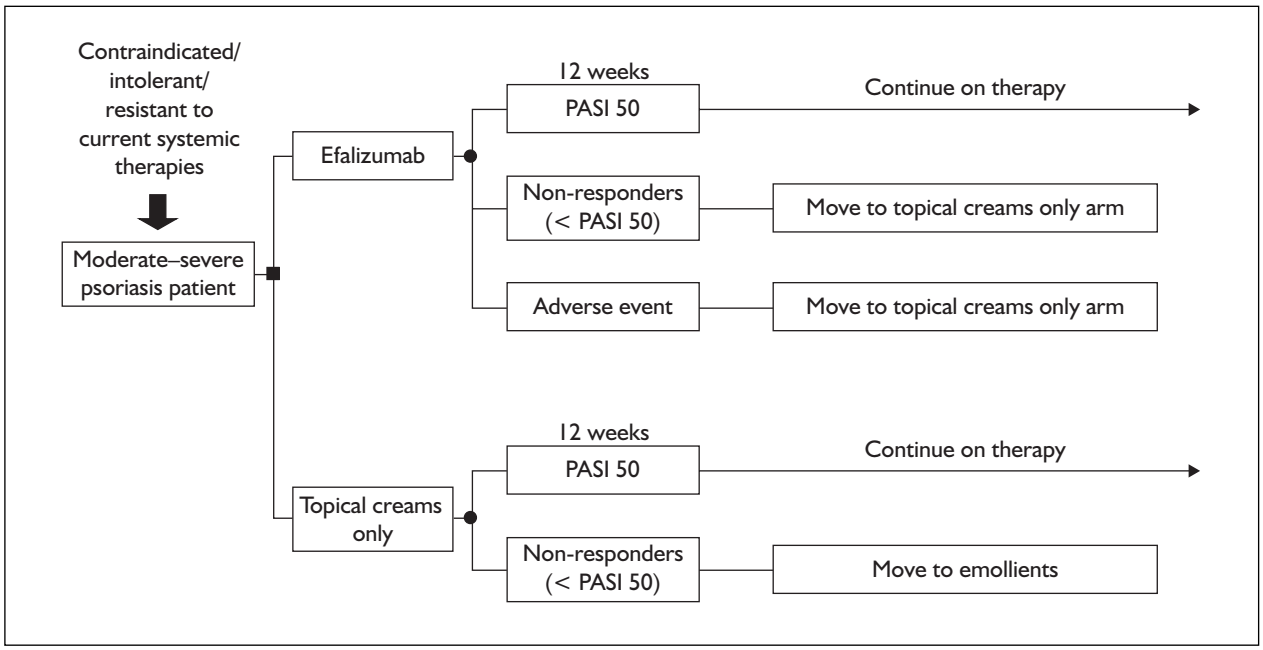

FIGURE 2 *The decision tree used in the Serono model*

limited amount of uncertainty analysis undertaken. This relates to parameter uncertainty (the precision with which the various parameters in the analysis are estimated and its implications for cost-effectiveness), where no deterministic or probabilistic sensitivity analysis appears to have been undertaken. There is also no use of scenario analysis in order to assess the importance of the key assumptions used in the analysis.

Serono's cost-effectiveness model

Details of Serono's model are presented in Appendix 10 in terms of a data extraction table and a quality assessment.

Summary

Methods

The Serono analysis compares two general management strategies for patients with moderate to severe psoriasis: one strategy starting with efalizumab and the other starting with topical therapy based on calcipotriol or betamethasone. The analysis uses PASI 50 as the criterion for treatment response. It is assumed that patients are assessed for response 12 weeks after initiation of therapy (based on the design of the registration trials). Those who are not responding with efalizumab or who experience adverse events with that treatment are assumed to discontinue therapy and move to topicals. Those who do not respond to or suffer adverse events from topical therapy are assumed to move to emollients, which are taken as conferring no response in terms of PASI 50. Responders to treatment at 12 weeks are assumed to maintain that response (and the gain in QoL associated with it) over a 10-year period unless they discontinue therapy for reasons not related to lack of efficacy or adverse events. Mortality is not considered in the model despite a 10-year time horizon. In terms of structure, the model is implemented as a simple decision tree as shown in *Figure 2*. Costs are assessed from the perspective of the NHS, and health effects are expressed in terms of successfully-treated years (defined in terms of PASI 50) and QALYs.

The evidence used to populate the Serono model is taken largely from five registration trials: ACD2058g, ACD2059g, ACD2390g, ACD2600g and IMP24011 [see the section 'Clinical evaluation: efficacy of interventions' (p. 15) for more details of these trials]. These studies are used to derive response rates and rates of adverse events, and also discontinuation from therapy for reasons other than lack of response or adverse events. In addition, a review of trials of calcipotriol and betamethasone is used to generate similar estimates for topical therapy. A key input into the analysis is related to the utilities which are used to translate treatment response (in terms of PASI 50) to QALYs. Serono had no primary sources of utility data for this purpose (for example, from trials). Instead, a literature search identified a study by Zug and colleagues[26] which elicited utilities, based on the time trade-off instrument, from 87 patients with psoriasis. Serono argues that non-response in their model can appropriately be given a utility value that accords with Zug and

TABLE 35 *Total cost results from the Serono model over three time horizons (£)*

Time horizon (years)	Efalizumab	Topical therapy
1	27,032	453
5	18,488	303
10	5,611	123

colleagues' 'severe' state [0.59 on a 0 (equivalent to death) to 1 (equivalent to good health) scale]. They assume that response is valued at 0.945, which is an average of full health (1.0) and the utility estimated for 'mild' psoriasis by Zug and colleagues (0.89). Resource use data are taken from a mixture of the trials and assumptions. Unit costs are taken from routine NHS sources.

Results

Serono presents total costs (with no disaggregation between different components) for efalizumab and topical therapy for three different time horizons. These costs are shown in *Table 35*. Over an apparent 10-year time horizon, expected 'quality-adjusted response-years' with efalizumab are reported as 1.39 compared with 0.36 for a strategy starting with topical therapy. These are not the same as 10-year QALYs and it is not clear how they have been derived, but they do appear to be used to derive the 10-year incremental cost per QALY gained for efalizumab of £25,582.

A range of deterministic sensitivity analyses is reported. Most are one-way analyses, which show the ICER remaining below £30,000 under all scenarios. The exception is a two-way analysis looking at utility values for responders and non-responders to therapy and the impact of the differences in these utilities on the ICER of efalizumab. This sensitivity analysis is reproduced in *Table 36*.

It can be seen that, depending on the assumptions about the two utilities in the model, the cost per QALY gained from efalizumab can vary between £15,237 and £92,001.

Limitations of the Serono model

The Serono analysis has the strength of using efficacy data from five registration trials for efalizumab. It does, however, have some important weaknesses, as follows.

Comparators

As for etanercept, given the licence for efalizumab, which suggests the use of the treatment when other (non-biological) systemic therapies have been tried, it seems reasonable for Serono to compare efalizumab against topical therapy rather than one or more other systemic therapies. As described above in the context of the Wyeth model, however, in routine clinical practice there is likely to be a choice between biological therapy and other systemic therapies, and this decision is not informed by the Serono analysis. There is also no comparison with etanercept. The Serono analysis cannot inform decisions about whether to use efalizumab or etanercept or, more realistically, in what order to use these therapies.

Utilities

Probably the most important weakness of the Serono analysis is the utility data linking response to QALYs. This is taken from a previously published study in which utilities were elicited directly from patients. The difference between the utility of a responder and non-responder is, in the base case, taken to be 0.455. This may be considered to be an implausibly large difference for this disease. To put this into context, with the EQ-5D index this difference would accord with that between full health and a health state characterised by moderate problems in mobility, self-care, ability to undertake usual activities and pain/discomfort. As shown in *Table 36*, variation in

TABLE 36 *Results of the two-way sensitivity analysis undertaken by Serono looking at the effect on the ICER of efalizumab of variation in the utilities associated with treatment response and non-response (values in £)*

Responder utility	Non-responder utility				
	0.40	0.50	0.59	0.60	0.70
1.00	15,237	18,628	22,439	22,836	30,415
0.95	16,801	20,643	25,473	26,764	37,559
0.90	18,253	22,964	29,402	30,397	46,409
0.89	18,604	23,559	30,710	31,896	48,144
0.80	22,850	30,581	43,573	45,824	92,001
0.70	30,397	45,576	83,937	91,486	–

utilities can have a major impact on the ICER of efalizumab.

Modelling
A major assumption with the model is that those patients who are responding at 12 weeks (in terms of PASI 50) will continue to respond for a further 10 years with the exception of a small proportion of patients who discontinue therapy for reasons unrelated to efficacy or adverse events. This is a strong extrapolation assumption that may be considered to be clinically unrealistic. Furthermore, together with the assumption about the difference between responders and non-responders in terms of utility, it will have a major effect on the ICER of efalizumab.

Chapter 6
Economic modelling

Introduction

The review of the company cost-effectiveness models in Chapter 5 indicates a number of weaknesses. Perhaps the most fundamental is that neither considers all relevant treatment options; indeed, neither even compares the cost-effectiveness of the two licensed biological therapies. For this reason, it was considered necessary to develop a *de novo* cost-effectiveness model (hereafter referred to as 'the York Model'). Its aim is to assess the cost-effectiveness of efalizumab and etanercept within their licensed indications for the treatment of psoriasis.

Excerpts from the summaries of product characteristics (SPCs) for efalizumab and etanercept (currently in draft) that are relevant to the economic analysis are given in *Boxes 1* and *2*. These details are pivotal to various decisions that have been made about the specification of the cost-effectiveness model.

Psoriasis is a common, chronic, relapsing, inflammatory skin disorder. The extent and duration of the disease are highly variable from patient to patient. If an individual patient does not respond to or tolerate a particular treatment option, an alternative one may be tried; in other words, treatments are 'trialled' on individual patients. If an effective treatment is not found, then a patient will receive some form of supportive care. If the available treatments were only considered to be mutually exclusive options, this would leave the decision-maker with no information as to which treatment should be selected if the initial treatment failed and may not correctly identify the treatment that should be 'trialled' first. The York Model must, therefore consider *treatment sequences*.

A cost-effectiveness analysis may require the comparison of hundreds of alternative sequences. In addition, the optimum treatment sequence for an individual patient will depend on an individual

BOX 1 *Excerpt from SPC for efalizumab*

Indication:
…Treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant of other systemic therapies including cyclosporin, methotrexate and PUVA…

Dosage:
…Treatment with Raptiva should be initiated by a physician specialised in dermatology. An initial single dose of 0.7 mg/kg body weight is given followed by weekly injections of 1.0 mg/kg body weight (maximum single dose should not exceed a total of 200 mg). The volume to be injected should be calculated as follows: Dose Volume to be injected per 10 kg body weight Single initial dose: 0.7 mg/kg 0.07 ml Subsequent doses: 1 mg/kg 0.1 ml The duration of therapy is 12 weeks. Therapy may be continued only in patients who responded to treatment (PGA good or better). For discontinuation guidance see section 4.4…

Special warnings and special precautions for use:
…During treatment with Raptiva, cases of exacerbation of psoriasis, including pustular, erythrodermic, and guttate subtypes, have been observed (see section 4.8). In such cases, it is recommended to discontinue treatment with Raptiva. Abrupt discontinuation of treatment may cause a recurrence or exacerbation of plaque psoriasis including erythrodermic and pustular psoriasis…

…Management of patients discontinuing Raptiva includes close observation. In case of recurrence or exacerbation of disease, the treating physician should institute the most appropriate psoriasis treatment as necessary. In case re-treatment with Raptiva is indicated the same guidance should be followed as under Posology and method of administration. Re-treatment may be associated with lower or inadequate response to Raptiva than in the earlier treatment periods. Therapy may be continued only in those patients who respond adequately to treatment…

BOX 2 *Excerpt from SPC for etanercept*

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

Dosage:
…The recommended dose of Enbrel is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks…

TABLE 37 *Licensed or guideline doses used in the economic analysis*

Treatment	Dose
Etanercept	25–50 mg administered twice weekly until remission
Efalizumab	Initial single dose of 0.7 mg/kg, weekly injections of 1.0 mg/kg body
Ciclosporin	2.5–5 mg/kg/day
Fumaderm	120–240 mg three times per day
Methotrexate	10–25 mg/week
Infliximab	Loading dose of three infusions during first 6 weeks (3–5 mg/kg) then every 8 weeks or as needed

patient's characteristics, including medical history, renal and hepatic function, treatment history and associated response and adverse events, impact of current disease and willingness to accept the risk of specific side-effects. Therefore, it may not be useful to provide estimates of the expected cost-effectiveness of specific individual treatment sequences as not all of these may be relevant to an individual patient, the optimum treatment sequence identified may not be suitable and the decision-maker may be left without information as to the cost-effectiveness of alternative treatment sequences for the patient. To consider all possible treatments for all possible patient subpopulations may not be feasible. Therefore, this analysis seeks to identify an optimum overall **ordering** of treatments, from which the treatments suitable for an individual patient can be selected.

Methods

Comparators

Based on the indications described in the SPCs, a primary analysis was conducted comparing efalizumab, etanercept and supportive care. A secondary analysis was conducted to provide context for the use of the efalizumab and etanercept. This analysis included the following additional systemic therapies: ciclosporin, Fumaderm, methotrexate and infliximab. Although Fumaderm and infliximab are not licensed in the UK for psoriasis, they are used for selected patients in clinical practice. Therefore, the secondary analysis seeks to offer a pragmatic basis for NHS decision-making.

Dose ranges

The doses considered in the analysis for the comparators are shown in *Table 37*. These are based on licensed or anticipated licensed doses except for Fumaderm and infliximab where current guidelines are used (Chalmers R: Protocol for use of Fumaderm in psoriasis, personal communication, 2003, see Appendix 11). Only trial data corresponding to these dose ranges were included in the cost-effectiveness analysis. An exception was made for Fumaderm, where the only available trial evidence lay outside the guideline range.

Treatments are often licensed over a range of doses. In clinical practice, a clinician may select an initial dose based on an individual patient's characteristics such as renal and hepatic function, severity of disease and response to previous treatments. For chronic diseases, the clinician may modify the subsequent dose of a drug based on patient response and the occurrence of adverse events. This is reflected in the trials for ciclosporin, Fumaderm and methotrexate, which frequently allowed dose titration (see *Tables 24* and *28*). Owing to the wide range of doses and dose schedules employed in the trials, and considering clinical practice where individual dose selection and titration are to be expected, the trial results for different doses are grouped together in the analysis. It was assumed that the patterns of doses seen in the trials would reflect those in clinical practice. An exception was made for etanercept, where the results of the 25- and 50-mg trials were considered separately as this was one of the comparators in the primary analysis.

Continuous or intermittent use

Some treatments such as methotrexate are given continuously following the initial remission of disease and some treatments such as ciclosporin may be stopped following remission and the treatment used intermittently. In this analysis, it is assumed that all treatments are used continuously except for infliximab, which is given intravenously at discrete intervals, and etanercept, where the SPC specifies that treatment should continue until remission is achieved. The SPC for efalizumab specifically mentions that abrupt discontinuation of treatment may cause a recurrence or exacerbation of plaque psoriasis and retreatment may be associated with lower or inadequate response than in the earlier treatment periods. Efalizumab is, therefore, probably unsuitable for intermittent use.

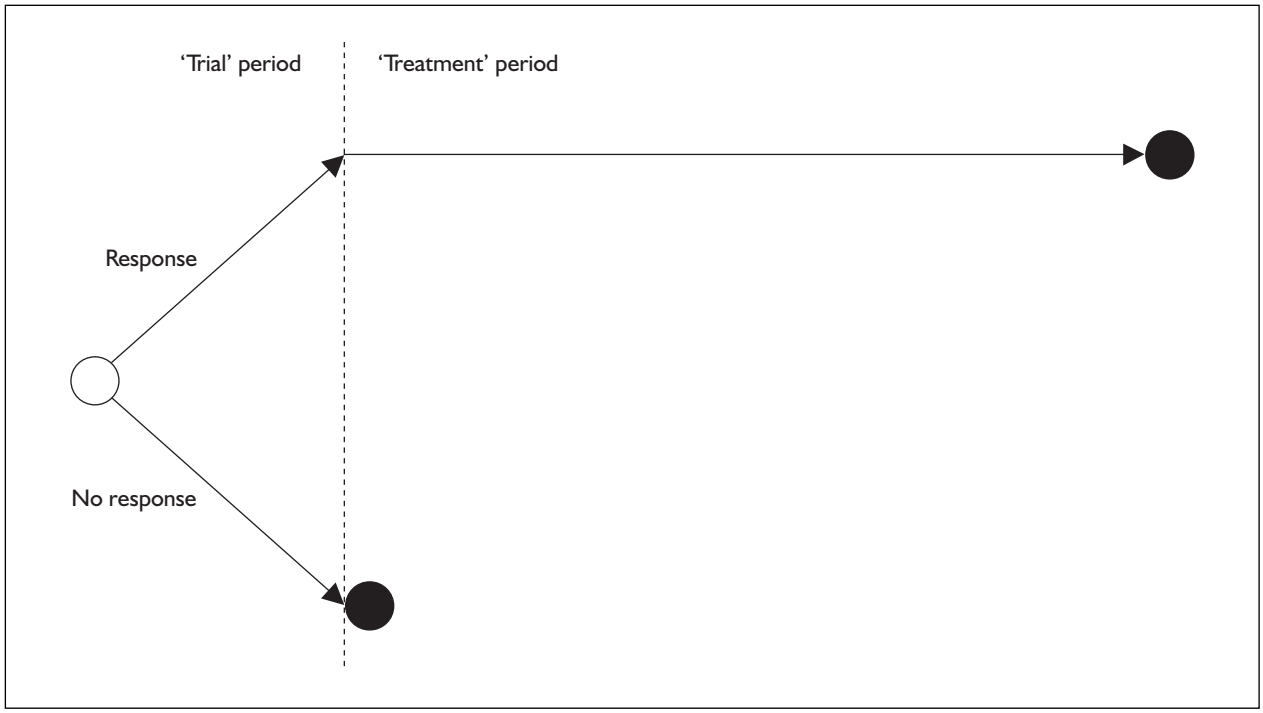

FIGURE 3 *Illustration of the structure of the cost-effectiveness analysis*

The model

The cost-effectiveness analysis was conducted by comparing estimates of expected costs and health effects per unit time for each treatment, incorporating both patients who 'respond' and continue treatment after a 'trial' period and those who do not 'respond' and stop treatment. This is illustrated in *Figure 3*.

To compute the expected costs and effects per unit time of interventions requires estimates of the proportion of patients responding and the costs, effects and total duration of treatment for responding and non-responding patients. The model can be specified based on the following equations:

$$u^{\text{placebo}} = u_{00} \times (1 - p^{\text{PASI 50}}_{\text{placebo}}) + u_{50} \times (p^{\text{PASI 50}}_{\text{placebo}} - p^{\text{PASI 75}}_{\text{placebo}}) + u_{75} \times (p^{\text{PASI 75}}_{\text{placebo}} - p^{\text{PASI 90}}_{\text{placebo}}) + u_{90} \times (p^{\text{PASI 90}}_{\text{placebo}})$$

$$u_t^{\text{responders}} = [u_{75} \times (p_t^{\text{PASI 75}} - p_t^{\text{PASI 90}}) + u_{90} \times (p_t^{\text{PASI 90}})]/p_t^{\text{PASI 75}}$$

$$u_t^{\text{all}} = u_{00} \times (1 - p_t^{\text{PASI 50}}) + u_{50} \times (p_t^{\text{PASI 50}} - p_t^{\text{PASI 75}}) + u_{75} \times (p_t^{\text{PASI 75}} - p_t^{\text{PASI 90}}) + u_{90} \times (p_t^{\text{PASI 90}})$$

$$Qalys_t = \frac{d_t^{\text{trial}} \times (u_{tx}^{\text{all}} - u^{\text{placebo}}) + p_t^{\text{PASI 75}} \times d_t^{\text{treatment, effect}} \times (u_t^{\text{responders}} - u^{\text{placebo}})}{d_t^{\text{trial}} + p_t^{\text{PASI 75}} \times d_t^{\text{treatment, effect}}}$$

$$c^{\text{placebo}} = c^{\text{hospital}} \times (1 - p^{\text{PASI 75}}_{\text{placebo}})$$

$$Cost_t = \frac{c_t^{\text{trial}} + p_t^{\text{PASI 75}} \times d_t^{\text{treatment, cost}} \times c_t^{\text{treatment}} + (1 - p_t^{\text{PASI 75}}) \times c^{\text{hospital}} \times d_t^{\text{trial}} - (d_t^{\text{trial}} + p_t^{\text{PASI 75}} \times t_t^{\text{treatment}}) \times c}{d_t^{\text{trial}} + p_t^{\text{PASI 75}} \times d_t^{\text{treatment, cost}}}$$

where the model outputs are:

$Cost_t$ = mean incremental cost per year for the tth treatment compared with 'supportive care'
$Qalys_t$ = mean incremental QALYs per year for the tth treatment compared with 'supportive care'.

The various parameters going into these equations are defined in *Table 38*.

Decision rule

The health effects of the alternative treatments are expressed as QALYs. This is a generic measure of health effect and allows the decision to allocate resources to the treatments for psoriasis to be based on the opportunity cost of the treatments they displace, which could be based in other specialties.

TABLE 38 *Definition of parameters used in the York Model, summary of sources and indication of how uncertainty is assessed*

Parameter	Description	Source	Uncertainty
c^{hospital}	Yearly cost of hospitalisation for non-responding patient	Assumption based on survey data	Scenario analysis
c_t^{trial}	Cost of treatment with the *t*th treatment for the 'trial' period	BNF 48[65]	Fixed
$c_t^{\text{treatment}}$	Yearly cost of treatment with *tx*	BNF 48[65]	Gamma distribution
c_t^{trial}	Duration (in years) of the 'trial' period for the *t*th treatment	Assumption based on clinical trial designs and BNF recommendations	Fixed
$d_t^{\text{treatment, cost}}$	Mean duration (in years) of the 'treatment' period for the calculation of costs for the *t*th treatment	Assumption based on limited observational data	Scenario analysis of patient attrition rate and cost discount rate
$d_t^{\text{treatment, effect}}$	Mean duration (in years) of the 'treatment' period for the calculation of effects for the *t*th treatment	Assumption based on limited observational data	Scenario analysis of patient attrition rate and effect discount rate
u_{00}	Utility for a patient not achieving a PASI 50 response	Pooled clinical trial and HODaR data	Normal distribution
u_{50}	Utility for a patient achieving a PASI 50 response but not a PASI 75 response	Pooled clinical trial and HODaR data	Normal distribution
u_{75}	Utility for a patient achieving a PASI 75 response but not a PASI 90 response	Pooled clinical trial and HODaR data	Normal distribution
u_{90}	Utility for a patient achieving a PASI 90 response	Pooled clinical trial and HODaR data	Normal distribution
$p_t^{\text{PASI 50}}$	Probability of a PASI 50 response for treatment *tx*	Bayesian hierarchical model of clinical trial data [see the section 'Clinical evaluation: adverse events for etanercept and efalizumab' (p. 27)]	Simulated posterior distribution from MCMC analysis of trial data
$p_t^{\text{PASI 75}}$	Probability of a PASI 75 response for treatment *tx*	Bayesian hierarchical model of clinical trial data [see the section 'Clinical evaluation: adverse events for etanercept and efalizumab' (p. 27)]	Simulated posterior distribution from MCMC analysis
$p_t^{\text{PASI 90}}$	Probability of a PASI 90 response for treatment *tx*	Bayesian hierarchical model of clinical trial data [see the section 'Clinical evaluation: adverse events for etanercept and efalizumab' (p. 27)]	Simulated posterior distribution from MCMC analysis

HODaR, Health Outcomes Data Repository; MCMC, Markov Chain Monte Carlo.

The most cost-effective order of treatments will be to use them in order of decreasing expected net benefit (NB_{tx}) per unit time,

$$E[NB_{tx}] = E[Qalys_{tx}] \times \lambda - E[Cost_{tx}]$$

where λ is the maximum threshold for cost-effectiveness (per additional QALY). As there is no single value for this threshold, the analysis will vary it across a wide range.

If any of the active treatments has an expected net benefit per unit time less than that for supportive care, its use is not cost-effective.

If we maximise the expected net benefit per unit time for a treatment sequence, we will maximise the total expected net benefit for a patient. As there will be attrition due to successful treatment or termination of treatment, the proportion of patients receiving a treatment will decline as we proceed along the treatment sequence; therefore, we will maximise the expected net benefit for the treatment sequence by using the treatments in order of their individual expected net benefit per unit time. This approach requires that patients only receive benefit while they receive treatment, that is, the treatments do not alter for the progression of the disease. A more detailed

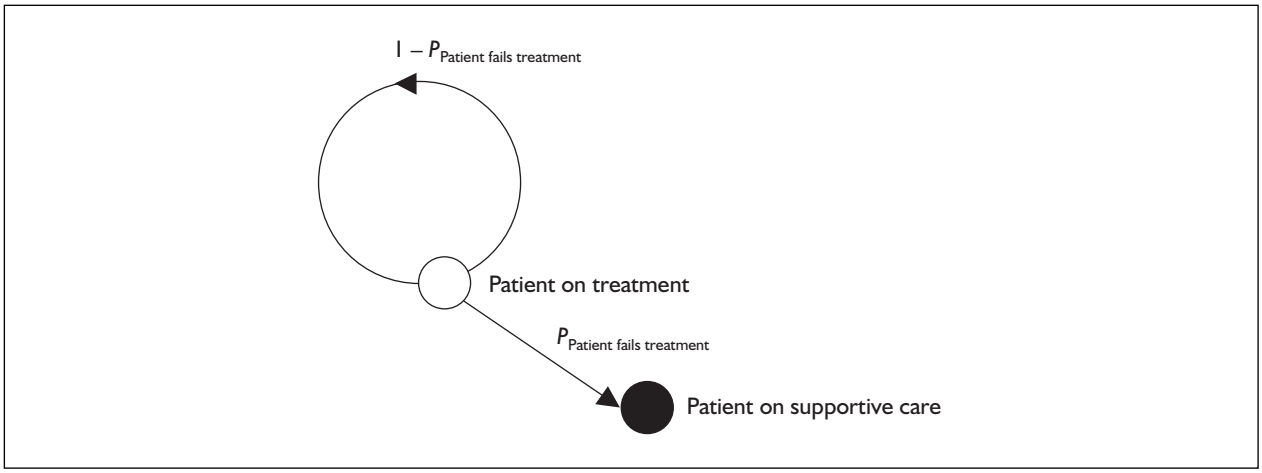

FIGURE 4 *Markov model of 'treatment' period*

description of this analytic approach is included in Appendix 12.

Input parameter estimates

The model assumes no difference between the treatments in terms of mortality. The model requires estimates of the following parameters for each of the treatments being compared:

- response rates
- duration of the 'trial' and 'treatment' periods
- costs
- the utility improvement associated with the various PASI response categories.

Response rates

The predicted response rates used in the model are taken directly from the mixed treatment comparison reported in the section 'Clinical evaluation: mixed treatment comparison analysis' (p. 39). If the trial only reported 'clear' or 'almost clear' as the endpoint, this was taken to be equivalent to a PASI 75 response.

The increased decision uncertainty arising from uncertainty in the predicted response rates was estimated by directly exporting the simulated posterior distribution from the Markov Chain Monte Carlo analysis in WinBUGS to the cost-effectiveness model preserving any correlations. This has been termed a **comprehensive** decision model.[137]

'Trial' period and 'treatment' duration for responders

The 'trial' period was estimated based on the period over which response was assessed in the efficacy trials for each treatment option and 'expert' opinion. The mean 'treatment' duration for responding patients was estimated based on an assumed annual drop-out rate for responding patients receiving treatment and a maximum assumed treatment period based on published guidelines if appropriate.[138,139] The mean treatment response period was then estimated from a 10-year Markov model with an annual cycle (*Figure 4*).

The estimated 'trial' and 'treatment' periods are shown in *Table 39*. There is very little experimental or observational evidence to inform these parameters and they are consequently subject to a great deal of uncertainty. These parameters were entered into the model as fixed values and sensitivity analysis of the annual withdrawal rate conducted.

The mean treatment period for intermittent use of etanercept was estimated to be 85 days based on the results of the 20021639 re-challenge study.[140]

Cost and effect discount rates were incorporated into the model by estimating separate 'treatment' durations for the estimation of cost and effects. Annual discount rates of 6% on costs and 1.5% on outcomes were applied.[141]

Resource use and costs

Resource use

Direct costs incurred by the NHS were assessed. The analysis included the cost of drugs and of their administration and monitoring and the cost of outpatient visits and of inpatient stays.

The cost of tests undertaken solely to screen patients for eligibility for treatment was excluded from the analysis, such as chest X-rays and HEAF tests for tuberculosis (etanercept and infliximab)

TABLE 39 *Estimated duration of 'trial' and 'treatment' periods*

Treatment	'Trial' period (weeks)	Maximum 'treatment' period (years)	Annual drop-out rate (%)	Mean 'treatment' period for responders (weeks)
Etanercept 25 mg	12	10	20	186
Etanercept 50 mg	12	10	20	186
Efalizumab	12	10	20	186
Ciclosporin	12	2	20	75
Fumaderm	16	10	20	186
Methotrexate	16	10	20	186
Infliximab	10	10	20	186

or biopsies of lesions atypical of psoriasis (ciclosporin). The reason for excluding these costs is that only a proportion of patients undergo these tests, and that this proportion is unknown and, for tuberculosis tests, likely to vary geographically.[142] We also excluded the cost of folic acid (used in conjunction with methotrexate), because its annual cost was so low (under £1). We did not estimate the costs of treating adverse events, owing to a lack of data on treatment pathways and resource use. Details of the adverse events associated with each drug can be found in the section 'Clinical evaluation: adverse events for etanercept and efalizumab' (p. 27) and Appendix 6.

Estimates of resource use (quantities) were derived from several sources. Drug dosage and titration rates were based on information in the BNF No. 48.[65] For the biological drugs, we referenced the manufacturers' SPCs[63,64,129] and the British Society of Rheumatology's guidelines.[136] Two drugs are not licensed for use in the UK. For Fumaderm, a Manchester protocol provided titration rates and doses (Chalmers R: Protocol for use of Fumaderm in psoriasis, personal communication, 2003, see Appendix 11). For infliximab, we assumed that retreatment intervals would match those of the drug's use for psoriatic arthritis, namely that infusions would take place at 0, 2 and 6 weeks and then at 8-week intervals thereafter (i.e. eight infusions in the first year, 6.5 infusions per year for maintenance treatment). There is some limited evidence to suggest that infliximab may require less frequent retreatment intervals for psoriasis patients,[124] and trials are under way to validate this finding.

It was assumed that there were no significant additional treatment costs associated with 'supportive care' compared to the other systemic treatment being considered. It was assumed that patients receiving supportive care would have two outpatient visits annually. The main additional cost associated with 'supportive care' in the model resulted from the increased rate of hospitalisation due to the lower rate of PASI 75 response associated with supportive care. No published data were available to inform an estimate of the rate of hospitalisation, so estimates were based on a range of scenarios, based on expert opinion, about the rate of hospitalisation and included the cost of outpatient visits and inpatient care.

The same sources provided some estimates of the types and frequency of laboratory tests undertaken for each drug (Chalmers R: Protocol for use of Fumaderm in psoriasis, personal communication, 2003, see Appendix 11).[63–65,129,136] Clinician and nurse time for clinical examinations (such as blood pressure) were not estimated because this was assumed to be included in the care covered by a standard outpatient visit. However, the time taken in administering drugs was estimated for etanercept, efalizumab and infliximab. We assumed that to educate patients to self-inject efalizumab or etanercept would involve three 1-hour sessions of nurse time during the 'trial period'. We based our estimates for infliximab infusions on the BSR guidelines,[136] which recommend that, for the first four 2-hour infusions, the monitoring period is 2 hours, reduced to 1 hour thereafter.

Length of stay for an inpatient admission was based on Department of Health Hospital Episode Statistics (2002–3) for psoriasis, which gave a mean of 19.6 days.[53] This statistic was supported by evidence from recent audits of two local hospitals, which had average lengths of stay of 22.3 and 22.7 days (Swindells K, Hope Hospital, Salford, and Woods A, St John's Institute of Dermatology, London: personal communications, 2004).

The frequency of liver biopsy with methotrexate, with or without concurrent use of the PIIINP (serum procollagen III aminopeptide) test, was based on estimates from a recent economic evaluation.[143] The retreatment intervals for intermittent etanercept were based on a clinical

trial report.[140] Expert opinion was used to generate the remaining estimates, including the frequency of outpatient visits, drug tablet sizes commonly used, monitoring requirements and titration rates not available from the published literature.

Unit costs

Prices (unit costs) of drugs were taken, where available, from the BNF No. 48.[65] The price of Fumaderm was obtained through a personal communication with the Director of Pharmacy of the Greater Manchester Dermatology Service. The cost of efalizumab was based on information from the manufacturer (*Table 40*).

Prices of monitoring tests were obtained from the Biochemistry Department at York NHS Trust. The cost of the PIIINP test and the cost of a liver biopsy for patients were based on a recent economic evaluation.[143] The cost of nurse time educating patients to self-inject was based on the Personal Social Services Research Unit (PSSRU) cost per patient-related hour (Ref. 144, Schemata 13.3). The cost of an infusion visit was based on the latest available NHS Reference Cost category 'Other attendance with other investigation or procedure (J09op)', which is the same cost as for intensive topical hospital treatment.[145] Outpatient visits were based on NHS Reference Cost category 'Other attendance without other investigation or procedure (J10op)'. The cost of an inpatient day was based on two NHS Reference Cost categories. An average of the categories 'Elective inpatient HRG data, major dermatological conditions J39 (>69 or w cc) (>69 or w cc: aged over 69 or with co-morbidities or complications)' and 'Elective inpatient HRG data, major dermatological conditions J40 (<70 or w/o cc)' was estimated, weighted by number of Finished Consultant Episodes.

Where necessary, costs were updated to the year 2003–4, the latest available year, using the PSSRU inflation index.[144] Remaining prices relate to the year 2004–5.

Costs and quantities were estimated for 1 year's maintenance treatment of each drug; discounting of costs was therefore unnecessary. For ciclosporin, only continuous treatment was costed: although intermittent treatment is recommended as a first-line option,[139] no trial providing adequate data was identified. Moreover, patients with recalcitrant disease, which reflects the population indicated for etanercept or efalizumab, are more likely to be candidates for long-term continuous ciclosporin therapy.[139]

For etanercept, both continuous treatment (with 25 mg) and intermittent treatment (with 25 or 50 mg) were included in the economic evaluation. The SPC for etanercept treatment states that the treatment should be continued until the patient responds. Treatment will then be repeated when the patient relapses. This was incorporated in the model by adjusting the cost of treatment to account for this pattern of usage. [**Confidential information removed.**] The time to loss of response, and hence the cost of treatment with etanercept, will vary between patients. Continuous treatment with etanercept was also included as an option in the model. All other treatments were assumed to be administered continuously.

The costs of treatment with methotrexate with or without the serum procollagen III aminopeptide (PIIINP) test were also estimated separately. Methotrexate without the PIIINP test was included in the model as it was considered to represent standard methotrexate therapy. The unit costs used in the model are given in *Tables 40–42* and the resource use quantities are shown in *Tables 43*

TABLE 40 *Unit costs: drug costs, 2004–5*

Drug	Price per mg, 2004–5 (£)	Price per tablet/vial, 2004–5 (£)	Source
Ciclosporin, 25 mg	0.03	0.68	BNF 48
Ciclosporin, 100 mg	0.03	2.54	BNF 48
Efalizumab, 125 mg	1.35	169.20	Manufacturer[a]
Etanercept, 25 mg	3.58	89.38	BNF 48
Fumaderm, initial (30 mg)	0.08	2.39	GMDS[b]
Fumaderm (120 mg)	0.02	2.03	GMDS[b]
Infliximab	4.51	451.20	BNF 48
Methotrexate, 2.5 mg	0.05	0.12	BNF 48

[a] Communication from Serono, 21 December 2004.
[b] Greater Manchester Dermatology Service.

TABLE 41 *Unit costs: laboratory costs, 2004–5*

Test	Cost/test, 2004–5 (£)[a]	Source
Blood glucose	0.43	York NHS Trust
Blood lipid profile	2.93	York NHS Trust
Full blood count with differential	2.42	York NHS Trust
Liver biopsy with overnight stay	479.67[b]	Chalmers *et al*., 2004[143] (mean)
Liver function test	0.61	York NHS Trust
PIIINP (serum procollagen III aminopeptide)	21.64	Chalmers *et al*., 2004;[143] York NHS Trust
Serum creatinine	0.31	York NHS Trust
Total protein	0.43	York NHS Trust
U&E	1.12	York NHS Trust

U&E, urea and electrolytes (includes test for serum creatinine).
[a] Excludes cost of tests undertaken to determine eligibility, i.e. TB HEAF test, chest X-ray (etanercept/infliximab).
[b] Price year 2003–4.

TABLE 42 *Unit costs: hospital visit costs*

	Category	Cost, 2003–4 (£)	Source
Cost/inpatient day	Elective inpatient Healthcare Resource Group (HRG) data, major dermatological conditions.	248.31[a]	NHS Reference Costs 2003 and National Tariff 2004
	Weighted average of J39 (>69 or w cc) and J40 (<70 or w/o cc)		
Cost/outpatient visit	Major dermatological conditions; other attendance without other investigation or procedure (J10op)	56.60[a]	NHS Reference Costs 2003 and National Tariff 2004
Cost/outpatient visit	Major dermatological conditions; other attendance with other investigation or procedure (J09op)	78.21[a]	NHS Reference Costs 2003 and National Tariff 2004
Cost/patient educational hour	Cost per patient-related hour, staff nurse	34.00	PSSRU Unit Costs of Health and Social Care 2004

[a] Updated to 2003–4 prices using PSSRU inflation index.[144]

TABLE 43 *Resource use: number of annual laboratory tests*

	CsA	Efalizumab	Etanercept continuous	Etanercept intermittent	Fumaderm	Infliximab	MTX, with PIIINP	MTX, no PIIINP
FBC[a]		4–8	2–4	2–4	Up to 15	4	4 to 5	4 to 5
Liver biopsy							0.04/patient/year	0.28/patient/year
LFT[a]					Up to 15	4	4–5	4–5
PIIINP							4	0
Serum creatinine	6–14							
Total protein		4–8	2–4	2–4				
U&E[a]	6–14	4–8	2–4	2–4	Up to 15	4	4–5	4–5

CsA, ciclosporin; FBC, Full blood count with differential; LFT, liver function test; MTX, methotrexate; PIIINP, serum procollagen III aminopeptide (test); U&E, urea and electrolytes. Sources: BNF 48;[65] RCN and BSR Guideline;[136,142] SPCs;[63,64,129] Fumaderm protocol (Chalmers R: Protocol for use of Fumaderm in psoriasis, personal communication, 2003, see Appendix 11); expert opinion.
[a] U&E, FBC and LFT: expert opinion suggests 8–9 tests in the first year of treatment, reducing to 4–5 annually thereafter.

TABLE 44 *Resource use: number of outpatient visits*

	No. of visits, week 0 to week 12	Number of visits annually (maintenance)	Source
CsA, continuous	5–6	6–7	Expert opinion
Efalizumab	3	4	Manufacturer's submission
Etanercept, intermittent	3	4	Assumption
Fumaderm	3–4	5–6	Expert opinion
Infliximab[a]	4–5	5–6	Expert opinion
Methotrexate	4–5	4–5	Expert opinion
Supportive care	–	2	Assumption

[a] To avoid double counting, the analysis adjusted the number of outpatient visits for infliximab by the number of infusion visits.

TABLE 45 *Total per-patient costs: 'trial period',[a] 2004–5*

Drug	Type of treatment	Drug cost (£)	Administration cost (£)	Monitoring cost (£)	Outpatient visits (£)	Total cost (£)
'Supportive care'	–	–	–	–	–	–
Ciclosporin	Continuous	643.89	0	8.96	311.29	964.14
Efalizumab	Continuous	2199.60	102.00	15.88	169.79	2487.27
Etanercept, 25 mg	Continuous	2145.12	102.00	8.30	169.79	2425.21
Etanercept, 25 mg	Intermittent	2145.12	102.00	8.30	169.79	2425.21
Etanercept, 50 mg	Intermittent	4290.24	102.00	8.30	169.79	4570.33
Fumaderm, 120–240 mg TD	Continuous	803.67	0	49.80	198.09	1051.56
Infliximab, 3 mg/kg	Continuous	4060.80	234.62	8.30	56.60	4360.32
Infliximab, 5 mg/kg	Continuous	5414.40	234.62	8.30	56.60	5713.92
Methotrexate, 10–25 mg without PIIINP	Continuous	9.87	0	20.75	254.69	285.31
Methotrexate, 10–25 mg PIIINP and reduced liver biopsy rate	Continuous	9.87	0	63.34	254.69	327.90

[a] Length of trial period varies by drug and is based on figures in *Table 39*.

TABLE 46 *Total per-patient annual 'treatment period' costs, 2004–5*

Drug	Type of treatment	Drug cost (£)	Administration cost (£)	Monitoring cost (£)	Outpatient visits (£)	Total cost (£)
'Supportive care'	–	–	–	–	113.20	113.20
Ciclosporin	Continuous	3,717.27	0	6.72	367.89	4,091.88
Efalizumab		8,828.61	0	15.88	226.39	9,070.89
Etanercept, 25 mg	Continuous	9,327.44		8.30	226.39	9,562.13
Etanercept, 25 mg	Intermittent	6,933.67		8.30	226.39	7,168.37
Etanercept, 50 mg	Intermittent	13,867.35		8.30	226.39	14,102.04
Fumaderm, 120 mg TD	Continuous	2,224.37	0	49.80	311.29	2,585.46
Fumaderm, 240 mg TD	Continuous	4,448.75	0	49.80	311.29	4,696.64
Infliximab, 3 mg/kg	Continuous	8,798.40	508.35	8.30	56.60	9,371.65
Infliximab, 5 mg/kg	Continuous	11,731.20	508.35	8.30	56.60	12,304.45
Methotrexate, 10 mg without PIIINP	Continuous	24.37		153.89	254.69	432.96
Methotrexate, 25 mg without PIIINP	Continuous	60.94		153.89	254.69	469.53

TABLE 47 *Mean change in DLQI between baseline and week 12 by PASI response and baseline DLQI*

		PASI response				
		<50	**≥50 and <75**	**≥75 and <90**	**≥90**	**All**
PASI DLQI data						
1st quartile	Mean Δ DLQI		[**Confidential information removed**]			
	SD		[**Confidential information removed**]			
	N		[**Confidential information removed**]			
2nd quartile	Mean Δ DLQI		[**Confidential information removed**]			
	SD		[**Confidential information removed**]			
	N		[**Confidential information removed**]			
Baseline DLQI						
3rd quartile	Mean Δ DLQI		[**Confidential information removed**]			
	SD		[**Confidential information removed**]			
	N		[**Confidential information removed**]			
4th quartile	Mean Δ DLQI		[**Confidential information removed**]			
	SD		[**Confidential information removed**]			
	N		[**Confidential information removed**]			
All	Mean Δ DLQI		[**Confidential information removed**]			
	SD		[**Confidential information removed**]			
	N		[**Confidential information removed**]			

and *44*. *Tables 45* and *46* show the total 'trial' period and total annual per-patient costs for each drug, respectively. Parameter uncertainty in drug costs is reflected in terms of a gamma distribution.

Except for the annual cost of treatment, these parameters were entered into the model as fixed values. For the annual cost of treatment, the mean costs were estimated as the average of the minimum and maximum cost, and the standard error was estimated as the difference between the minimum and maximum divided by 1.96. Uncertainty in the mean cost was then represented as a gamma distribution parameterised using the estimated mean cost and standard error method of moments estimates.

Utility

The utilities associated with treatment were based on the proportion of patients in the different PASI categories and the change in utility from baseline associated with the different PASI response categories. These were estimated from an analysis of data from the three etanercept regulatory trials and the HODaR Database (http://www.hodar.co.uk/). The estimation process consisted of two stages.

In the first stage, the mean change in the DLQI score between baseline and week 12 was estimated for patients from etanercept trials with different levels of PASI response and different baseline DLQI scores. This analysis was facilitated by access to patient-level data by Wyeth, and the placebo and treatment groups were pooled. The results of this stage are shown in *Table 47*. Higher scores on the DLQI indicate worse QoL.

Data within the HODaR database included patients who had completed both the DLQI and EQ-5D. These data were used to 'map' the change in DLQI associated with PASI responses to changes in EQ-5D utility. A scatterplot of DLQI and EQ-5D data are shown in *Figure 5*.

An ordinary least-squares (OLS) linear regression analysis of the DLQI–EQ-5D data from HODaR produced the following results (values in parentheses are standard errors, $n = 86$):

EQ-5D utility = [**Confidential information removed**]

Based on these data, the mean gain in utility was estimated for the various PASI response categories. These results are shown in *Table 48* and are reported for all patients and for those with the worst baseline QoL (fourth quartile DLQI). The probabilistic sensitivity analysis has used the standard error from the OLS regression of EQ-5D

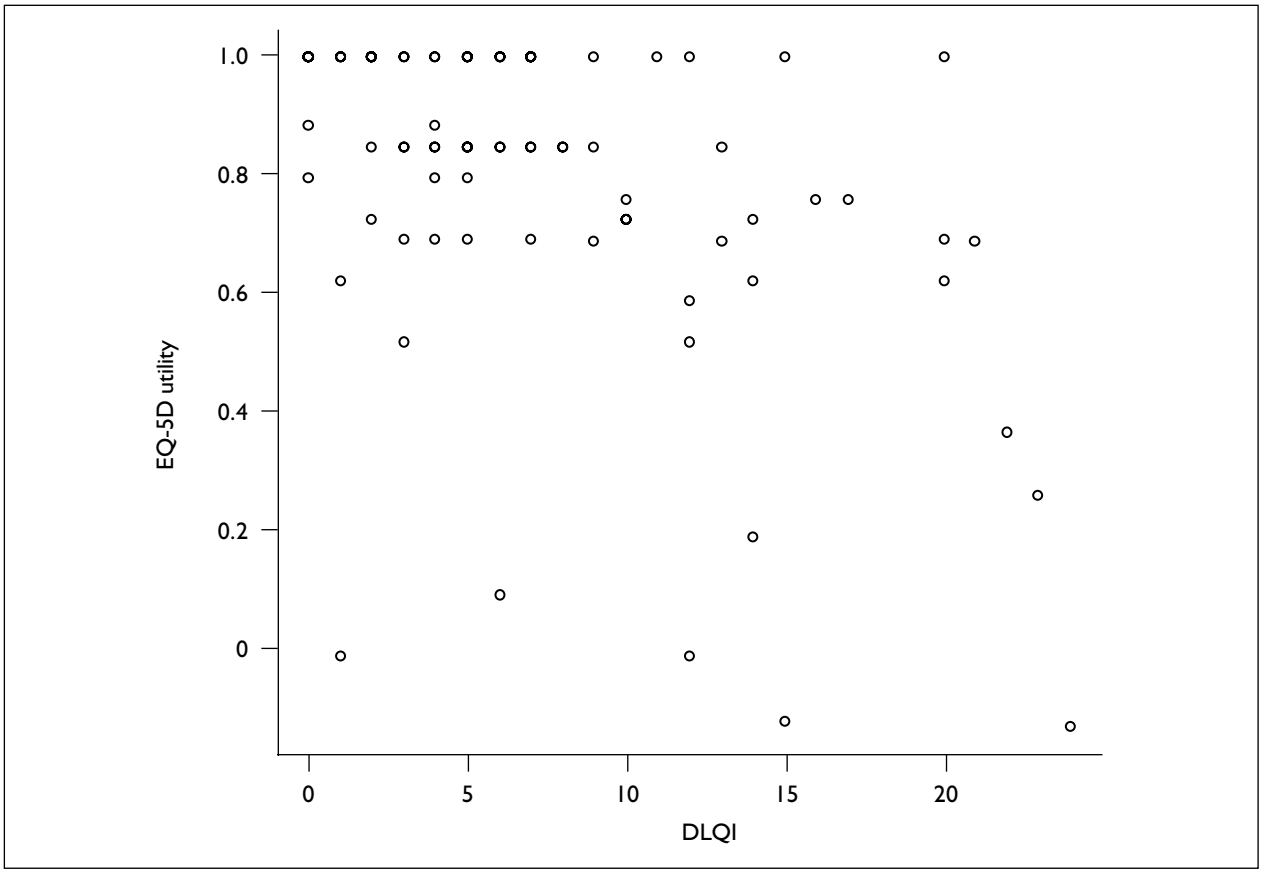

FIGURE 5 *Scatterplot of DLQI and EQ-5D data from the HODaR database (higher DLQI and lower EQ-5D utilities indicate worse QoL)*

TABLE 48 *Estimated gains in utility for the different PASI response categories: results are shown for all patients and for those with the worst baseline QoL (fourth quartile DLQI)*

PASI response category	Gains in utility: mean (SE)	
	All subjects	4th quartile DLQI
<50	0.05 (0.01)	0.12 (0.03)
≥50 and <75	0.17 (0.04)	0.29 (0.06)
≥75 and <90	0.19 (0.04	0.38 (0.08
≥90	0.21 (0.05)	0.41 (0.09)

and DLQI and the standard error from the change in DLQI conditional on PASI response and assumed normal distributions in both instances.

There are three key assumptions in how QALYs have been derived for the cost-effectiveness model. The first is that the PASI response is a perfect proxy for the change in utility arising from treatment. In effect, if we condition on PASI response, utility is independent of treatment. Second, if we condition on DLQI change, utility is independent of PASI response. These are assumptions of conditional independence. The third assumption is that the relationship between DLQI and utility is linear. In addition, we do not account for the impact of any adverse events on utility.

Analysis

All decision modelling was undertaken in the programming language R (see Appendix 8 for the code). The results of the York Model are presented as expected average costs and QALYs over the period of treatment for each drug. The ICER comparing all drugs only relates to a situation when the decision-maker can only choose one treatment and cannot try other treatments if that fails. This is not useful for decision-making as it does not identify which drugs should be included in a treatment sequence for a given threshold value for cost-effectiveness or in which order they should be tried. The ICER comparing all drugs with 'supportive care' is also given; this indicates the cost-effectiveness threshold at which a drug would be included somewhere in the sequence but does not indicate where.

In addition, tables are given which indicate the most cost-effective order in which to give the therapies based on the estimated average cost and

TABLE 49 *Results of the base-case analysis including only etanercept, efalizumab and supportive care and related to all patients (regardless of baseline DLQI) and assuming patients not responding to therapy are not hospitalised*[a]

	QALYs			Costs (£)				
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	ICER (£)	ICER against supportive care (£)
Supportive care	0	0	0	0	0	0	–	–
Etanercept 25 mg	0.116	0.064	0.17	7,743	7,437	8,337	66,703	66,703
Efalizumab	0.112	0.064	0.162	9,382	9,238	9,602	Dominated	84,018
Etanercept 25 mg continuous	0.116	0.064	0.17	9,665	9,569	9,851	Dominated	83,258
Etanercept 50 mg	0.123	0.071	0.178	14,860	14,569	15,365	103,5121	120,855

[a] All etanercept therapies are intermittent unless stated and efalizumab is continuous.

QALYs associated with each treatment. These vary according to the threshold value of cost-effectiveness. These should not be interpreted as a strict sequence to which all patients should adhere. Rather, the order shows that, if a patient is unable to have a particular therapy (e.g. owing to contraindications or intolerance), they would move to the next treatment in the order. Decision uncertainty, based on the results of the probabilistic sensitivity analysis, is presented as the probability that each treatment would be included in the optimum treatment sequence and the probability that each treatment would be first in the sequence as a function of the threshold value of cost-effectiveness.

The cost-effectiveness results vary considerably according to two important baseline characteristics of a given patient. The first is their baseline QoL, as assessed using the DLQI. The second is the probability of the patient being hospitalised if they fail to respond to treatment. Below, results are presented using various scenarios regarding these two baseline variables.

Results

Base-case results

The base-case results relate to all patients (regardless of baseline QoL in terms of DLQI) and assume that patients not responding to therapy are not hospitalised. The base-case analysis focuses only on etanercept, efalizumab and supportive care. The base-case results are shown in *Table 49*. The ICERs in the last column, relative to supportive care, indicate the ICER at which the particular therapy might enter a sequence. Under base-case assumptions, these ICERs are relatively high, ranging from £66,703 (etanercept 25 mg) to £120,855 (etanercept 50 mg).

TABLE 50 *Most cost-effective ordering of therapies for base-case results as a function of the threshold value of cost-effectiveness*[a]

Threshold value of cost-effectiveness (£)	Sequence	
	First in sequence	Second in sequence
0	Supportive care	
5,000	Supportive care	
10,000	Supportive care	
15,000	Supportive care	
20,000	Supportive care	
25,000	Supportive care	
30,000	Supportive care	
35,000	Supportive care	
40,000	Supportive care	
45,000	Supportive care	
50,000	Supportive care	
55,000	Supportive care	
60,000	Supportive care	
65,000	Supportive care	
70,000	Etanercept 25 mg	Supportive care
75,000	Etanercept 25 mg	Supportive care

[a] Analysis includes only etanercept, efalizumab and supportive care and relates to all patients (regardless of baseline DLQI) and assuming patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

The more informative results are shown in *Table 50*, which indicates the most cost-effective sequence of therapies conditional on the threshold value of cost-effectiveness. The fact that supportive care is the only form of management listed until

TABLE 51 *Results of probabilistic sensitivity analysis for the base-case showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness*[a]

Threshold value of cost-effectiveness (£)	Probability	Etanercept 25 mg	Etanercept 50 mg	Efalizumab	Etanercept 25 mg continuous	Supportive care
20,000	Probability first in sequence	0.00	0.00	0.00	0.00	1.00
30,000	Probability first in sequence	0.00	0.00	0.00	0.00	1.00
50,000	Probability first in sequence	0.09	0.00	0.00	0.00	0.91
20,000	Probability included in sequence	0.00	0.00	0.00	0.00	1.00
30,000	Probability included in sequence	0.00	0.00	0.00	0.00	1.00
50,000	Probability included in sequence	0.09	0.00	0.00	0.00	1.00

[a] Analysis includes only etanercept, efalizumab and supportive care and relates to all patients (regardless of baseline DLQI) and assumes patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

TABLE 52 *Results of the Alternative Scenario I including only etanercept, efalizumab and supportive care and relating only to patients with the worst QoL (4th quartile DLQI) at baseline, and assuming patients not responding to therapy are not hospitalised*[a]

	QALYs			Costs (£)				
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	ICER (£)	ICER against supportive care (£)
Supportive care	0	0	0	0	0	0	–	–
Etanercept 25 mg	0.222	0.124	0.324	7,743	7,437	8,337	34,834	34,834
Efalizumab	0.214	0.122	0.311	9,382	9,238	9,602	Dominated	43,821
Etanercept 25 mg continuous	0.222	0.124	0.324	9,665	9,569	9,851	Dominated	43,479
Etanercept 50 mg	0.235	0.137	0.34	14,860	14,569	15,365	539,083	63,103

[a] All etanercept therapies are intermittent unless stated and efalizumab is continuous.

the threshold reaches £70,000 per QALY gained indicates that, under base-case assumptions, neither biological therapy would be sufficiently cost-effective to enter the sequence until that threshold.

Table 51 shows the results of the probabilistic sensitivity analysis for the base-case analysis. This is presented for each of the therapies conditional on the threshold value of cost-effectiveness. For each therapy, two probabilities are shown: the probability of being the first treatment in the sequence and the probability of being in the sequence at all. Only when the threshold reaches £50,000 per QALY do the biological therapies have a non-zero probability of being first in sequence or in the sequence at all but, even at this threshold, the probability is only 0.09 for etanercept 25 mg and remains zero for the other biological therapies.

Alternative Scenario I: fourth quartile DLQI at baseline

A series of alternative scenarios is run to contrast with the base-case results. In the first, patients with poor baseline QoL (in terms of DLQI) are considered. The results of the gains in utility by PASI response categories, conditional on baseline DLQI, in *Table 47*, show that the utility gains are greater in patients who have worse baseline DLQI. In this scenario, there are no hospitalisations on supportive care as in the base case.

Table 52 shows the expected costs, QALYs and ICERs of this scenario. The ICERs against supportive care are lower than in the base case, reflecting that the therapies will enter the most cost-effective sequence at lower ICER levels. *Table 53* shows the most cost-effective sequence of therapies conditional on the threshold value of cost-effectiveness. It can be seen that the biological

TABLE 53 *Most cost-effective ordering of therapies for base-case results as a function of the cost-effectiveness threshold*[a]

Threshold value of cost-effectiveness (£)	Sequence				
	First in sequence	**Second in sequence**	**Third in sequence**	**Fourth in sequence**	**Fifth in sequence**
0	Supportive care				
5,000	Supportive care				
10,000	Supportive care				
15,000	Supportive care				
20,000	Supportive care				
25,000	Supportive care				
30,000	Supportive care				
35,000	Etanercept 25 mg	Supportive care			
40,000	Etanercept 25 mg	Supportive care			
45,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care	
50,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care	
55,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care	
60,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care	
65,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
70,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
75,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care

[a] Analysis includes only etanercept, efalizumab and supportive care and relates only to patients with the worst QoL (4th quartile DLQI) at baseline and assumes patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

therapies appear much earlier in these sequences than was the case under base-case assumptions. The first to appear is etanercept 25 mg, which is first in the sequence at a threshold of £35,000 per QALY gained. Etanercept 25 mg (continuous) and efalizumab appear in the sequence at a threshold of £45,000 and above. Etanercept 50 mg appears in a cost-effective sequence at a threshold of £65,000 and above. *Table 54* shows the results of the probabilistic sensitivity analysis for this scenario, and indicates that the probabilities of being first in sequence and of appearing in the sequence at all are higher than under the base-case assumptions.

Alternative Scenario II: patients with any DLQI at baseline and 21 days annual inpatient hospitalisation when not responding to therapy

The second alternative scenario considers all patients in terms of baseline QoL but now assumes that patients not responding to therapy spend 21 days per year as hospital inpatients. This figure is a mean length of stay for a single hospitalisation and is based on an average of that from the Hospital Episode Statistics (2002–3) for psoriasis and two local audits [see the section 'Resource use and costs' (p. 57)]. The assumption is effectively that non-responding patients experience one hospitalisation per annum consisting of a 21-day stay.

Table 55 shows expected QALYs, costs and ICERs for this alternative scenario. Compared with the base-case assumptions, the ICERs against supportive care are lower, indicating that the biological therapies would enter a sequence at lower ICERs. These ICERs are not greatly different to those in Alternative Scenario I.

Table 56 shows the most cost-effective sequence of therapies conditional on the threshold value of

TABLE 54 *Results of probabilistic sensitivity analysis for Alternative Scenario I showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness*[a]

Threshold value of cost-effectiveness (£)	Probability	Etanercept 25 mg	Etanercept 50 mg	Efalizumab	Etanercept 25 mg continuous	Supportive care
20,000	Probability first in sequence	0.00	0.00	0.00	0.00	1.00
30,000	Probability first in sequence	0.25	0.00	0.00	0.00	0.75
50,000	Probability first in sequence	0.86	0.00	0.05	0.00	0.09
20,000	Probability included in sequence	0.00	0.00	0.00	0.00	1.00
30,000	Probability included in sequence	0.25	0.00	0.02	0.03	1.00
50,000	Probability included in sequence	0.90	0.12	0.70	0.71	1.00

[a] Analysis includes only etanercept, efalizumab and supportive care and relates only to patients with the worst QoL (4th quartile DLQI) at baseline, and assumes patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

TABLE 55 *Results of Alternative Scenario II including only etanercept, efalizumab and supportive care and relating to all patients (regardless of baseline DLQI) and assuming patients not responding to therapy are hospitalised for 21 days per year*[a]

	QALYs			Costs (£)				
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	ICER (£)	ICER against supportive care (£)
Supportive care	0	0	0	0	0	0	–	–
Etanercept 25 mg	0.116	0.065	0.168	3,415	2,623	4,971	29,420	29,420
Efalizumab	0.112	0.065	0.162	5,232	4,656	6,116	Dominated	46,866
Etanercept 25 mg continuous	0.116	0.065	0.168	5,337	4,753	6,484	Dominated	45,975
Etanercept 50mg	0.123	0.073	0.176	10,258	9,696	11,248	984,856	83,378

[a] All etanercept therapies are intermittent unless stated and efalizumab is continuous.

TABLE 56 *Most cost-effective ordering of therapies for Alternative Scenario II as a function of the threshold value for cost-effectiveness*[a]

Threshold value of cost-effectiveness (£)	Sequence			
	First in sequence	Second in sequence	Third in sequence	Fourth in sequence
0	Supportive care			
5,000	Supportive care			
10,000	Supportive care			
15,000	Supportive care			
20,000	Supportive care			
25,000	Supportive care			
30,000	Etanercept 25 mg	Supportive care		
35,000	Etanercept 25 mg	Supportive care		
40,000	Etanercept 25 mg	Supportive care		
45,000	Etanercept 25 mg	Supportive care		
50,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care
55,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care
60,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care
65,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care
70,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care
75,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care

[a] Analysis includes only etanercept, efalizumab and supportive care and relates to all patients (regardless of baseline DLQI) and assumes patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

TABLE 57 *Results of probabilistic sensitivity analysis for Alternative Scenario II showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness*[a]

Threshold value of cost-effectiveness (£)	Probability	Etanercept 25 mg	Etanercept 50 mg	Efalizumab	Etanercept 25 mg continuous	Supportive care
20,000	Probability first in sequence	0.09	0.00	0.00	0.00	0.91
30,000	Probability first in sequence	0.56	0.00	0.00	0.00	0.44
50,000	Probability first in sequence	0.91	0.00	0.04	0.00	0.05
20,000	Probability included in sequence	0.09	0.00	0.00	0.00	1.00
30,000	Probability included in sequence	0.56	0.00	0.02	0.03	1.00
50,000	Probability included in sequence	0.93	0.00	0.60	0.63	1.00

[a] Analysis includes only etanercept, efalizumab and supportive care and relates to all patients (regardless of baseline DLQI) and assumes patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

TABLE 58 *Results of Alternative Scenario III including only etanercept, efalizumab and supportive care and relating to patients with the worst QoL (4th quartile DLQI) at baseline and assuming patients not responding to therapy are hospitalised for 21 days per year*[a]

	QALYs			Costs (£)				
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	ICER (£)	ICER against supportive care (£)
Supportive care	0	0	0	0	0	0	–	–
Etanercept 25 mg	0.223	0.126	0.326	3,415	2,623	4,971	15,297	15,297
Efalizumab	0.215	0.127	0.312	5,232	4,656	6,116	Dominated	24,346
Etanercept 25 mg continuous	0.223	0.126	0.326	5,337	4,753	6,484	Dominated	23,905
Etanercept 50 mg	0.236	0.141	0.342	10,258	9,696	11,248	521,054	43,395

[a] All etanercept therapies are intermittent unless stated and efalizumab is continuous.

cost-effectiveness. As for Alternative Scenario I, the biological therapies appear much earlier in these sequences than was the case under base-case assumptions. Again, the first to appear is etanercept 25 mg (at £30,000 per QALY gained). Etanercept 25 mg (continuous) and efalizumab appear in the sequence at a threshold of £50,000 and above. Etanercept 50 mg does not appear in a sequence based on the thresholds shown. *Table 57* shows the results of the probabilistic sensitivity analysis for this scenario and indicates that the probabilities of being first in sequence and of appearing in the sequence at all are higher than under the base-case assumptions.

Alternative Scenario III: fourth quartile DLQI and 21 days annual inpatient hospitalisation when not responding to therapy

The third alternative scenario effectively combines the first and second by including a subgroup of patients with poor baseline QoL (highest quartile DLQI) and high inpatient hospitalisation when not responding to therapy (21 days per year). *Table 58* shows the expected QALYs, costs and ICERs for all therapies. It can be seen that the ICERs compared with supportive care are lower than the base-case and the two previous alternative scenarios, indicating that biological therapies will enter a cost-effective sequence at lower ICERs.

Table 59 shows the most cost-effective sequence of therapies conditional on the threshold value of cost-effectiveness. Compared with the base-case and earlier scenarios, the biological therapies appear much earlier in these sequences. Again, the first to appear is etanercept 25 mg (at £20,000 per QALY gained). Etanercept 25 mg (continuous) and efalizumab appear in the sequence at a threshold of £25,000 and above. Etanercept 50 mg appears in the sequence at a threshold of £45,000 per QALY gained. *Table 60* shows the results of the probabilistic sensitivity analysis for this scenario,

TABLE 59 *Most cost-effective ordering of therapies for Alternative Scenario III as a function of threshold value for cost-effectiveness*[a]

Threshold value of cost-effectiveness (£)	Sequence				
	First in sequence	**Second in sequence**	**Third in sequence**	**Fourth in sequence**	**Fifth in sequence**
0	Supportive care				
5,000	Supportive care				
10,000	Supportive care				
15,000	Supportive care				
20,000	Etanercept 25 mg	Supportive care			
25,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care	
30,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care	
35,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care	
40,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care	
45,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
50,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
55,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
60,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
65,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
70,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
75,000	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care

[a] Analysis includes only etanercept, efalizumab and supportive care, relates to patients with the worst QoL (4th quartile DLQI) at baseline and assumes patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

and indicates that the probabilities of being first in sequence and of appearing in the sequence at all are the highest of all the scenarios.

Alternative Scenario IV: comparison of biologicals with other systemic therapies (patients with any baseline DLQI and assumption that non-responding patients are hospitalised for 21 days per year)

The final scenario widens the basis of comparison to include all systemic therapies for which effectiveness parameters could be estimated in the mixed treatment comparison analysis [see the section 'Clinical evaluation: mixed treatment comparison analysis' (p. 39)]. In addition to supportive care and therapies based on etanercept and efalizumab, this scenario includes methotrexate, ciclosporin, Fumaderm and infliximab. By way of illustration, the scenario is run for all patients (regardless of baseline DLQI) and assuming that patients not responding to therapy are hospitalised for 21 days per year.

Table 61 shows the expected QALYs, costs and ICERs for this scenario. As a result of their higher effectiveness (compared with supportive care) and lower acquisition costs (compared with the biological therapies), methotrexate, ciclosporin and Fumaderm all dominate supportive care. The ICERs for etanercept-based therapies and efalizumab, compared with supportive care, are similar to those in Alternative Scenario II. The ICER of infliximab, compared with supportive care, lies between those for etanercept 25 mg (continuous) and etanercept 50 mg.

TABLE 60 *Results of probabilistic sensitivity analysis for Alternative Scenario III showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness*[a]

Threshold value of cost-effectiveness (£)	Probability	Etanercept 25 mg	Etanercept 50 mg	Efalizumab	Etanercept 25 mg continuous	Supportive care
20,000	Probability first in sequence	0.80	0.00	0.02	0.00	0.18
30,000	Probability first in sequence	0.92	0.00	0.05	0.00	0.02
50,000	Probability first in sequence	0.92	0.00	0.08	0.00	0.00
20,000	Probability included in sequence	0.81	0.00	0.20	0.24	1.00
30,000	Probability included in sequence	0.96	0.03	0.78	0.80	1.00
50,000	Probability included in sequence	0.99	0.72	0.99	0.98	1.00

[a] Analysis includes only etanercept, efalizumab and supportive care and relates to patients with the worst QoL (4th quartile DLQI) at baseline and assumes patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

TABLE 61 *Results of the base-case analysis including supportive care and full range of systemic therapies*[a]

	QALYs			Costs (£)				
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	ICER (£)	ICER against supportive care (£)
Methotrexate	0.126	0.072	0.182	–4,223	–4,604	–3,224	–	Dominates
Ciclosporin	0.122	0.072	0.175	–452	–795	41	Dominated	Dominates
Fumaderm	0.101	0.036	0.16	–162	–2,192	2,309	Dominated	Dominates
Supportive care	0	0	0	0	0	0	Dominated	–
Etanercept 25 mg	0.116	0.065	0.168	3,415	2,623	4,971	Dominated	29,451
Efalizumab	0.112	0.066	0.161	5,232	4,656	6,116	Dominated	46,893
Etanercept 25 mg continuous	0.116	0.065	0.168	5,337	4,753	6,484	Dominated	46,025
Infliximab	0.134	0.079	0.192	6,918	4,396	9,850	1,393,179	51,748
Etanercept 50 mg	0.123	0.072	0.176	10,258	9,696	11,248	Dominated	83,477

[a] Includes all patients (regardless of baseline DLQI) and assumes that patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Table 62 show the most cost-effective treatment sequences, conditional on the threshold for cost-effectiveness, for this broader comparison. It shows that methotrexate, ciclosporin and Fumaderm would be the first three treatments in the sequence whatever threshold value is used. The first biological to appear is etanercept 25 mg (fourth in sequence at £30,000 per QALY gained). Etanercept 25 mg (continuous) and efalizumab appear fifth and sixth in the sequence, respectively, at a threshold of £50,000 and above. Etanercept 50 mg does not appear in any sequence at the thresholds used in the analysis. *Table 63* shows the results of the probabilistic sensitivity analysis for this scenario, and indicates that the probabilities of being first in sequence and of appearing in the sequence are highest for methotrexate, ciclosporin and Fumaderm.

TABLE 62 *Most cost-effective ordering of therapies for Alternative Scenario IV as a function of threshold value for cost-effectiveness*[a]

Threshold value of cost-effectiveness (£)	Sequence							
	First in sequence	Second in sequence	Third in sequence	Fourth in sequence	Fifth in sequence	Sixth in sequence	Seventh in sequence	Eighth in sequence
0		Methotrexate	Ciclosporin	Fumaderm	Supportive care			
5,000	Methotrexate	Ciclosporin	Fumaderm	Supportive care				
10,000	Methotrexate	Ciclosporin	Fumaderm	Supportive care				
15,000	Methotrexate	Ciclosporin	Fumaderm	Supportive care				
20,000	Methotrexate	Ciclosporin	Fumaderm	Supportive care				
25,000	Methotrexate	Ciclosporin	Fumaderm	Supportive care				
30,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Supportive care			
35,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Supportive care			
40,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Supportive care			
45,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Supportive care			
50,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Supportive care	
55,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Infliximab	Supportive care
60,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Infliximab	Supportive care
65,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Infliximab	Supportive care
70,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Infliximab	Supportive care
75,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg	Etanercept 25 mg continuous	Efalizumab	Infliximab	Supportive care

[a] Analysis includes supportive care and full range of systemic therapies. Includes all patients (regardless of baseline DLQI) and assumption that patients not responding to therapy are hospitalised for 21 days per annum. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

TABLE 63 *Results of probabilistic sensitivity analysis for Alternative Scenario IV showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness*[a]

Threshold value of cost-effectiveness (£)	Probability	Etanercept 25 mg	Etanercept 50 mg	Efalizumab	Supportive care	Ciclosporin	Methotrexate	Fumaderm	Infliximab	Etanercept 25 mg continuous
20,000	Probability first in sequence	0	0	0	0	0	1.00	0	0	0
30,000	Probability first in sequence	0	0	0	0	0.	0.99	0	0	0
50,000	Probability first in sequence	0	0	0	0	0.01	0.99	0	0	0
20,000	Probability included in sequence	0.09	0	0	1.00	1.00	1.00	0.92	0	0
30,000	Probability included in sequence	0.56	0	0.02	1.00	1.00	1.00	0.95	0.04	0.03
50,000	Probability included in sequence	0.93	0	0.60	1.00	1.00	1.00	0.97	0.46	0.63

[a] Analysis includes supportive care and full range of systemic therapies. Includes all patients (regardless of baseline DLQI) and assumption that patients not responding to therapy are hospitalised for 21 days per annum. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Chapter 7
Discussion

Our review of the clinical effectiveness of etanercept and efalizumab demonstrated that both are both more efficacious than placebo in the treatment of moderate to severe psoriasis. Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the other treatments available for the relief of moderate to severe chronic plaque psoriasis. Furthermore, all other treatments are associated with the risk of serious and possibly long-term adverse events. In a mixed treatment comparison, including etanercept, efalizumab, ciclosporin, Fumaderm, methotrexate, infliximab and placebo, infliximab appeared the most effective followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. However, there is uncertainty around these response rates. Only one study examining the cost-effectiveness of biological therapy in psoriasis met the inclusion criteria for the systematic review of economic evaluations, but its methods and US focus give it limited relevance to UK practice. The York economic modelling, which took into account flaws in the companies' own models, demonstrates that etanercept and efalizumab are likely to be cost-effective only in patients with poor baseline QoL and who are at risk of hospitalisation for the treatment of their psoriasis.

Clinical evaluation

Limitations of our review

The literature searches conducted for this review were comprehensive. With these and the data made available in the company submissions and clinical trial reports provided by Wyeth, we are confident that we have been able to include all the relevant RCTs in our evaluation of efficacy. We are similarly confident that all relevant studies have been included in our review of adverse events and all RCTs identified regarding the efficacy of other treatments for moderate to severe psoriasis.

Although we adhered to standard systematic review practice to evaluate the best evidence from clinical trials, it may be considered a limitation of our review that it is based firmly on the available clinical trials data and as such may not properly reflect UK clinical practice and experience. First, there is a shortage of good-quality data on the various treatment options used in routine practice for the treatment of moderate to severe psoriasis. Second, the excellent degree of efficacy seen with PUVA in clinical practice, with clearance of symptoms being the expected outcome of treatment, has resulted in a complete lack of placebo-controlled trials. We therefore found it impossible to compare (even indirectly) PUVA with other therapies. Similarly, placebo-controlled trials of methotrexate are lacking. Finally, the outcome measures used in clinical trials, primarily PASI, do not help to unify clinical trial evidence and clinical experience, because of its lack of relevance for and applicability to clinical practice. However, one of the most important parameters, with respect to cost-effectiveness, is the probability that a patient continues on therapy beyond an initial trial period – the PASI may be a good proxy for this.

One of the difficulties in comparing older systemic therapies with the newer biologicals is that trials of older therapies report fewer and less clearly defined outcomes than those of the biologicals. However, some of the trials of the biological therapies place heavy emphasis on PASI 50 as an appropriate measure of effectiveness. In clinical practice, it is likely that dermatologists will consider this an insufficient definition of treatment success.

Another area of importance to clinical practice that has not been addressed in this review, owing to a lack of trial-based evidence, is that of the use of combination therapies: neither of the new biologicals has been studied in combination with any older treatment (except methotrexate). All systemic therapies for psoriasis are, however, complemented by use of topical preparations.

Efficacy of etanercept and efalizumab

There are limited data available for the evaluation of the efficacy of the two biological drugs reviewed: only three RCTs for etanercept and five for efalizumab. All eight trials were double-blind, placebo-controlled trials, conducted by the pharmaceutical companies developing the drugs. All eight trials provided reliable data regarding

the short-term (12 weeks) use of the biological therapies; however, far fewer data are available for 24 weeks of use, with only one RCT available for etanercept and none for efalizumab. Although there is good evidence that etanercept and efalizumab are both more efficacious than placebo in the treatment of moderate to severe psoriasis, the clinical significance of the level of efficacy is debatable. It is unclear whether the achievement with etanercept 25 mg of PASI 50 by 60% of patients treated and PASI 75 by 33% of patients treated should be considered an acceptable, or clinically important, level of efficacy. Clinical advice that we have received suggests that UK dermatologists do not consider the PASI 50 to represent a sufficient clinical response. The 50-mg dose of etanercept achieved higher levels of efficacy, with 76% of treated patients achieving PASI 50 and 49% achieving PASI 75, but corresponding figures for efalizumab were lower, with only around 55% achieving PASI 50 and 27% PASI 75.

Although trials demonstrate the efficacy of etanercept and efalizumab under controlled conditions, there is some question over how generalisable these findings are to the real-life clinical situation, particularly in relation to the degree of debility suffered by the patients to be treated with these drugs. The patients included in the clinical trials can all be appropriately classified as having moderate to severe psoriasis, with baseline PASI scores of at least 10 or 12, and the populations are comparable across the trials. However, given the product licences for both etanercept and efalizumab and the high cost of these drugs, it is likely that patients in clinical practice will be much more severely affected than those participating in the majority of clinical trials and, therefore, response rates may differ.

As a chronic condition, psoriasis requires many patients to undergo continuous treatment for long periods. RCT data to support this type of use are lacking for both biological therapies. Uncontrolled data from long-term continuation of RCTs of etanercept suggest that for up to 36 weeks at least, the short-term efficacy is maintained. Unfortunately, similar data for efalizumab are not available. Intermittent treatment of psoriasis is often advocated, with short treatment periods to induce remission and then a treatment-free period until relapse, upon which active therapy is re-initiated. There are some limited data for etanercept to support this approach, with relapse occurring on average some 3 months after treatment. Importantly, the data indicate that there is no rebound of psoriasis upon withdrawal of treatment, or any loss of efficacy upon retreatment in patients who have relapsed. However, these findings for intermittent use of etanercept may not be reliable as they are based on uncontrolled data. Supporting evidence for intermittent use of efalizumab is even weaker. The time to relapse is possibly shorter than that for etanercept at around 2 months and, although the efalizumab SPC states that efficacy may be reduced upon retreatment, we found no RCT or RCT-extension data to support or confirm this.

Overall, both drugs have clearly demonstrated some degree of efficacy for the short-term (12 weeks) treatment of moderate to severe psoriasis, but only for etanercept did we find any real evidence that longer term (24 weeks) or intermittent use is an effective therapy option.

In the context of the etanercept product licence for use up to 24 weeks, the adverse effects profile of etanercept appears acceptable and is supported by long-term data from other clinical indications. However, given that clinical use is likely to be intermittent over a very long period, probably years, then long-term effects specifically in psoriasis patients are relevant and further information is required. The publicly available information for efalizumab indicates that the drug is well tolerated when used to treat psoriasis patients over a 12-week period with a low rate of withdrawals. As yet unpublished longer term data were not evaluable in this review. For both etanercept and efalizumab, it must be remembered that patients with moderate to severe psoriasis will have been exposed to the hepatotoxicity of methotrexate, the nephrotoxicity of ciclosporin and the increased risk of skin cancer with PUVA, before being treated with either biological agent. The significance of the serious adverse events reported in association with etanercept or efalizumab is not readily discernible from the published reports of clinical trials.

Efficacy of other treatments available for the relief of moderate to severe psoriasis

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the treatments available for the relief of moderate to severe psoriasis. Only infliximab and ciclosporin have had their efficacy demonstrated in placebo-controlled RCTs, and even these data are relatively few, with most trials having included a small number of patients and only a short treatment period. Although clinical experience has demonstrated excellent efficacy of PUVA and

methotrexate, no placebo-controlled trials have been conducted. In head-to-head clinical trials, methotrexate appears to be as effective as ciclosporin. The trials of other treatments – acitretin, RePUVA, and NBUVB, in comparison with PUVA – provide only limited evidence, demonstrating some degree of effectiveness but making it difficult to draw firm conclusions regarding the relative efficacy. All comparator treatments are associated with a risk of serious and long-term adverse events.

Findings from the mixed treatment comparison analysis

By using a mixed treatment comparison analysis, it was possible to make some form of comparison between etanercept and efalizumab with each other and with ciclosporin, Fumaderm, methotrexate, infliximab and placebo. The availability of trial data limited the therapies that could be compared, but the majority of widely used systemic psoriasis treatments were included. Our failure to include PUVA in the analysis is not of great importance, since the level of efficacy to be achieved with phototherapy is very different to that achieved with other therapies: with PUVA or NBUVB the ability to achieve clearance is the expected outcome. Unfortunately, phototherapy can only be used for a limited number of exposures over a lifetime; other therapies are only considered when the exposure limit has been reached or other factors make phototherapy unsuitable.

In a mixed treatment comparison, including etanercept, efalizumab, ciclosporin, Fumaderm, methotrexate, infliximab and placebo, infliximab appeared the most effective followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. It should be emphasised, however, that response rates for all therapies were uncertain and 95% CIs frequently overlapped.

It is important to note that this analysis is limited by the data available. Conclusions are restricted to those relating to short-term use; relative efficacy at 12 weeks for treatment of a chronic condition is not ideal. However, this lack of information reflects the evidence base for all treatments, not just the new biological therapies. What is lacking with the newer drugs is, of course, long-term clinical experience. Without long-term data, it is impossible to understand fully the relative value of the therapies reviewed. It is unknown if short-term efficacy is maintained in the long term or if indeed it might improve, or if, in the case of infliximab, tachyphylaxis is common with continued use.

The mixed treatment comparison also omits the adverse effects of the various treatments. Owing to long experience with the other treatments, their long-term serious adverse effects, and how these should be managed, is well known. The relative efficacy of the new biological therapies needs to be considered in the light of what is known about their safety profiles; so far they appear well tolerated and safe; however, much more experience of use with these agents is required before a clear picture can emerge.

Another area of importance to clinical practice that has not been addressed in this report owing to a lack of trial-based evidence is that of the use of combination therapies: neither of the new biological therapies has been studied in combination with any older treatment (except methotrexate). All systemic therapies for psoriasis are, however, complemented by use of topical preparations.

Economic evaluation

Comparison of the economic models: structural differences

In assessing the cost-effectiveness of efalizumab and etanercept in psoriasis, little information was available in the published literature. Only one study was identified, which had several methodological limitations and has little relevance to NHS decision-making. It was therefore necessary to rely on the economic models submitted by Wyeth and Serono and the *de novo* York Model.

The three models share some important features. For example, all models use PASI to determine whether, over a short period (usually 12 weeks, following trial evidence), patients are showing adequate response to continue therapy.

There are, however, some important differences between the three models that are likely to impact on results. One difference is a general one. Both the Serono and Wyeth models sought to estimate the cost-effectiveness of the relevant biological therapy, relative to a comparator of no systemic therapy, as a single mutually exclusive comparison. The premise of such an analysis is that clinicians will only be able to use one therapy and this

should be the one that is identified as the most cost-effective. Although this is a fairly standard approach to economic evaluation, it has some important limitations in the context of the treatment of chronic relapsing diseases such as psoriasis. Such diseases show high variability between individuals and, if a patient does not appear to respond to (or cannot tolerate) one treatment, another will be tried. Once all active therapies have been tried, some form of 'best supportive care' would be the only remaining option. In this context, the comparison of mutually exclusive treatment options does not provide useful information to decision-makers. Instead, the appropriate focus is to identify the most cost-effective **sequence** of therapies, and this was the objective of the York Model. The latter indicated the most cost-effective sequence of treatments conditional on a decision-maker's threshold value of cost-effectiveness (willingness to pay for an additional QALY).

There are also some more specific differences between the manufacturers' models and the York Model. The first is the choice of PASI response category to determine whether a patient has experienced sufficient benefit from treatment to justify continuing on that therapy. In the Serono and Wyeth models, PASI 50 is used. Clinical advice received, however, suggests that, in routine practice, dermatologists will consider this too modest a gain to justify continuation. Of course, the choice of this response threshold is one aspect of defining the most appropriate intervention/sequence. In the York Model, clinical advice has prompted the use of PASI 75 as the response criterion, but other scenarios could be run to assess the implications of using alternatives.

A second specific difference between the models is the methods used to relate the measure of efficacy in the trials (PASI) with HRQoL and utility. The Serono model has used utility estimates from the literature and sought to 'map' these to general health states of 'severe psoriasis' and 'treatment response to severe psoriasis'. As discussed in the section 'Serono's cost-effectiveness model' (p. 50), the resulting utility gain from a PASI 50 treatment response can be considered to be unrealistically high. The Wyeth and York models have some similarity, in terms of utility, as both have used survey data to link QoL (in terms of DLQI) to utility (in terms of EQ-5D). The Wyeth model has linked PASI to DLQI by, in effect, averaging the DLQI changes for responders and non-responders in terms of PASI 50. On the basis of access to patient-level data supplied by Wyeth, the York Model analysis may be considered somewhat more sophisticated in that the changes in DLQI for all levels of PASI response are considered, and these are conditioned on baseline DLQI.

Comparison of results of the three available economic models

Despite the difference in modelling approach, it is possible to compare the ICERs generated by the company models with those against supportive care in the York Model. The ICER range for intermittent use of etanercept 25 mg in the Wyeth model was £24,229–37,199 per QALY gained dependent on baseline severity. The range for the same therapy in the York Model was £15,297–66,703 per QALY gained, depending on assumptions about baseline QoL and the number of days in hospital for patients not responding to therapy. Hence the Wyeth range lies within the York Model range, which indicates that the latter explored more extreme scenarios. This is also the case in comparing the ICERs for continuous use of etanercept 25 mg (£25,926–53,056 per QALY gained for Wyeth and £23,905–83,258 per QALY gained for the York Model). Etanercept 50 mg was evaluated as a continuous therapy in the Wyeth model and as an intermittent therapy in the York Model, so the results are not directly comparable.

In comparing the Serono and York models, two features of the former are likely to generate optimistic results for the cost-effectiveness of efalizumab. The first is the methods Serono have used to introduce utility values into their analysis, as discussed above. The second is the assumption that those patients who are responding at 12 weeks (in terms of PASI 50) will continue to respond for a further 10 years with the exception of a small proportion of patients who discontinue therapy for reasons unrelated to efficacy or adverse events. This drop-out rate is set at 8% per annum compared to the 20% in the York Model based on available longer term data. These assumptions explain the base-case ICER for efalizumab from Serono of £25,582 per QALY gained (over 10 years), compared to a range of £24,346–84,018 for the York Model. In other words, Serono's base-case estimate for all patients is close to that from the York Model for patients with poor baseline QoL and a 21-day annual hospitalisation for patients not responding to therapy.

An important issue with respect to cost-effectiveness is the choice of comparators against which to assess efalizumab and etanercept. In the York Model, two alternative approaches to

comparators have been used. The primary analysis includes only etanercept, efalizumab and supportive care. One alternative scenario (IV) was included which assessed the cost-effectiveness of a wider set of systemic therapies which are used in routine practice and which were included in the systematic review and mixed treatment comparison analysis. For purposes of decision-making in a broader clinical context, it is this wider comparison that is likely to be most useful.

Limitations of the York Model

Some parameters in the modelling are highly uncertain. In part, this simply reiterates the point made above (in the context of the clinical evaluation) that relates to the limitations in the efficacy evidence. Parameters, other than those relating to efficacy, have been used in the cost-effectiveness model and are characterised by significant uncertainty. Perhaps the most important of these relate to the long-term experience with biological therapies including the annual drop-out rate from therapy and the 'remission' period assumed between spells of intermittent etanercept. Another area of parameter uncertainty relates to the cost of adverse events. In the York Model, no such costs have been included for any therapy on the assumption that common adverse events generally resolve once therapy is discontinued and the latter is explicitly part of the model. The cost implications of more serious adverse events are unclear given the uncertainty about the incidence of such events.

Other parameters in the York Model are highly variable. This is particularly the case with baseline QoL and the assumed number of inpatient days spent in hospital by patients not responding to therapy. Hence the cost-effectiveness analysis results have been presented conditional on a baseline DLQI and the probability of being hospitalised. It is clear that etanercept and efalizumab are more cost-effective in patients whose psoriasis has a greater impact on their baseline QoL and who are likely to spend more days in hospital when not responding to therapy.

Recommendations for research

The following areas are recommended for further study.

- Efficacy trials conducted in the specific population for which etanercept and efalizumab are licensed, that is, patients with moderate to severe chronic plaque psoriasis in whom conventional therapy has failed or is inappropriate. Trials should assess duration of remission following treatment withdrawal.
- Long-term comparisons of etanercept and efalizumab with other treatments for moderate to severe psoriasis, particularly infliximab, methotrexate and ciclosporin.
- Long-term efficacy trials, to provide data on how etanercept and efalizumab perform as maintenance therapies.
- Long-term safety/tolerability data for patients treated with etanercept or efalizumab.
- RCTs of various combination therapies.
- Psoriasis is a heterogeneous group of diseases; trials to identify specific subtypes that respond better to one drug compared with another.
- Research on the rate of inpatient hospitalisation in patients with moderate to severe psoriasis, and the effect of treatment on this rate.

Chapter 8
Conclusions

There is good evidence that etanercept is efficacious in the treatment of moderate to severe psoriasis, and that the response is maintained up to 24 weeks. The most common adverse effect of etanercept is injection site reaction. Other serious adverse events, as identified from earlier reviews, are uncommon and not readily identified from clinical trials.

There is evidence that efalizumab is efficacious in the treatment of moderate to severe psoriasis. There is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks. The publicly available information for efalizumab indicates that the drug is well tolerated over a 12-week period; however, few data for any longer term treatment are available for evaluation.

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the other treatments available for the relief of moderate to severe psoriasis. All other treatments are associated with serious and possibly long-term adverse events.

In a mixed treatment comparison, including etanercept, efalizumab, ciclosporin, Fumaderm, methotrexate, infliximab and placebo, infliximab appeared the most effective, followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. The pattern is consistent across the different PASI response categories.

For the primary analysis comparing etanercept, efalizumab and supportive care, the results of the York Model suggest that the biological therapies would only be cost-effective in a treatment sequence for all patients with moderate to severe psoriasis if the NHS were willing to pay over £60,000 per QALY gained. Efalizumab would only be a cost-effective option for patients with poor baseline DLQI (fourth quartile) in a treatment sequence if the NHS were willing to pay up to £45,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment (21 inpatient days annually), efalizumab could be a cost-effective option if the NHS were willing to pay up to £25,000 per QALY gained. Intermittent use of etanercept 25 mg would only be a cost-effective option in a treatment sequence for patients with poor baseline DLQI (fourth quartile) if the NHS were willing to pay up to £35,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment, intermittent etanercept 25 mg would be a cost-effective option if the NHS were willing to pay up to £20,000 per QALY gained. Continuous use of etanercept 25 mg would only be a cost-effective option in a treatment sequence for patients with poor baseline DLQI (fourth quartile) if the NHS were willing to pay up to £45,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment, this therapy could be a cost-effective option if the NHS were willing to pay up to £25,000 per QALY gained. Intermittent use of etanercept 50 mg would only be a cost-effective option in a treatment sequence for patients with poor baseline DLQI (fourth quartile) if the NHS were willing to pay up to £65,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment it could be a cost-effective option if the NHS were willing to pay up to £45,000 per QALY gained.

As part of a secondary analysis including a wider range of systemic therapies as comparators, the York Model found that it would only be cost-effective to use etanercept and efalizumab in a sequence after methotrexate, ciclosporin and Fumaderm.

Overall, clinical trial data indicate that both etanercept and efalizumab are efficacious in patients who are eligible for systemic therapy, but the economic evaluation demonstrates that these biological therapies are likely to be cost-effective only in patients with poor baseline QoL and who are at risk of hospitalisation.

Acknowledgements

We thank the expert advisory panel for their useful advice and constructive comments on the report. We thank Dr Craig Currie and colleagues at the Cardiff Research Consortium–Health Outcomes Group for access to HODaR data and assistance with the utility mapping work. We are indebted to Kirsty Swindells, Hope Hospital, Salford, and Amanda Woods, St John's Institute of Dermatology, London, for providing preliminary bed audit findings to inform the resource use estimates. Thanks also go to Margaret Sinclair of the Biochemistry Department at York NHS Trust for providing us with the cost of laboratory tests. We also wish to thank Professor Tony Ades of the MRC Health Services Research Collaboration at the University of Bristol for his help and advice on the mixed treatment comparison model applied in the mixed treatment comparison analysis.

Contribution of authors

Nerys Woolacott (Research Fellow) was the lead reviewer responsible for writing the protocol, all aspects of the clinical evaluation and coordinating the final report. Neil Hawkins (Research Fellow) was responsible for the mixed treatment comparison analysis and development of the economic model and contributed to the protocol and report writing. Anne Mason (Research Fellow) was responsible for the systematic review of economic evaluations, involved in the economic model and contributed to the protocol and report writing. Anita Kainth (Research Fellow) was the lead reviewer responsible for writing the protocol, all aspects of the clinical evaluation and coordinating the review up to the end of November 2004 and was involved in study selection, data extraction and validity assessment. Zarnie Khadjesari (Research Fellow) was the reviewer involved in the clinical evaluation section and was involved in study selection, data extraction, validity assessment and writing the final report. Yolanda Bravo Vergel (Research Fellow) was involved in the economic evaluation and responsible for the review and re-analysis of the company submissions. Kate Misso (Information Officer) devised the search strategy and carried out the literature searches. Kate Light (Information Officer) wrote the search methodology sections of the report. Robert Chalmers (Consultant Dermatologist) provided input at all stages, contributed to the protocol, commented on various drafts of the report and contributed to the discussion section of the report. Mark Sculpher (Professor of Health Economics) provided input at all stages, commented on various drafts of the report and had overall responsibility for the economic evaluation sections of the report. Rob Riemsma (Senior Research Fellow) provided input at all stages, commented on various drafts of the report and had overall responsibility for project coordination.

This report was commissioned by the NHS R&D HTA Programme. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D Programme.

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Appendix 1

Literature searches

Clinical effectiveness

Searching for the clinical effectiveness component of this review was addressed by several separate searches to identify:

- reports of RCTs of etanercept or efalizumab in psoriasis
- reports of RCTs and reports of adverse events for etanercept or efalizumab
- reports of RCTs of comparator treatments in psoriasis
- reports of adverse events of comparators treatments
- reports of RCTs of infliximab in psoriasis.

Separate strategies were devised for each topic. Full details of the databases searched and search strategies used are provided below.

Search A: RCTs of etanercept or efalizumab in psoriasis

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
1966–2004/02 week 3

This search retrieved 64 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

EMBASE (OVID Online – http://www.ovid.com/)
1980–2004 week 9

This search retrieved 184 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. 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

National Research Register (NRR) (CD-ROM)
2004 Issue 1

This search retrieved 1 reference.

#1 PSORIASIS explode all trees (MeSH)
#2 (PSORIA* or (ANTI NEXT PSORIA*) or ANTIPSORIA)
#3 (#1 or #2)
#4 ETANERCEPT
#5 ENBREL
#6 EFALIZUMAB
#7 RAPTIVA
#8 (#4 or #5 or #6 or #7)
#9 (#3 and #8)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
2004 Issue 1

This search retrieved 6 references.

#1 PSORIASIS*:me
#2 (psoria* or (anti next psoria*) or antipsoria)
#3 (#1 or #2)
#4 etanercept
#5 enbrel
#6 efalizumab
#7 raptiva
#8 (#4 or #5 or #6 or #7)
#9 (#3 and #8)

ISI Science and Technology Proceedings (Web of Knowledge)
1990–2004 (28 February update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981–2004 (29 February update) – **http://wos.mimas.ac.uk/**

The search of ISI Science and Technology Proceedings retrieved two references.

The search of Social Science Citation Index and Science Citation Index retrieved 24 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*)
#5 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

All databases were searched from inception date. In total, 218 references were retrieved for this topic.

Search B: RCTs and reports of adverse events for etanercept or efalizumab

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
1966–2004/02 week 3

This search retrieved 217 references.

1. Adverse Drug Reaction Reporting Systems/
2. drug eruptions/ or erythema nodosum/
3. Drug Hypersensitivity/
4. Drug Toxicity/
5. treatment emergent.tw.
6. (safe or safety).ti,ab.
7. (tolerability or toxicity or adrs or harm$).ti,ab.
8. (hypersensiti$ or hyper sensiti$).ti,ab.
9. (undesirable$ adj2 (outcome$ or event$ or reaction$ or effect or effects)).ti,ab.
10. (side effects or side effect).tw.
11. (adverse adj2 (event$ or effect or effects or outcome$ or reaction$)).ti,ab.
12. (po or ae or de or co or to).fs.
13. Injections/ae
14. Erythema/ci
15. Pruritus/ci
16. pain/ci
17. Headache/ci
18. Fever/ci
19. chills/ci
20. Nausea/ci
21. vomiting/ci
22. Infection/ci
23. Abdominal Pain/ci
24. Depression/ci
25. Personality Disorders/ci

26. Immunocompromised Host/
27. Immunosuppressive Agents/ae
28. Abnormalities, Drug-Induced/
29. (site reaction$ or injection$ reaction$ or erythema or itching or pain or swelling or swollen or swelled).ti,ab.
30. (headache$ or head ache$ or head pain$ or chill or chills or fever or temperature or nausea or nauseous or sickness or vomiting or vomit or vomited).ti,ab.
31. (myalgia or muscle$ pain or infection$ or immunocompromise$ or immuno compromise$).ti,ab.
32. (immunosuppress$ or immuno suppress$ or depression or depressive or depressed or personality disorder$).ti,ab.
33. or/1-32
34. randomized controlled trial.pt.
35. exp randomized controlled trials/
36. random allocation/
37. double blind method/
38. single blind method/
39. clinical trial.pt.
40. exp clinical trials/
41. controlled clinical trials/
42. clin$ trial$.ti,ab.
43. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
44. placebo$.ti,ab.
45. placebos/
46. random$.ti,ab.
47. exp evaluation studies/
48. follow up studies/
49. exp research design/
50. prospective studies/
51. (control$ or prospectiv$ or volunteer$).ti,ab.
52. or/34-51
53. animals/
54. human/
55. 53 not (53 and 54)
56. 33 and 52
57. 56 not 55
58. 57 not (comment or letter or editorial).pt.
59. etanercept.mp.
60. enbrel.mp.
61. efalizumab.mp.
62. raptiva.mp.
63. or/59-62
64. 58 and 63

EMBASE (OVID Online – http://www.ovid.com/)
1980–2004 week 9

This search retrieved 826 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$).ti,ab.
16. or/1-15
17. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18. exp ANIMAL/
19. Animal Experiment/
20. Nonhuman/
21. Human/
22. Human Experiment/
23. or/17-20
24. 21 or 22
25. 16 not (23 not (23 and 24))
26. adverse drug reaction/ or drug eruption/ or drug fatality/ or drug fever/ or drug induced disease/ or flu like syndrome/ or retinoic acid syndrome/ or drug hypersensitivity/ or side effect/
27. drug surveillance program/
28. exp Drug Toxicity/
29. drug safety/ or drug tolerability/
30. treatment emergent.tw.
31. (safe or safety).ti,ab.
32. (tolerability or toxicity or adrs or harm$).ti,ab.
33. (hypersensiti$ or hyper sensiti$).ti,ab.
34. (undesirable$ adj2 (outcome$ or event$ or reaction$ or effect or effects)).ti,ab.
35. (side effects or side effect).tw.
36. (adverse adj2 (event$ or effect or effects or outcome$ or reaction$)).ti,ab.
37. (si or it or ae or to or po).fs.
38. injection/
39. injection site/
40. Erythema/si {Side Effect}
41. Erythema Nodosum/si {Side Effect}
42. Pruritus/si {Side Effect}
43. Skin Tingling/si {Side Effect}
44. Pain/si {Side Effect}
45. Headache/si {Side Effect}
46. Fever/si {Side Effect}
47. Chill/si {Side Effect}
48. Nausea/si {Side Effect}

49. vomiting/si
50. Infection/si {Side Effect}
51. Abdominal Pain/si {Side Effect}
52. Depression/si {Side Effect}
53. Personality Disorder/si {Side Effect}
54. Immune Deficiency/si {Side Effect}
55. Immunosuppressive Agent/ae, it, to {Adverse Drug Reaction, Drug Interaction, Drug Toxicity}
56. (site reaction$ or injection$ reaction$ or erythema or itching or pain or swelling or swollen or swelled).ti,ab.
57. (headache$ or head ache$ or head pain$ or chill or chills or fever or temperature or nausea or nauseous or sickness or vomiting or vomit or vomited).ti,ab.
58. (myalgia or muscle$ pain or infection$ or immunocompromise$ or immuno compromise$).ti,ab.
59. (immunosuppress$ or immuno suppress$ or depression or depressive or depressed or personality disorder$).ti,ab.
60. or/26-59
61. 25 and 60
62. etanercept/
63. etanercept.mp.
64. efalizumab/
65. efalizumab.mp.
66. (raptiva or enbrel).mp.
67. or/62-66
68. 61 and 67
69. 68 not (letter or note or editorial).pt.

National Research Register (NRR) (CD-ROM)
2003 Issue 4

This search retrieved 22 references.

#1 ETANERCEPT or ENBREL or EFALIZUMAB or RAPTIVA

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
2004 Issue 1

This search retrieved 26 references.

#1 ADVERSE DRUG REACTION REPORTING SYSTEMS single term (MeSH)
#2 DRUG ERUPTIONS single term (MeSH)
#3 ERYTHEMA NODOSUM single term (MeSH)
#4 DRUG HYPERSENSITIVITY single term (MeSH)
#5 DRUG TOXICITY single term (MeSH)
#6 (treatment next emergent)
#7 (safe or safety)
#8 (tolerability or toxicity or adrs or harm*)
#9 (hypersensiti* or (hyper next sensiti*))
#10 ((undesirable* next outcome*) or (undesirable* next event*) or (undesirable* next reaction*) or (undesirable* next effect) or (undesirable* next effects))
#11 ((side next effects) or (side next effect))
#12 ((adverse next event*) or (adverse next effect) or (adverse next effects) or (adverse next outcome*) or (adverse next reaction*))
#13 INJECTIONS {ae} single term (MeSH)
#14 ERYTHEMA {ci} single term (MeSH)
#15 PRURITUS {ci} single term (MeSH)
#16 PAIN {ci} single term (MeSH)
#17 HEADACHE {ci} single term (MeSH)
#18 FEVER {ci} single term (MeSH)
#19 CHILLS {ci} single term (MeSH)
#20 NAUSEA {ci} single term (MeSH)
#21 VOMITING {ci} single term (MeSH)
#22 INFECTION {ci} single term (MeSH)
#23 ABDOMINAL PAIN {ci} single term (MeSH)
#24 DEPRESSION {ci} single term (MeSH)
#25 PERSONALITY DISORDERS {ci} single term (MeSH)
#26 IMMUNOCOMPROMISED HOST single term (MeSH)
#27 IMMUNOSUPPRESSIVE AGENTS {ae} single term (MeSH)
#28 ABNORMALITIES DRUG-INDUCED single term (MeSH)
#29 ((site next reaction*) or (injection* next reaction*) or erythema or itching or pain or swelling or swollen or swelled)
#30 (headache* or (head next ache*) or (head next pain*) or chill or chills or fever or temperature or nausea or nauseous or sickness or vomiting or vomit or vomited)
#31 (myalgia or (muscle* next pain) or infection* or immunocompromise* or (immuno next compromise*))
#32 (immunosuppress* or (immuno next suppress*) or depression or depressive or depressed or (personality next disorder*))
#33 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#34 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33)
#35 (etanercept or enbrel or efalizumab or raptiva)
#36 (#34 and #35)

CenterWatch (Internet – http://www.centerwatch.com/)
Searched 3 March 2004

This search retrieved 110 references.

etanercept OR efalizumab OR raptiva OR enbrel {ALL-FIELDS}

Current Controlled Trials (Internet – http://controlled-trials.com/)
Searched 3 March 2004

This search retrieved 31 references.

etanercept OR efalizumab OR raptiva OR enbrel

ClinicalTrials.gov (Internet – http://clinicaltrials.gov/)
Searched 3 March 2004

This search retrieved 15 references.

etanercept OR efalizumab OR raptiva OR enbrel

ISI Science and Technology Proceedings (Web of Knowledge)
1990–2004 (28 February update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981–2004 (29 February update) – **http://wos.mimas.ac.uk/**

The search of ISI Science and Technology Proceedings retrieved 13 references.

The search of Social Science Citation Index and Science Citation Index retrieved 44 references.

#1 TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
#2 TS=((clinic* trial*) or placebo* or random* or (control* or prospectiv* or volunteer*))
#3 TS=((study or studies) SAME design*)
#4 TS=((ADVERSE same REACTION*) or (DRUG same ERUPTION*) or hypersensiti* or (hyper same sensiti*))
#5 TS=((treatment same emergent) or (safe or safety) or (tolerability or toxicity or adrs or harm*))
#6 TS=((undesirable* same outcome*) or (undesirable* same event*) or (undesirable* same reaction*) or (undesirable* same effect) or (undesirable* same effects))
#7 TS=((adverse same event*) or (adverse same effect) or (adverse same effects) or (adverse same outcome*) or (adverse same reaction*))
#8 TS=(drug same ABNORMALIT*)
#9 TS=((site same reaction*) or (injection* same reaction*) or erythema or itching or pain or swelling or swollen or swelled)
#10 TS=(headache* or head-ache* or (head same ache*) or (head same pain*) or chill or chills or fever or temperature or nausea or nauseous or sickness or vomiting or vomit or vomited)
#11 TS=(myalgia or (muscle* same pain) or infection* or immunocompromise* or (immuno-compromise*) or (side same effects) or (side same effect))
#12 TS=(immunosuppress* or (immuno-suppress*) or depression or depressive or depressed or (personality same disorder*))
#13 #1 or #2 or #3
#14 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#15 #13 and #14
#16 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
#17 #15 not #16
#18 TS=(etanercept or enbrel or efalizumab or raptiva)
#19 #17 and #18

All databases were searched from inception date.

Search C: RCTs of comparator treatments in psoriasis

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
1966–2004/01 week 4

This search retrieved 381 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$).ti,ab.
19. or/1-18
20. animals/
21. human/
22. 20 not (20 and 21)
23. 19 not 22
24. psoriasis/
25. (psoria$ or anti psoria$ or antipsoria$).mp.
26. or/24-25
27. exp Psoralens/
28. psoralen$.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 yr=1999-2004

EMBASE (OVID Online – http://www.ovid.com/)
1980–2004 week 6

This search retrieved 957 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$).ti,ab.
16. or/1-15
17. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18. exp ANIMAL/
19. Animal Experiment/
20. Nonhuman/
21. Human/
22. Human Experiment/
23. or/17-20
24. 21 or 22
25. 23 not (23 and 24)
26. 16 not 25
27. exp Psoriasis/
28. (psoria$ 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 yr=1999-2004

National Research Register (NRR) (CD-ROM)
2003 Issue 4

This search retrieved 93 references.

#1 PSORIASIS single term (MeSH)
#2 ((PSORIA* or ANTI-PSORIA*) or ANTIPSORIA*)
#3 PSORALENS explode all trees (MeSH)
#4 (PSORALEN* or ((((PHOTOTHERAP* or PHOTO-THERAP*) or PHOTOCHEMOTHERAP*) or PHOTO-CHEMOTHERAP*) or PHOTO-CHEMO-THERAP*))
#5 (PHOTOTHERAPY single term (MeSH) or HELIOTHERAPY single term (MeSH) or PHOTOCHEMOTHERAPY single term (MeSH))
#6 (ULTRAVIOLET-THERAPY single term (MeSH) or PUVA-THERAPY single term (MeSH))
#7 (((((((PUVA or ULTRAVIOLET-A) or ULTRA-VIOLET-A) or UVA) or UVB) or ULTRAVIOLET-B) or ULTRA-VIOLET-B) or (NBUVB or BBUVB))
#8 ((NARROWBAND next UVB) or (NARROWBAND next ULTRAVIOLET) or (NARROW-BAND NEXT UVB) or (NARROW-BAND next ULTRAVIOLET next B))
#9 ((((NARROWBAND next UVB) or (NARROWBAND next ULTRAVIOLET)) or (NARROW-BAND next UVB)) or (NARROW-BAND next ULTRAVIOLET))
#10 ((BROADBAND next UVB) or (BROADBAND next ULTRAVIOLET)) or (BROAD-BAND next UVB)) or (BROAD-BAND next ULTRAVIOLET)) or (PNBUVB or REPUVA))
#11 ((MOP:TI or METHOXYPSORALEN*) or ACITRETIN single term (MeSH))
#12 ((RETINOIDS single term (MeSH) or ETRETINATE single term (MeSH)) or VITAMIN-A single term (MeSH))
#13 (TRETINOIN:ME or ((RETINOID* or ACITRETIN*) or ETRETINATE*))
#14 ((TMP:TI or TRIMETHYLPSORALEN) or CYCLOSPORINS:ME)
#15 (((CYCLOSPORIN* or CICLOSPORIN*) or CSA) or HYDROXYUREA single term (MeSH))
#16 ((HYDROXYUREA* or HYDROXYCARBAMIDE*) or (FUMARATE* or ((FUMARIC next ACID) next ESTER*)))
#17 ((FUMADERM or FUMARATES single term (MeSH)) or ((DMFAE or DIMETHYLFUMAR*) or MONOETHYLFUMAR*))
#18 ((((MEFAE-CA or MEFAE-MG) or MEFAE-NA) or MEFAE-ZN) or (OHFAE or ((OCTYL next HYDROGEN) next FUMAR*)))
#19 (ANTHRALIN single term (MeSH) or (DITHRANOL or ANTHRALIN))
#20 ((GOECKERMAN next METHOD*) or (GOECKERMAN next REGIME*))

#21 ((((((INGRAM next THERAPY) or (INGRAM next THERAPIES)) or (INGRAM next TREATMENT)) or (INGRAM next TREATMENTS)) or (INGRAM next METHOD*)) or (INGRAM next REGIME*))
#22 (METHOTREXATE single term (MeSH) or METHOTREXATE)
#23 (((((((((#3 or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12)
#24 (((((((((#13 or #14) or #15) or #16) or #17) or #18) or #19) or #20) or #21) or #22)
#25 (#23 or #24)
#26 (#1 or #2)
#27 (#25 and #26) limited to Start Date 1999-2004

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
2004 Issue 1

This search retrieved 124 references.

#1 PSORIASIS single term (MeSH)
#2 (psoria* or anti-psoria* or antipsoria*)
#3 (#1 or #2)
#4 PSORALENS explode all trees (MeSH)
#5 psoralen*
#6 (phototherap* or photo-therap* or photochemotherap* or photo-chemotherap* or photo-chemo-therap*)
#7 PHOTOTHERAPY single term (MeSH)
#8 HELIOTHERAPY single term (MeSH)
#9 PHOTOCHEMOTHERAPY single term (MeSH)
#10 ULTRAVIOLET THERAPY single term (MeSH)
#11 PUVA THERAPY single term (MeSH)
#12 (puva or ultraviolet-a or ultra-violet-a or uva or uvb or ultraviolet-b or ultra-violet-b)
#13 (nbuvb or bbuvb)
#14 ((narrowband next uvb) or (narrowband next ultraviolet) or (narrow-band next uvb) or (narrow-band next ultraviolet next b))
#15 ((broadband next uvb) or (broadband next ultraviolet) or (broad-band next uvb) or (broad-band next ultraviolet))
#16 (pnbuvb or repuva)
#17 mop:ti
#18 methoxypsoralen*
#19 ACITRETIN single term (MeSH)
#20 RETINOIDS single term (MeSH)
#21 ETRETINATE single term (MeSH)
#22 vitamin-a
#23 VITAMIN A single term (MeSH)
#24 TRETINOIN single term (MeSH)
#25 (retinoid* or acitretin* or etretinate*)
#26 tmp:ti
#27 trimethylpsoralen
#28 CYCLOSPORINS single term (MeSH)
#29 (cyclosporin* or ciclosporin* or csa)
#30 HYDROXYUREA single term (MeSH)
#31 (hydroxyurea* or hydroxycarbamide*)
#32 (fumarate* or (fumaric next acid next ester*))
#33 fumaderm
#34 FUMARATES single term (MeSH)
#35 (dmfae or dimethylfumar* or monoethylfumar*)
#36 (mefae-ca or mefae-mg or mefae-na or mefae-zn)
#37 (ohfae or (octyl next hydrogen next fumar*))
#38 ANTHRALIN single term (MeSH)
#39 (dithranol or anthralin)
#40 ((goeckerman next therapy) or (goeckerman next treatments))
#41 ((goeckerman next therapies) or (goeckerman next treatment))
#42 ((goeckerman next method*) or (goeckerman next regime*))
#43 ((ingram next therapy) or (ingram next therapies) or (ingram next treatment) or (ingram next treatments) or (ingram next method*) or (ingram next regime*))
#44 METHOTREXATE single term (MeSH)
#45 methotrexate
#46 (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#47 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
#48 (#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
#49 (#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48)
#50 (#3 and #49)
#51 (#3 and #49) (1999 to current date)

CenterWatch (Internet – http://www.centerwatch.com/)
Searched 12 February 2004

This search retrieved 309 references.

etanercept OR efalizumab OR raptiva OR enbrel {ALL-FIELDS}

Current Controlled Trials (Internet – http://controlled-trials.com/)
Searched 12 February 2004

This search retrieved 75 references.

etanercept OR efalizumab OR raptiva OR enbrel

ClinicalTrials.gov (Internet – http://clinicaltrials.gov/)
Searched 12 February 2004

This search retrieved seven references.

etanercept OR efalizumab OR raptiva OR enbrel

ISI Science and Technology Proceedings (Web of Knowledge)
1990–2004 (6 February update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981–2004 – **http://wos.mimas.ac.uk/**

The search of ISI Science and Technology Proceedings retrieved 80 references.

The search of Social Science Citation Index and Science Citation Index retrieved 119 references.

#1 TS=(Psoria* or anti-psoria* or antipsoria*)
#2 TS=(psoralen* or phototherap* or photo-therap* or photochemotherap* or photo-chemotherap* or photo-chemo-therap*)
#3 TS=(puva or ultraviolet-A or ultra-violet-A or UVA or UVB or ultraviolet-B or ultra-violet-B or NBUVB or BBUVB)
#4 TS=((narrowband or narrow-band) SAME (UVB or ultraviolet))
#5 TS=((broadband or broad-band) SAME (UVB or ultraviolet))
#6 TS=(pnbuvb or repuva or MOP or methoxypsoralen* or retinoid* or acitretin* or etretinate*)
#7 TS=((vitamin-A SAME deriv*) or (synthet* SAME vitamin-A))
#8 TS=(tmp or trimethylpsoralen or cyclosporin* or ciclosporin* or csa or fumaderm)
#9 TS=(hydroxyurea* or hydroxycarbamide* or fumarate* or (fumaric SAME acid SAME ester*))
#10 TS=(dmfae or dimethylfumar* or monoethylfumar* or mefae-ca or mefae-mg or mefae-na or mefae-zn)
#11 TS=(ohfae or (octyl SAME hydrogen SAME fumar*) or dithranol or anthralin or methotrexate)
#12 TS=(goeckerman or ingram)
#13 TS=((animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea))
#14 #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#15 #1 and #14
#16 #15 not #13

Search D: reports of adverse events of comparator treatments

The following resources were examined for references to adverse events:

- BMJ Publishing Group. *Clinical evidence*. London: BMJ Publishing Group; 2004.
- Dukes MNG and Aronson JK, editors. *Meyler's side effects of drugs: an encyclopedia of adverse reactions and interactions*. 14th ed. Oxford: Elsevier; 2000.
- British Medical Association. *British National Formulary, No. 47*. London: British Medical Association; 2004. URL: http://bnf.org.
- Sweetman SC, editor. *Martindale: the complete drug reference [CD-ROM]*. London: Pharmaceutical Press; 2002.
- EMC Trust. *Medicines compendium [CD-ROM]*. Alton: Virtual Health Network; Version 3.4, 3rd quarter 2003.
- Aronson JK, editor. *Side effects of drugs annual*. Oxford: Elsevier; 2004.
- United States Pharmacopeial Convention. *USPDI, vol. 1: drug information for the health care professional*. Rockville, MD: United States Pharmacopeial Convention; 2004.

Search E: RCTs of infliximab in psoriasis

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
1966–2004/03 week 2

This search retrieved 80 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$).ti,ab.
26. or/24-25
27. (letter or comment or editorial).pt.
28. (infliximab or remicade).mp.
29. 23 and 26 and 28
30. 29 not 27

EMBASE (OVID Online – http://www.ovid.com/)
1980–2004 week 11

This search retrieved 183 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$).ti,ab.
16. or/1-15
17. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18. exp ANIMAL/
19. Animal Experiment/
20. Nonhuman/
21. Human/
22. Human Experiment/
23. or/17-20
24. 21 or 22
25. 23 not (23 and 24)
26. 16 not 25
27. exp Psoriasis/
28. (psoria$ or anti psoria$ or antipsoria$).ti,ab.
29. or/27-28
30. Infliximab/
31. (infliximab or remicade).ti,ab.
32. or/30-31
33. 26 and 29 and 32

National Research Register (NRR) (CD-ROM)
2004 Issue 1

This search retrieved one reference.

#1 PSORIASIS single term (MeSH)
#2 ((PSORIA* or ANTI-PSORIA*) or ANTIPSORIA*)
#3 (#1 or #2)
#4 (INFLIXIMAB or REMICADE)
#5 (#3 and #4)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
2004 Issue 1

This search retrieved four references.

#1 PSORIASIS single term (MeSH)
#2 (psoria* or anti-psoria* or antipsoria*)
#3 (#1 or #2)
#4 (infliximab or remicade)
#5 (#3 and #4)

ISI Science and Technology Proceedings (Web of Knowledge)
1990–2004 (17 March update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981–2004 (15 March update) – **http://wos.mimas.ac.uk/**

The search of ISI Science and Technology Proceedings retrieved 19 references.

The search of Social Science Citation Index and Science Citation Index retrieved 134 references.

#1 TS=(Psoria* or anti-psoria* or antipsoria*)
#2 TS=(infliximab or remicade)
#3 #1 and #2
#4 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
#5 #3 not #4

All databases were searched from inception date.

Cost-effectiveness

Searching for the cost-effectiveness component of this review was addressed by several separate searches to identify:

- reports of economic evaluations of etanercept or efalizumab in psoriasis
- reports of economic evaluations of comparator treatments in psoriasis
- reports of QoL measures in psoriasis.

Internet searches to locate reports of economic evaluations of etanercept or efalizumab in psoriasis

- reports of treatment pathways for psoriasis
- reports of treatment pathways for psoriasis (on the Internet)
- guidelines for psoriasis (on the Internet)
- to locate economic models for psoriasis.

Separate strategies were devised for each topic. Full details of the databases searched and search strategies used are provided below.

Search 1: economic evaluations of etanercept or efalizumab in psoriasis

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
1966–2004/02 week 1

This search retrieved five references.

1 economics/
2 exp "Costs and Cost Analysis"/
3 VALUE OF LIFE/ec {Economics}
4 economics, dental/
5 exp economics, hospital/
6 economics, medical/
7 economics, nursing/
8 economics, pharmaceutical/
9 or/1-8
10 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).tw.
11 (expenditure$ not energy).tw.
12 (value adj1 money).tw.
13 budget$.tw.
14 or/10-13
15 9 or 14
16 letter.pt.
17 editorial.pt.
18 historical article.pt.
19 or/16-18
20 15 not 19
21 animals/
22 human/
23 21 not (21 and 22)
24 20 not 23
25 (metabolic adj cost).ti,ab,sh.
26 ((energy or oxygen) adj cost).ti,ab,sh.
27 24 not (25 or 26)
28 psoriasis/
29 psoria$.mp.
30 antipsoria$.mp.
31 anti psoria$.mp.
32 or/28-31
33 etanercept.mp.
34 enbrel.mp.
35 efalizumab.mp.
36 raptiva.mp.
37 or/33-36
38 27 and 32 and 37

EMBASE (OVID Online – http://www.ovid.com/)
1980–2004 week 7

This search retrieved 113 references.

1. economics/ or exp health economics/
2. cost/ or exp health care cost/
3. exp fee/ or exp health insurance/ or exp pharmacoeconomics/ or health care organization/ or exp health care quality/
4. economic aspect/ or budget.mp.
5. economic aspect/ or budget/
6. exp disease management/
7. or/1-6
8. (econom$ or cost or costs or costly or costing or costed or price or prices or pricing or pharmacoeconom$).tw.
9. (expenditure$ not energy).tw.
10. (value adj5 money).tw.
11. budget$.tw.
12. or/9-11
13. 7 or 12
14. 13 not (editorial or letter or note).pt.
15. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
16. Human/ or Human Experiment/
17. 15 not (15 and 16)
18. 14 not 17
19. (metabolic adj cost).mp.
20. ((energy or oxygen) adj cost).mp.
21. 18 not (19 or 20)
22. exp Psoriasis/
23. (psoria$ or anti psoria$ or antipsoria$).mp.
24. or/22-23
25. Etanercept/
26. Efalizumab/
27. (etanercept or efalizumab or enbrel or raptiva).mp.
28. or/25-27
29. 21 and 24 and 28

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
2004 Issue 1

This search retrieved six references.

1. PSORIASIS single term (MeSH)
2. (psoria* or anti-psoria* or antipsoria*)
3. (#1 or #2)
4. (etanercept or efalizumab or enbrel or raptiva)
5. (#3 and #4)

NHS Economic Evaluation Database (NHS EED) (CRD administration database)
1990–2004/02

This search retrieved no references.

1. s psoria$ or anti(w1)psoria$ or antipsoria$
2. s (etanercept or efalizumab or enbrel or raptiva)
3. s s1 and s2

Health Economic Evaluation Database (HEED) (CD-ROM)
February 2004

This search retrieved no references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics or antipsoriasis or antipsoriatic or antipsoriatics
AND
etanercept or efalizumab or enbrel or raptiva

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/)
1969–2004/01

This search retrieved no references.

1. PSORIASIS
2. psoria* or anti-psoria* or antipsoria*
3. (psoria* or anti-psoria* or antipsoria*) and (PSORIASIS)
4. (etanercept or efalizumab or enbrel or raptiva)
5. ((etanercept or efalizumab or enbrel or raptiva)) and ((psoria* or anti-psoria* or antipsoria*) or (PSORIASIS))

ISI Science and Technology Proceedings (Web of Knowledge)
1990–2004 (13 February update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981–2004 (15 February update) – **http://wos.mimas.ac.uk/**

The search of ISI Science and Technology Proceedings retrieved no references.

The search of Social Science Citation Index and Science Citation Index retrieved seven references.

#1 TS=((Psoria* or anti-psoria* or antipsoria*))
#2 TS=(etanercept or enbrel or efalizumab or raptiva)
#3 #1 and #2
#4 TS=((econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom* or budget*))
#5 #3 and #4

All databases were searched from inception date.

Search 2: economic evaluations of comparator treatments in psoriasis

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
1966–2004/03 week 4

This search retrieved 89 references.

1. economics/
2. exp "Costs and Cost Analysis"/
3. VALUE OF LIFE/
4. economics, dental/
5. exp economics, hospital/
6. economics, medical/
7. economics, nursing/
8. economics, pharmaceutical/
9. or/1-8
10. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).ti,ab.
11. (expenditure$ not energy).ti,ab.
12. (value adj1 money).ti,ab.
13. budget$.ti,ab.
14. or/10-13
15. 9 or 14
16. letter.pt.
17. editorial.pt.
18. historical article.pt.
19. or/16-18
20. 15 not 19
21. animals/
22. human/
23. 21 not (21 and 22)
24. 20 not 23
25. (metabolic adj cost).ti,ab.
26. ((energy or oxygen) adj cost).ti,ab.
27. 24 not (25 or 26)

28. psoriasis/
29. psoria$.ti,ab.
30. antipsoria$.ti,ab.
31. anti psoria$.ti,ab.
32. or/28-31
33. exp Psoralens/
34. psoralen$.mp.
35. puva.ti,ab.
36. (phototherap$ or photo therap$ or photochemotherap$ or photo chemotherap$ or photo chemo therap$).ti,ab.
37. Phototherapy/
38. Heliotherapy/
39. photochemotherapy/
40. ultraviolet therapy/
41. puva therapy/
42. (puva or ultraviolet A or ultra violet A or UVA or UVB or ultraviolet B or ultra violet B).ti,ab.
43. (NBUVB or BBUVB).ti,ab.
44. (pnbuvb or repuva).ti,ab.
45. MOP.mp.
46. methoxypsoralen$.mp.
47. Acitretin/
48. retinoids/
49. etretinate/
50. exp vitamin A/
51. (retinoid$ or acitretin$ or etretinate$ or vitamin A deriv$).mp.
52. synthet$ vitamin A.mp.
53. tmp.mp.
54. trimethylpsoralen.mp.
55. exp Cyclosporins/
56. (cyclosporin$ or csa or cya or cyc-a or ciclosporin$ or sandimmun$).mp.
57. Hydroxyurea/
58. (hydroxyurea$ or hydroxycarbamide$).mp.
59. (fumarate$ or fumaric acid ester$).mp.
60. fumaderm.mp.
61. Fumarates/
62. (dmfae or dimethylfumar$ or monoethylfumar$).mp.
63. (mefae-ca or mefae-mg or mefae-na or mefae-zn).mp.
64. (ohfae or octyl hydrogen fumar$).mp.
65. Anthralin/
66. (dithranol or anthralin).mp.
67. (goeckerman adj1 (therap$ or treatment$ or method$ or regime$)).ti,ab.
68. (ingram adj1 (therap$ or treatment$ or method$ or regime$)).ti,ab.
69. Methotrexate/ or (methotrexate or mtx).mp.
70. (infliximab or remicade).mp.
71. or/33-70
72. 27 and 32 and 71

EMBASE (OVID Online – http://www.ovid.com/)
1980–2004 week 13

This search retrieved 688 references.

1. economics/ or exp health economics/
2. cost/ or exp health care cost/
3. exp fee/ or exp health insurance/ or exp pharmacoeconomics/ or health care organization/ or exp health care quality/
4. economic aspect/ or budget.mp. {mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name}
5. economic aspect/ or budget/
6. exp disease management/
7. or/1-6
8. (econom$ or cost or costs or costly or costing or costed or price or prices or pricing or pharmacoeconom$).ti,ab.
9. (expenditure$ not energy).ti,ab.
10. (value adj5 money).ti,ab.
11. budget$.ti,ab.
12. or/9-11
13. 7 or 12
14. 13 not (editorial or letter or note).pt.
15. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
16. Human/ or Human Experiment/
17. 15 not (15 and 16)
18. 14 not 17
19. (metabolic adj cost).ti,ab.
20. ((energy or oxygen) adj cost).ti,ab.
21. 18 not (19 or 20)
22. exp Psoriasis/
23. (psoria$ or anti psoria$ or antipsoria$).ti,ab.
24. or/22-23
25. psoralen$.ti,ab.
26. puva.ti,ab.
27. (puva or ultraviolet A or ultra violet A or UVA or UVB or ultraviolet B or ultra violet B).ti,ab.
28. (NBUVB or BBUVB).ti,ab.
29. (pnbuvb or repuva).ti,ab.
30. MOP.ti,ab.
31. methoxypsoralen$.ti,ab.
32. (retinoid$ or acitretin$ or etretinate$ or vitamin A deriv$).ti,ab.
33. synthet$ vitamin A.ti,ab.
34. tmp.ti,ab.
35. trimethylpsoralen.ti,ab.
36. (cyclosporin$ or ciclosporin$ or csa or cya or cyc-a or ciclosporin$ or sandimmun$).ti,ab.
37. (hydroxyurea$ or hydroxycarbamide$).ti,ab.
38. (fumarate$ or fumaric acid ester$).ti,ab.
39. fumaderm.ti,ab.
40. (dmfae or dimethylfumar$ or monoethylfumar$).ti,ab.

41. (mefae-ca or mefae-mg or mefae-na or mefae-zn).ti,ab.
42. (ohfae or octyl hydrogen fumar$).ti,ab.
43. (dithranol or anthralin).ti,ab.
44. (goeckerman adj1 (therap$ or treatment$ or method$ or regime$)).ti,ab.
45. (ingram adj1 (therap$ or treatment$ or method$ or regime$)).ti,ab.
46. methotrexate.ti,ab.
47. (phototherap$ or photo therap$ or photochemotherap$ or photo chemotherap$ or photo chemo therap$).ti,ab.
48. psoralen/ or psoralen derivative/
49. phototherapy/ or photochemotherapy/ or puva/
50. ultraviolet radiation/ or ultraviolet a radiation/ or ultraviolet b radiation/
51. methoxsalen/ or methoxsalen derivative/
52. retinoid/ or etretin/ or etretinate/
53. retinol/ or retinol derivative/
54. Retinoic Acid/
55. Trimethylpsoralen/
56. Cyclosporin/
57. HYDROXYUREA/
58. fumaric acid/ or fumaric acid derivative/
59. fumaric acid dimethyl ester/ or fumaric acid ethyl ester/
60. dithranol/ or dithranol derivative/
61. METHOTREXATE/
62. antipsoriasis agent/ or 4' aminomethyl 4,5',8 trimethylpsoralen/ or fumaderm/ or psoralon/ or psorin/
63. or/25-62
64. 21 and 24 and 63

National Research Register (NRR) (CD-ROM)
2004 Issue 1

This search retrieved 99 references.

#1 PSORIASIS single term (MeSH)
#2 ((PSORIA* or ANTI-PSORIA*) or ANTIPSORIA*)
#3 PSORALENS explode all trees (MeSH)
#4 (PSORALEN* or ((((PHOTOTHERAP* or PHOTO-THERAP*) or PHOTOCHEMOTHERAP*) or PHOTO-CHEMOTHERAP*) or PHOTO-CHEMO-THERAP*))
#5 ((PHOTOTHERAPY single term (MeSH) or HELIOTHERAPY single term (MeSH)) or PHOTOCHEMOTHERAPY single term (MeSH))
#6 (ULTRAVIOLET-THERAPY single term (MeSH) or PUVA-THERAPY single term (MeSH))
#7 (((((((PUVA or ULTRAVIOLET-A) or ULTRA-VIOLET-A) or UVA) or UVB) or ULTRAVIOLET-B) or ULTRA-VIOLET-B) or (NBUVB or BBUVB))
#8 ((NARROWBAND next UVB) or (NARROWBAND next ULTRAVIOLET) or (NARROW-BAND next UVB) or (NARROW-BAND next ULTRAVIOLET next B))
#9 ((((NARROWBAND next UVB) or (NARROWBAND next ULTRAVIOLET)) or (NARROW-BAND next UVB)) or (NARROW-BAND next ULTRAVIOLET))
#10 (((((BROADBAND next UVB) or (BROADBAND next ULTRAVIOLET)) or (BROAD-BAND next UVB)) or (BROAD-BAND next ULTRAVIOLET)) or (PNBUVB or REPUVA))
#11 ((MOP:TI or METHOXYPSORALEN*) or ACITRETIN single term (MeSH))
#12 ((RETINOIDS single term (MeSH) or ETRETINATE single term (MeSH)) or VITAMIN-A single term (MeSH))
#13 (TRETINOIN single term (MeSH) or ((RETINOID* or ACITRETIN*) or ETRETINATE*))
#14 ((TMP:TI or TRIMETHYLPSORALEN) or CYCLOSPORINS single term (MeSH))
#15 (((CYCLOSPORIN* or CICLOSPORIN* or SANDIMMUN*) or CSA) or HYDROXYUREA single term (MeSH))
#16 ((HYDROXYUREA* or HYDROXYCARBAMIDE*) OR (FUMARATE* or ((FUMARIC next ACID) next ESTER*)))
#17 ((FUMADERM or FUMARATES single term (MeSH)) or ((DMFAE or DIMETHYLFUMAR*) or MONOETHYLFUMAR*))
#18 ((((MEFAE-CA or MEFAE-MG) or MEFAE-NA) or MEFAE-ZN) or (OHFAE or ((OCTYL next HYDROGEN) next FUMAR*)))
#19 (ANTHRALIN single term (MeSH) or (DITHRANOL or ANTHRALIN))
#20 ((GOECKERMAN next METHOD*) or (GOECKERMAN next REGIME*))
#21 ((((((INGRAM next THERAPY) or (INGRAM next THERAPIES)) or (INGRAM next TREATMENT)) or (INGRAM next TREATMENTS)) or (INGRAM next METHOD*)) or (INGRAM next REGIME*))
#22 (METHOTREXATE single term (MeSH) or METHOTREXATE or MTX)
#23 (((((((((#3 or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12)
#24 (((((((((#13 or #14) or #15) or #16) or #17) or #18) or #19) or #20) or #21) or #22)
#25 #23 or #24
#26 #1 or #2
#27 #26 and #27

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
2004 Issue 1

This search retrieved 652 references.

#1 PSORIASIS single term (MeSH)
#2 (psoria* or anti-psoria* or antipsoria*)
#3 (#1 or #2)
#4 PSORALENS explode all trees (MeSH)
#5 psoralen*
#6 (phototherap* or photo-therap* or photochemotherap* or photo-chemotherap* or photo-chemo-therap*)
#7 PHOTOTHERAPY single term (MeSH)
#8 HELIOTHERAPY single term (MeSH)
#9 PHOTOCHEMOTHERAPY single term (MeSH)
#10 ULTRAVIOLET THERAPY single term (MeSH)
#11 PUVA THERAPY single term (MeSH)
#12 (puva or ultraviolet-a or ultra-violet-a or uva or uvb or ultraviolet-b or ultra-violet-b)
#13 (nbuvb or bbuvb)
#14 ((narrowband next uvb) or (narrowband next ultraviolet) or (narrow-band next uvb) or (narrow-band next ultraviolet next b))
#15 ((broadband next uvb) or (broadband next ultraviolet) or (broad-band next uvb) or (broad-band next ultraviolet))
#16 (pnbuvb or repuva or infliximab or remicade)
#17 mop:ti
#18 methoxypsoralen*
#19 ACITRETIN single term (MeSH)
#20 RETINOIDS single term (MeSH)
#21 ETRETINATE single term (MeSH)
#22 vitamin-a
#23 VITAMIN A single term (MeSH)
#24 TRETINOIN single term (MeSH)
#25 (retinoid* or acitretin* or etretinate*)
#26 tmp:ti
#27 trimethylpsoralen
#28 CYCLOSPORINS single term (MeSH)
#29 (cyclosporin* or ciclosporin* or csa or sandimmun*)
#30 HYDROXYUREA single term (MeSH)
#31 (hydroxyurea* or hydroxycarbamide*)
#32 (fumarate* or (fumaric next acid next ester*))
#33 fumaderm
#34 FUMARATES single term (MeSH)
#35 (dmfae or dimethylfumar* or monoethylfumar*)
#36 (mefae-ca or mefae-mg or mefae-na or mefae-zn)
#37 (ohfae or (octyl next hydrogen next fumar*))
#38 ANTHRALIN single term (MeSH)
#39 (dithranol or anthralin)
#40 ((goeckerman next therapy) or (goeckerman next treatments))
#41 ((goeckerman next therapies) or (goeckerman next treatment))
#42 ((goeckerman next method*) or (goeckerman next regime*))
#43 ((ingram next therapy) or (ingram next therapies) or (ingram next treatment) or (ingram next treatments) or (ingram next method*) or (ingram next regime*))
#44 METHOTREXATE single term (MeSH)
#45 methotrexate or mtx
#46 (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#47 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
#48 (#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
#49 (#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48)
#50 (#3 and #49)

NHS Economic Evaluation Database (NHS EED) (CRD administration database)
1990–2004/04

This search retrieved seven references.

1. s psoria$ or antiw1)psoria$ or antipsoria$
2. s psoralen$ or puva or phototherap$ or photo(w)therap$ or photochemotherap$
3. s photo(w)chemotherap$ or photo(w)chemo(w)therap$ or Heliotherap$
4. s helio(w)therapy or ultraviolet or NBUVB or BBUVB or pnbuvb or repuva
5. s MOP or methoxypsoralen$ or Acitretin or retinoid$ or etretinate
6. s vitamin(w1)A or tmp or trimethylpsoralen
7. s cyclosporin$ or csa or cya or cyc(w1)a or ciclosporin$ or sandimmun$
8. s hydroxyurea$ or hydroxycarbamide$ or fumarate$ or fumaric(w)acid(w)ester$
9. s fumaderm or dmfae or dimethylfumar$ or monoethylfumar$
10. s mefae or ohfae or octyl(w)hydrogen(w)fumar$ or dithranol or anthralin
11. s goeckerman(w2)(therap$ or treatment$ or method$ or regime$)
12. s ingram(w2)(therap$ or treatment$ or method$ or regime$)
13. s methotrexate or mtx or infliximab or remicade

14. s s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13
15. s s1 and s14

Health Economic Evaluation Database (HEED) (CD-ROM)
May 2004

This search retrieved no references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics or antipsoriasis or antipsoriatic or antipsoriatics

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/)
1969–2004/03

This search retrieved one reference.

(psoria* or anti-psoria* or antipsoria*) and (PSORIASIS)

ISI Science and Technology Proceedings (Web of Knowledge)
1990–2004 (26 March update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981–2004 (29 March update) – **http://wos.mimas.ac.uk/**

The search of ISI Science and Technology Proceedings retrieved one reference.

The search of Social Science Citation Index and Science Citation Index retrieved 28 references.

#1 TS=(Psoria* or anti-psoria* or antipsoria*)
#2 TS=(psoralen* or phototherap* or photo-therap* or photochemotherap* or photo-chemotherap* or photo-chemo-therap*)
#3 TS=(puva or ultraviolet-A or ultra-violet-A or UVA or UVB or ultraviolet-B or ultra-violet-B or NBUVB or BBUVB)
#4 TS=((narrowband or narrow-band) SAME (UVB or ultraviolet))
#5 TS=((broadband or broad-band) SAME (UVB or ultraviolet))
#6 TS=(pnbuvb or repuva or MOP or methoxypsoralen* or retinoid* or acitretin* or etretinate*)
#7 TS=((vitamin-A SAME deriv*) or (synthet* SAME vitamin-A))
#8 TS=(tmp or trimethylpsoralen or cyclosporin* or ciclosporin* or csa or fumaderm)
#9 TS=(hydroxyurea* or hydroxycarbamide* or fumarate* or (fumaric SAME acid SAME ester*))
#10 TS=(dmfae or dimethylfumar* or monoethylfumar* or mefae-ca or mefae-mg or mefae-na or mefae-zn)
#11 TS=(ohfae or (octyl SAME hydrogen SAME fumar*) or dithranol or anthralin or methotrexate)
#12 TS=(goeckerman or ingram)
#13 TS=(sandimmun* or infliximab or remicade or hydroxycarbamide)
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 TS=((econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom* or budget*))
#16 #14 and #15
#17 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
#18 #16 not #17

All databases were searched from inception date.

Search 3: QoL measures in psoriasis

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
1966–2004/02 week 2

This search retrieved 253 references.

1. (sf36 or sf 36).tw.
2. (eq5d or eq 5d or euroqol or euro qol).tw.
3. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
4. (hrql or hrqol or h qol or hql or hqol).tw.
5. (hye or hyes or health$ year$ equivalent$ or health utilit$).tw.
6. health related quality of life.tw.
7. rosser.tw.
8. (standard gamble$ or time trade off or time tradeoff or tto or willingness to pay).tw.
9. (utilities or utility or daly or disability adjusted life).tw.
10. quality of life/ or (quality of life or life quality).tw.
11. health status indicators/
12. quality adjusted life year/
13. (qaly$ or quality adjusted).tw.
14. (qwb$ or hui or hui1 or hui2 or hui3 or qwi).tw.
15. (quality of wellbeing or quality of well being).tw.
16. preference based.tw.

17. (dermatology life quality index or health status).tw.
18. (state adj2 (value or values or valuing or valued)).tw.
19. (dlqi or hspv).ti,ab.
20. general health questionnaire.tw.
21. nottingham health profile.tw.
22. patient generated index.tw.
23. sickness impact profile.tw.
24. (ghq or nhp or pgi or sip or uksip or wtp).ti,ab.
25. psoriasis/
26. psoria$.mp.
27. antipsoria$.mp.
28. anti psoria$.mp.
29. or/25-28
30. or/1-24
31. 30 and 29
32. limit 31 to yr=1990-2004
33. animals/
34. human/
35. 33 not (33 and 34)
36. 32 not 35
37. 36 not (letter or editorial or comment).pt.

EMBASE (OVID Online – http://www.ovid.com/)
1980–2004 week 8

This search retrieved 320 references.

1. (sf36 or sf 36).tw.
2. (eq5d or eq 5d or euroqol or euro qol).tw.
3. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
4. (hrql or hrqol or h qol or hql or hqol).tw.
5. (hye or hyes or health$ year$ equivalent$ or health utilit$).tw.
6. health related quality of life.tw.
7. rosser.tw.
8. (standard gamble$ or time trade off or time tradeoff or tto or willingness to pay).tw.
9. (utilities or utility or daly or disability adjusted life).tw.
10. (qaly$ or quality adjusted).tw.
11. (qwb$ or hui or hui1 or hui2 or hui3 or qwi).tw.
12. (quality of wellbeing or quality of well being).tw.
13. preference based.tw.
14. (dermatology life quality index or health status).tw.
15. (state adj2 (value or values or valuing or valued)).tw.
16. (dlqi or hspv).ti,ab.
17. general health questionnaire.tw.
18. nottingham health profile.tw.
19. patient generated index.tw.
20. sickness impact profile.tw.
21. (ghq or nhp or pgi or sip or uksip or wtp).ti,ab.
22. (quality of life or life quality).tw.
23. quality of life/ or quality adjusted life year/
24. or/1-23
25. exp Psoriasis/
26. (psoria$ or anti psoria$ or antipsoria$).mp.
27. or/25-26
28. 24 and 27
29. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (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.
30. Human/ or Human Experiment/
31. 29 not (29 and 30)
32. 28 not 31
33. 32 not (editorial or letter or note).pt.
34. limit 33 to yr=1990-2004

National Research Register (NRR) (CD-ROM)
2003 Issue 4

This search retrieved 24 references.

#1 PSORIASIS single term (MeSH)
#2 ((PSORIA* or ANTIPSORIA*) or ANTI-PSORIA*)
#3 (#1 or #2)
#4 (((((SF36 or SF-36) or EQ5D) or EQ-5D) or EUROQOL) or EURO-QOL)
#5 ((((SHORT next FORM-36) or SHORTFORM-36) OR (SF next THIRTYSIX)) or (SF next THIRTY-SIX))
#6 ((((SHORTFORM next THIRTYSIX) or (SHORTFORM next THIRTY-SIX)) or ((SHORT next FORM) next THIRTYSIX)) or ((SHORT next FORM) next THIRTY-SIX))
#7 (((((((HRQL or HRQOL) or H-QOL) or HQL) or HQOL) or HYE) or HYES) or ((HEALTH* next YEAR*) next EQUIVALENT*)) or (HEALTH next UTILIT*))
#8 ((((((HEALTH next RELATED) next QUALITY) next LIFE) or ROSSER) or (STANDARD next GAMBLE*)) or ((TIME next TRADE) next OFF))
#9 (((((((TIME next TRADEOFF) or TTO) or (WILLINGNESS next PAY)) or UTILITIES) or UTILITY) or DALY) or ((DISABILITY next ADJUSTED) next LIFE))
#10 ((QUALITY next LIFE) or (LIFE next QUALITY))

#11 QUALITY-OF-LIFE single term (MeSH)
#12 QUALITY-ADJUSTED-LIFE-YEARS single term (MeSH)
#13 HEALTH-STATUS-INDICATORS single term (MeSH)
#14 (((((((QALY* or (QUALITY next ADJUSTED)) or QWB*) or HUI) or HUI1) or HUI2) or HUI3) or QWI)
#15 (((QUALITY next WELLBEING) or (QUALITY next WELL-BEING)) OR (PREFERENCE next BASED))
#16 ((((DERMATOLOGY next LIFE) next QUALITY) next INDEX) or (HEALTH next STATUS))
#17 (DLQI or HSPV)
#18 ((((GENERAL next HEALTH) next QUESTIONNAIRE) or ((NOTTINGHAM next HEALTH) next PROFILE)) or ((PATIENT next GENERATED) next INDEX))
#19 (((((((SICKNESS next IMPACT) next PROFILE) or GHQ) or NHP) or PGI) or SIP) or UKSIP) or WTP)
#20 ((((STATE next VALUE) or (STATE next VALUES)) or (STATE next VALUING)) or (STATE NEXT VALUED))
#21 (((((((((#4 or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12) or #13)
#22 (((((((#14 or #15) or #16) or #17) or #18) or #19) or #20) or #21)
#23 (#3 and #22)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
2004 Issue 1

This search retrieved 913 references.

#1 (sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol)
#2 ((short next form-36) or shortform-36 or (sf next thirtysix) or (sf next thirty-six))
#3 ((shortform next thirtysix) or (shortform next thirty-six) or (short next form next thirtysix) or (short next form next thirty-six))
#4 (hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* next year* next equivalent*) or (health next utilit*))
#5 ((health next related next quality next life) or rosser or (standard next gamble*) or (time next trade next off))
#6 ((time next tradeoff) or tto or (willingness next pay) or utilities or utility or daly or (disability next adjusted next life))
#7 ((quality next life) or (life next quality))
#8 QUALITY OF LIFE single term (MeSH)
#9 QUALITY-ADJUSTED LIFE YEARS single term (MeSH)
#10 HEALTH STATUS INDICATORS single term (MeSH)
#11 (qaly* or (quality next adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)
#12 ((quality next wellbeing) or (quality next well-being) or (preference next based))
#13 ((dermatology next life next quality next index) or (health next status))
#14 (dlqi or hspv)
#15 ((general next health next questionnaire) or (nottingham next health next profile) or (patient next generated next index))
#16 ((sickness next impact next profile) or ghq or nhp or pgi or sip or uksip or wtp)
#17 ((state next value) or (state next values) or (state next valuing) or (state next valued))
#18 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#19 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#20 (psoria* or antipsoria* or anti-psoria*)
#21 PSORIASIS single term (MeSH)
#22 (#20 or #21)
#23 #22 and #19 (1990 to current date)

NHS Economic Evaluation Database (NHS EED) (CRD administration database)
1990–2004/02

This search retrieved 6 references.

1. s sf36 or sf(w)36 or eq5d or eq(w)5d or euroqol or euro(w)qol
2. s short(w)form(w)36 or shortform(w)36 or sf(w)thirtysix or sf(w)thirty(w)six
3. s shortform(w)thirtysix or shortform(w)thirty(w)six or short(w)form(w)thirtysix
4. s short(w)form(w)thirty(w)six or hrql or hrqol or h(w)qol or hql or hqol or hye or hyes
5. s health$(w)year$(w)equivalent$ or health(w)utilit$ or health(w)related(w)quality(w)life
6. s rosser or standard(w)gamble$ or time(w)trade(w)off or time(w)tradeoff
7. s tto or willingness(w)pay or utilities or utility or daly or disability(w)adjusted(w)life
8. s quality(w2)life or life(w)quality
9. s health(w)status(w)indicator$ or quality(w)adjusted(w)life(w)year$
10. s qaly$ or quality(w)adjusted or qwb$ or hui or hui1 or hui2 or hui3 or qwi
11. s quality(w2)wellbeing or quality(w2)well(w)being or preference(w)based

12. s dermatology(w)life(w)quality(w)index or health(w)status
13. s (state(w2)(value or values or valuing or valued)) or dlqi or hspv
14. s general(w)health(w)questionnaire or nottingham(w)health(w)profile
15. s patient(w)generated(w)index or sickness(w)impact(w)profile
16. s ghq or nhp or pgi or sip or uksip or wtp
17. s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14
18. s s15 or s16 or s17
19. s psoria$ or antipsoria$ or anti(w)psoria$
20. s s18 and s19
21. s 1990:2004/xyr
22. s s20 and s21

Health Economic Evaluation Database (HEED) (CD-ROM)
February 2004

This search retrieved no references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics or antipsoriasis or antipsoriatic or antipsoriatics

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/)
1969–2004/01

This search retrieved one reference.

1. (sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short form-36) or shortform-36 or (sf thirtysix) or (sf thirty-six))or((shortform thirtysix) or (shortform thirty-six) or (short form thirtysix) or (short form thirty-six))or(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* year* equivalent*) or (health utilit*))
2. ((health related quality life) or rosser or (standard gamble*) or (time trade off) or (time tradeoff))or(tto or (willingness pay) or utilities or utility or daly or (disability adjusted life) or (quality of life))or((life quality) or qaly* or (quality adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)
3. ((quality wellbeing) or (quality well-being) or (preference based) or (dermatology life quality index))or((health status) or (state value) or (state values) or (state valuing) or (state valued) or dlqi or hspv)
4. ((general health questionnaire) or (nottingham health profile) or (patient generated index))or((sickness impact profile) or ghq or nhp or pgi or sip or uksip or wtp)
5. (((general health questionnaire) or (nottingham health profile) or (patient generated index))or((sickness impact profile) or ghq or nhp or pgi or sip or uksip or wtp)) or (((quality wellbeing) or (quality well-being) or (preference based) or (dermatology life quality index))or((health status) or (state value) or (state values) or (state valuing) or (state valued) or dlqi or hspv)) or (((health related quality life) or rosser or (standard gamble*) or (time trade off) or (time tradeoff))or(tto or (willingness pay) or utilities or utility or daly or (disability adjusted life) or (quality of life))or((life quality) or qaly* or (quality adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)) or ((sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short form-36) or shortform-36 or (sf thirtysix) or (sf thirty-six))or((shortform thirtysix) or (shortform thirty-six) or (short form thirtysix) or (short form thirty-six))or(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* year* equivalent*) or (health utilit*)))
6. psoria* or antipsoria* or anti-psoria*
7. (psoria* or antipsoria* or anti-psoria*) and ((((general health questionnaire) or (nottingham health profile) or (patient generated index))or((sickness impact profile) or ghq or nhp or pgi or sip or uksip or wtp)) or (((quality wellbeing) or (quality well-being) or (preference based) or (dermatology life quality index))or((health status) or (state value) or (state values) or (state valuing) or (state valued) or dlqi or hspv)) or (((health related quality life) or rosser or (standard gamble*) or (time trade off) or (time tradeoff))or(tto or (willingness pay) or utilities or utility or daly or (disability adjusted life) or (quality of life))or((life quality) or qaly* or (quality adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)) or ((sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short form-36) or shortform-36 or (sf thirtysix) or (sf thirty-six))or((shortform thirtysix) or (shortform thirty-six) or (short form thirtysix) or (short form thirty-six))or(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* year* equivalent*) or (health utilit*))))

ISI Science and Technology Proceedings (Web of Knowledge)
1990–2004 (February update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981–2004 (22 February update) – **http://wos.mimas.ac.uk/**

The search of ISI Science and Technology Proceedings retrieved 27 references.

The search of Social Science Citation Index and Science Citation Index retrieved 302 references.

#1 TS=(sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short SAME form-36) or shortform-36 or (sf SAME thirtysix) or (sf SAME thirty-six))
#2 TS=((shortform SAME thirtysix) or (shortform SAME thirty-six) or (short SAME form SAME thirtysix) or (short SAME form SAME thirty-six))
#3 TS=(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* SAME year* SAME equivalent*) or (health SAME utilit*))
#4 TS=(tto or (willingness SAME to SAME pay) or utilities or utility or daly or (disability SAME adjusted SAME life) or (quality SAME of SAME life))
#5 TS=((quality SAME of SAME wellbeing) or (quality SAME of SAME well-being) or (preference SAME based) or (dermatology SAME life SAME quality SAME index))
#6 TS=((health SAME status) or (state SAME value) or (state SAME values) or (state SAME valuing) or (state SAME valued) or dlqi or hspv)
#7 TS=((health SAME related SAME quality SAME life) or rosser or (standard SAME gamble*) or (time SAME trade SAME off) or (time SAME tradeoff))
#8 TS=((life SAME quality) or qaly* or (quality SAME adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)
#9 TS=((general SAME health SAME questionnaire) or (nottingham SAME health SAME profile) or (patient SAME generated SAME index))
#10 TS=((sickness SAME impact SAME profile) or ghq or nhp or pgi or sip or uksip or wtp)
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 TS=(psoria* or antipsoria* or anti-psoria*)
#13 #11 and #12
#14 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
#15 #13 not #14

All databases were searched from inception date.

Search 4: Internet searches to locate economic evaluations of etanercept or efalizumab in psoriasis

Google (http://www.google.co.uk)
Searched 8 March 2004

This search retrieved 1851 references.

The simple search interface was used. Owing to the high volume of hits, a pragmatic cut-off point was used. The first 100 references were saved from each set. The following keywords were searched in combination:

Etanercept	Psoriasis	Economic
Efalizumab	Psoriatic	Economics
Raptiva		Cost
Enbrel		Costs
		Costly
		Costing
		Price
		Prices
		Pricing
		Pharmacoeconomic
		Pharmacoeconomics

Organising Medical Networked Information (OMNI) (http://www.omni.ac.uk)
Searched 8 March 2004

This search retrieved three references.

etanercept AND (economic OR cost or price OR pricing OR pharmacoeconomic)
OR
efalizumab AND (economic OR cost or price OR pricing OR pharmacoeconomic)
OR
enbrel AND (economic OR cost or price OR pricing OR pharmacoeconomic)
OR
raptiva AND (economic OR cost or price OR pricing OR pharmacoeconomic)

Copernic (http://www.copernic.com)
Searched 4 March 2004

This search retrieved 68 references.

(economics or economic or cost or costs) and (etanercept or efalizumab or enbrel or raptiva)
OR
(costly or costing or price or prices) and (etanercept or efalizumab or enbrel or raptiva)
OR
(pricing or pharmacoeconomics or pharmacoeconomic) and (etanercept or efalizumab or enbrel or raptiva)

Search 5: treatment pathways for psoriasis

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
1966–2004/02 week 1

This search retrieved 112 references.

1. guideline.pt.
2. practice guideline.pt.
3. exp guidelines/
4. health planning guidelines/
5. treatment$ pathway$.mp.
6. treatment$ path way$.mp.
7. care pathway$.mp.
8. care path way$.mp.
9. clinical pathway$.mp.
10. clinical path way$.mp.
11. treatment$ path$.mp.
12. (treatment$ route$ or guideline$ or guide line$).mp.
13. or/1-12
14. psoriasis/
15. psoria$.mp.
16. antipsoria$.mp.
17. anti psoria$.mp.
18. or/14-17
19. 13 and 18

EMBASE (OVID Online – http://www.ovid.com/)
1980–2004 week 7

This search retrieved 220 references.

1. exp practice guideline/
2. (treatment pathway$ or treatment path way$).mp.
3. (care pathway$ or care path way$).mp.
4. (clinical path way$ or clinical pathway$).mp.
5. (treatment$ path$ or treatment$ route$).mp.
6. (guide line$ or guideline$).mp.
7. or/1-6
8. exp Psoriasis/
9. (psoria$ or anti psoria$ or antipsoria$).mp.
10. or/8-9
11. 7 and 10
12. limit 11 to yr=1990-2004

National Research Register (NRR) (CD-ROM)
2003 Issue 4

This search retrieved seven references.

#1 PSORIASIS single term (MeSH)
#2 ((PSORIA* or ANTIPSORIA*) or ANTI-PSORIA*)
#3 (#1 or #2)
#4 GUIDELINES explode all trees (MeSH)
#5 HEALTH-PLANNING-GUIDELINES single term (MeSH)
#6 ((TREATMENT next PATH*) or (TREATMENTS next PATH*))
#7 ((((CARE next PATH*) or (CLINICAL next PATH*)) or GUIDELINE*) or GUIDE-LINE*)
#8 ((TREATMENT next ROUTE*) or (TREATMENTS next ROUTE*))
#9 ((((#4 or #5) or #6) or #7) or #8)
#10 (#3 and #9) (limited to start date = 1990-2004)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
2004 Issue 1

This search retrieved nine references.

#1 GUIDELINES explode all trees (MeSH)
#2 HEALTH PLANNING GUIDELINES single term (MeSH)
#3 ((treatment next pathway*) or (treatment next path-way*) or (treatments next pathway*) or (treatments next path-way*))
#4 ((care next pathway*) or (care next path-way*) or (clinical next pathway*) or (clinical next path-way*))
#5 ((treatment next path*) or (treatments next path*) or (treatment next route*) or (treatments next route*))
#6 (guideline* or guide-line*)
#7 (#1 or #2 or #3 or #4 or #5 or #6)
#8 PSORIASIS single term (MeSH)
#9 (psoria* or antipsoria* or anti-psoria*)
#10 (#8 or #9)
#11 (#7 and #10)
#12 #11 (1990 to current date)

NHS Economic Evaluation Database (NHS EED) (CRD administration database)
1990–2004/02

This search retrieved seven references.

1. s treatment$(w)pathway$ or treatment$(w)path(w)way$
2. s care(w)pathway$ or care(w)path(w)way$
3. s clinical(w)pathway$ or clinical(w)path(w)way$
4. s treatment$(w)path$ or treatment$(w)route$ or guideline$ or guide(w)line$
5. s s1 or s2 or s3 or s4
6. s psoria$ or antipsoria$ or anti(w)psoria$
7. s s5 and s6
8. s 1990:2004/xyr
9. s s7 and s8

Health Economic Evaluation Database (HEED) (CD-ROM)
February 2004

This search retrieved seven references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics or antipsoriasis or antipsoriatic or antipsoriatics

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/)
1969–2004/01

This search retrieved no references.

1. PSORIASIS
2. psoria* or antipsoria* or anti-psoria*
3. (psoria* or antipsoria* or anti-psoria*) or (PSORIASIS)
4. pathway* or path-way* or route* or guideline* or guide-line* or path*
5. (pathway* or path-way* or route* or guideline* or guide-line* or path*) and ((psoria* or antipsoria* or anti-psoria*) or (PSORIASIS))

ISI Science and Technology Proceedings (Web of Knowledge)
1990–2004 (15 February update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981–2004 (15 Februray update) – **http://wos.mimas.ac.uk/**

The search of ISI Science and Technology Proceedings retrieved seven references.

The search of Social Science Citation Index and Science Citation Index retrieved 244 references.

#1 TS=((treatment* same pathway*) or (treatment* same path-way*) or (care same pathway*) or (care same path-way*))
#2 TS=((clinical same pathway*) or (clinical same path-way*) or (treatment* same path*) or (treatment* same route*))
#3 TS=(guideline*)
#4 TS=(guide-line*)
#5 #1 or #2 or #3 or #4
#6 TS=(psoria* or antipsoria* or anti-psoria*)
#7 #5 and #6

All databases were searched from 1990 to date.

Search 6: Internet searches to locate reports of treatment pathways for psoriasis

Google (http://www.google.co.uk)
Searched 8 March 2004

This search retrieved 1600 references.

The simple search interface was used. Owing to the high volume of hits, a pragmatic cut-off point was used. The first 100 references were saved from each set. The following keywords were searched in combination:

Psoriasis	Guideline
Psoriatic	Guidelines
	Path
	Paths
	Pathway
	Pathways
	Route
	Routes

Organising Medical Networked Information (OMNI) (http://www.omni.ac.uk)
Searched 8 March 2004

This search retrieved two references.

psoriasis and (path or paths or pathways or pathway or path-way or path-ways or route or routes or guideline or guidelines or guide-line or guide-lines)
OR
Psoriatic and (path or paths or pathways or pathway or path-way or path-ways or route or routes or guideline or guidelines or guide-line or guide-lines)

Copernic (http://www.copernic.com)
Searched 8 March 2004

This search retrieved 48 references.

psoriasis and (path or paths or pathways or pathway or path-way or path-ways or route or routes or guideline or guidelines or guide-line or guide-lines)
OR
Psoriatic and (path or paths or pathways or pathway or path-way or path-ways or route or routes or guideline or guidelines or guide-line or guide-lines)

All resources were searched from inception date.

Search 7: Internet searches to locate guidelines for psoriasis

The websites below were searched using the following keywords:
Psoriasis
Psoriatic

NeLH Guidelines Finder
http://rms.nelh.nhs.uk/guidelinesfinder/
Searched 9 March 2004

This search retrieved two references.

eGuidelines
http://www.eguidelines.co.uk/
Searched 9 March 2004

This search retrieved 25 references.

Health Services/Technology Assessment Text (HSTAT)
http://hstat.nlm.nih.gov/hq/Hquest/screen/HquestHome/s/52877
Searched 11 March 2004

This search retrieved 14 references.

National Guidelines Clearinghouse
http://www.guideline.gov/
Searched 11 March 2004

This search retrieved six references.

Scottish Intercollegiate Guidelines Network (SIGN)
http://www.sign.ac.uk/index.html
Searched 11 March 2004

This search retrieved three references.

Clinicians Health Channel
http://www.clinicians.vic.gov.au/guidelines/index.html
Searched 12 March 2004

This search retrieved no references.

Medical Services Advisory Committee (MSAC)
http://www.health.gov.au/msac/msacapps.htm
Searched 12 March 2004

This search retrieved no references.

New Zealand Health Technology Assessment (NZHTA)
http://nzhta.chmeds.ac.nz/
Searched 12 March 2004

This search retrieved 1 reference.

National Health and Medical Research Council (NHMRC)
http://www.health.gov.au/nhmrc/publications/cphome.htm
Searched 12 March 2004

This search retrieved no references.

New Zealand Guidelines Group (NZGG)
http://www.nzgg.org.nz/
Searched 12 March 2004

This search retrieved no references.

Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP)
http://www.surgeons.org/asernip-s/
Searched 12 March 2004

This search retrieved no references.

Centre for Clinical Effectiveness (CCE – Monash)
http://www.med.monash.edu.au/healthservices/cce/
Searched 12 March 2004

This search retrieved one reference.

All resources were searched from inception date.

Search 8: economic models for psoriasis

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
1966–2004/02 week 4

This search retrieved 85 references.

1. exp decision support techniques/ or exp survival analysis/
2. exp models, economic/ or decision trees/
3. markov.mp. or exp models, statistical/
4. (decision analytic model$ or decision tree$ or simulation model$ or decision analysis).ti,ab.
5. (explanatory model$ or statistical model$ or monte carlo or decision model$).ti,ab.
6. (survival analy$ or mathematical model$).ti,ab.
7. or/1-6
8. psoriasis/
9. (psoria$ or antipsoria$ or anti-psoria$).mp.
10. or/8-9
11. 7 and 10
12. animals/
13. human/
14. 12 not (12 and 13)
15. 11 not 14
16. 15 not (letter or editorial or comment).pt.

Embase (OVID Online – http://www.ovid.com/)
1980–2004 week 9

This search retrieved 61 references.

1. decision support system/
2. medical decision making/
3. decision theory/
4. survival/
5. statistical model/
6. probability/
7. monte carlo method/
8. (decision support technique$ or economic model$ or decision tree$).tw.
9. (decision analytic model$ or simulation model$ or decision analysis).tw.
10. (explanatory model$ or markov or statistical model$ or monte carlo or decision model$).tw.
11. (survival analy$ or mathematical model$).tw.
12. or/1-11
13. exp psoriasis/
14. (psoria$ or antipsoria$ or anti-psoria$).mp.
15. 13 or 14
16. 12 and 15
17. 16 not (editorial or letter or note).pt.
18. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (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.
19. Human/ or Human Experiment/
20. 18 not (18 and 19)
21. 17 not 20

National Research Register (NRR) (CD-ROM)
2003 Issue 4

This search retrieved 1 reference.

#1 PSORIASIS single term (MeSH)
#2 ((PSORIA* or ANTIPSORIA*) or ANTI-PSORIA*)
#3 (#1 or #2)
#4 DECISION-SUPPORT-TECHNIQUES explode all trees (MeSH)
#5 SURVIVAL-ANALYSIS explode all trees (MeSH)
#6 MODELS-ECONOMIC explode all trees (MeSH)
#7 DECISION-TREES single term (MeSH)
#8 MODELS-STATISTICAL explode all trees (MeSH)
#9 MARKOV
#10 (((((DECISION next ANALYTIC) next MODEL*) or (SIMULATION next MODEL*)) or (DECISION next ANALYSIS)) or (DECISION next TREE*))
#11 ((((EXPLANATORY next MODEL*) or (STATISTICAL next MODEL*)) or (MONTE next CARLO)) or (DECISION next MODEL*))
#12 ((SURVIVAL next ANALY*) or (MATHEMATICAL next MODEL*))
#13 (((((((#4 or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12)
#14 (#3 and #13)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
2004 Issue 1

This search retrieved nine references.

#1 DECISION SUPPORT TECHNIQUES explode all trees (MeSH)
#2 SURVIVAL ANALYSIS explode all trees (MeSH)
#3 MODELS ECONOMIC explode all trees (MeSH)
#4 DECISION TREES single term (MeSH)
#5 MODELS STATISTICAL explode all trees (MeSH)
#6 (markov:ti or markov:ab)
#7 ((decision next analytic next model*) or (simulation next model*) or (decision next analysis) or (decision next tree*))
#8 ((explanatory next model*) or (statistical next model*) or (monte next carlo) or (decision next model*))
#9 ((survival next analy*) or (mathematical next model*))
#10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#11 PSORIASIS single term (MeSH)
#12 (psoria* or antipsoria* or anti-psoria*)
#13 (#11 or #12)
#14 (#10 and #13)

NHS Economic Evaluation Database (NHS EED) (CRD administration database)
1990–2004/03

This search retrieved four references.

1. s decision(w)analytic(w)model$ or simulation(w)model$ or decision(w)analysis or decision(w)tree$
2. s explanatory(w)model$ or statistical(w)model$ or monte(w)carlo or decision(w)model$
3. s survival(w)analy$ or mathematical(w)model$ or markov
4. s s1 or s2 or s3

5. s psoria$ or antipsoria$ or anti(w)psoria$
6. s s4 and s5

Health Economic Evaluation Database (HEED) (CD-ROM)
February 2004

This search retrieved no references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics or antipsoriasis or antipsoriatic or antipsoriatics

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/)
1969–2004/02

This search retrieved no references.

1. (psoria* or antipsoria* or anti-psoria*)
2. ((decision analytic model*) or (simulation model*) or (decision analysis) or (decision tree*))or((explanatory model*) or (statistical model*) or (monte carlo) or (decision model*))or((survival analy*) or (mathematical model*) or markov)
3. (((decision analytic model*) or (simulation model*) or (decision analysis) or (decision tree*))or((explanatory model*) or (statistical model*) or (monte carlo) or (decision model*))or((survival analy*) or (mathematical model*) or markov)) and ((psoria* or antipsoria* or anti-psoria*))

ISI Science and Technology Proceedings (Web of Knowledge)
1990–2004 (28 February update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981–2004 (29 February update) – **http://wos.mimas.ac.uk/**

The search of ISI Science and Technology Proceedings retrieved five references.

The search of Social Science Citation Index and Science Citation Index retrieved 21 references.

#1 TS=((decision same analytic same model*) or (simulation same model*) or (decision same analysis) or (decision same tree*))
#2 TS=((explanatory same model*) or (statistical same model*) or (monte same carlo) or (decision same model*))
#3 TS=((survival same analy*) or (mathematical same model*) or markov)
#4 #1 or #2 or #3
#5 TS=((psoria* or antipsoria* or anti-psoria*))
#6 #4 and #5
#7 TS=((animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*))
#8 #6 not #7

All databases were searched from inception date.

Appendix 2

Quality assessment tool

All of the criteria listed below should be scored with one of the following responses:
Yes (Y)
No (N)
Partial (P)
Not stated (NS)
Not applicable (NA)
Unclear (U).

Study:

1	Were the eligibility criteria for the study adequately specified? *Adequate: study population clearly defined*	
2	Was an *a priori* power calculation for adequate sample size performed?	
3	Was the sample size adequate for the analysis of the primary outcome variable?	
4	Was the number of participants who were randomised stated?	
5	Was the method used to assign participants to treatment groups truly random? *Adequate: computer-generated random numbers, random number tables* *Inadequate: alternation, case record numbers, birth dates, days of the week*	
6	Was the trial described as double-blind?	
7	Was allocation of treatment concealed? *Adequate: centralised or pharmacy controlled assignment, serially numbered containers, serially numbered opaque envelopes, on-site computer-based systems where assignment is unreadable until after allocation, other robust measures to prevent revelation of a participant's treatment* *Inadequate: alternation, case record numbers, days of the week, open random number lists*	
8	Were the individuals administering the treatment blinded to the treatment allocation?	
9	Were the outcome assessors blinded to the treatment allocation?	
10	Were the participants blinded to the treatment allocation?	
11	Was the blinding procedure successful?	
12	Were adequate details of the treatment groups at baseline presented? *Adequate: information on age, nature and severity of psoriasis, previous treatments*	
13	Were the treatment groups comparable at baseline? *Answer 'Yes' if no important differences or if appropriate adjustments had been made for any differences in the baseline characteristics of the treatment groups*	
14	Were the treatment groups similar in terms of co-interventions that could influence the results?	
15	Was participant compliance with the assigned treatment adequate?	
16	Were all participants who were randomised accounted for at the end of the trial?	
17	Was a valid ITT analysis performed? *Adequate: all participants randomised included in efficacy analysis, all randomised participants who took at least one dose of trial medication included in efficacy analysis*	
18	Were at least 80% of those randomised included in the follow-up assessment? *Answer 'Yes' if at least 80% of those randomised provided complete data with regard to the primary outcome(s)*	

Quality rating =

Excellent: The answer is 'Yes' to all of the criteria
Good: The answer is 'Yes' to all of the following criteria: 1, 3, 4, 6, 10, 12–14, 16–18
Satisfactory: The answer is 'Yes' to all of the following criteria: 1, 3, 6, 13, 17
Poor: The answer is NOT 'Yes' to one or more of the criteria listed for 'Satisfactory'

Appendix 3

Excluded studies

Cameron H, Dawe RS, Yule I, Man SH, Ibbotson I, Ferguson AD. A comparison of 2× and 3× weekly narrow-band (TL-OI) UVB phototherapy in the treatment of chronic plaque psoriasis. Abstract. *Br J Dermatol* 2001;**144**:655.

Cameron H, Dawe RS, Yule S, Murphy J, Ibbotson SH, Ferguson J. A randomized, observer-blinded trial of twice vs three times weekly narrowband ultraviolet B phototherapy for chronic plaque psoriasis. *Br J Dermatol* 2002;**147**:973–8.

Cooper EJ, Herd RM, Priestley GC, Hunter JA. A comparison of bathwater and oral delivery of 8-methoxypsoralen in PUVA therapy for plaque psoriasis. *Clin Exp Dermatol* 2000;**25**:111–14.

Dawe RS, Cameron H, Yule S, Man I, Ibbotson SH, Ferguson J. UV-B phototherapy clears psoriasis through local effects. *Arch Dermatol* 2002;**138**:1071–6.

Griffiths CEM, George SA, Harris PV, Goodfield M, Kemmett D, Lewis H, *et al*. Intermittent short courses of cyclosporin for psoriasis unresponsive to topical therapy: a one year multicentre, randomised study Abstract. *Br J Dermatol* 1999;**141**:73.

Kirkup ME, Sabroe RA, Kavanagh GM, Downs AMR, Sansom JE, DeBerker DARD, *et al*. Twice daily versus once daily inpatient dithranol for psoriasis. Abstract. *Br J Dermatol* 1999;**141**:72.

Kirkup ME, Sabroe RA, Kavanagh GM, Downs AM, Sansom JE, de Berker DA, *et al*. Twice-daily vs once-daily inpatient dithranol for psoriasis. *Clin Exp Dermatol* 2002;**27**:695–9.

McBride SR, Walker P, Reynolds NJ. Optimizing the frequency of outpatient short-contact dithranol treatment used in combination with broadband ultraviolet B for psoriasis: a randomized, within-patient controlled trial. *Br J Dermatol* 2003;**149**:1259–65.

Ohtsuki M, Nakagawa H, Sugai J, Ozawa A, Ohkido M, Nakayama J, *et al*. Long-term continuous versus intermittent cyclosporin: therapy for psoriasis. *J Dermatol* 2003;**30**:290–8.

Thaci D, Brautigam M, Kaufmann R, Weidinger G, Paul C, Christophers E. Body-weight-independent dosing of cyclosporine micro-emulsion and three times weekly maintenance regimen in severe psoriasis. A randomised study. *Dermatology* 2002;**205**:383–8.

Appendix 4

Data extraction tables: intervention efficacy

Data extraction tables: intervention efficacy – etanercept

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
Elewski, 2004,[72] USA, Canada and Europe **Type of publication** Conference poster **Other publications/reports** Industry trial report[146] Industry trial report[147] Gordon,[148] Conference poster Gottlieb,[149] Conference poster Industry submission (study no. 20021642), 2004[69] **Funding** Immunex Corp. (wholly-owned subsidiary of Amgen Inc.); Wyeth Pharmaceuticals Inc. **Study design** Double-blind RCT, parallel with open follow-up Monotherapy The trial was conducted in two stages: Stage 1, RCT; Stage 2, open follow-up **Setting** Outpatient **Duration of follow-up** Stage 1: 12 wks Stage 2: 36 wks **Frequency of follow-up** Stage 1: 0, 2, 4, 8 and 12 wks; Stage 2: 18, 20, 24, [**Confidential information**	**Inclusion/exclusion criteria** Active clinically stable plaque psoriasis involving >10% BSA, minimum PASI score of 10, previously treated with at least one systemic therapy or phototherapy or to be a candidate for such therapy. Aged >18 yrs. Those previously treated with etanercept or with antibodies to TNF or who had received investigational drugs, biologicals, systemic psoriasis therapy, systemic corticosteroids or PUVA within previous 4 wks or had received UVB topical steroids, topical vitamin A or D analogues or anthralin within 2 wks were excluded. **Number randomised and treated** 583 **Age (years)** *Mean (SD)* Etanercept 25 mg: 45.4 [**Confidential information removed**] Etanercept 50 mg: 45.2 [**Confidential information removed**] Placebo: 44.8 [**Confidential information removed**] Total 45.2 [**Confidential information removed**]	*Stage 1* **Intervention etanercept** Dose regimen: 25 mg s.c. twice a wk Length of treatment: 12 wks No. randomised: 196 No. completed: [**Confidential information removed**] **Intervention etanercept** Dose regimen: 50 mg s.c. twice a wk Length of treatment: 12 wks No. randomised: 194 No. completed: [**Confidential information removed**] **Comparator placebo** Dose regimen: equivalent Length of treatment: 12 wks No. randomised: 193 No. completed: [**Confidential information removed**] *Stage 2* **Etanercept** Dose regimen: 25 mg s.c. twice a wk Length of treatment: 36 wks No.: 557 **Primary outcome** PASI 75 at wk 12 **Sample size calculation** Based on PASI 75 at wk 12 assuming % on etanercept and placebo would be 30 and 5%, respectively, 200 patients per	*Stage 1* **PASI 75** Etanercept 25 mg 12 wks: 67/196 (34%); etanercept 50 mg 12 wks: 96/194 (49%); placebo 12 wks: 6/193 (3%); $p < 0.0001$ for placebo vs both etanercept doses; $p = 0.002$ for etanercept 25 mg vs 50 mg **PASI 50** [**Confidential information removed**] **PASI 90** [**Confidential information removed**] **Clear or almost clear** [**Confidential information removed**] **PASI score** [**Confidential information removed**] **Mean PASI score** [**Confidential information removed**] *Stage 2* Note: all patients were on etanercept 25 mg twice a week. The stated group denotes the treatment participants were on in stage 1 (from wk 0 to wk 12) **PASI 75** Etanercept 25 mg 24 wks: [**Confidential information removed**] Etanercept 50 mg 24 wks: [**Confidential information removed**] Placebo 24 wks: [**Confidential information removed**] **PASI 50** Etanercept 25 mg 24 wks: [**Confidential information removed**]; 36 wks: [**Confidential information removed**] Etanercept 50 mg 24 wks: [**Confidential information removed**]; 36 wks: [**Confidential information removed**] Placebo 24 wks: [**Confidential information removed**]; 36 wks: [**Confidential information removed**] **PASI 90** Etanercept 25 mg 24 wks: [**Confidential information removed**]; 36 wks: [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
removed] 36 [**Confidential information removed**] wks Extracted by: NW Checked by: AK	**Gender** Etanercept 25 mg: male 65% [**Confidential information removed**] Etanercept 50 mg: male 67% [**Confidential information removed**] Placebo: male 64% (124/193) Total: male 66% (382/583) **Psoriasis history** *Duration of psoriasis [mean (SD)] (years)* Etanercept 25 mg: 22.2 [**Confidential information removed**] Etanercept 50 mg: 19.9 [**Confidential information removed**] Placebo: 19.4 [**Confidential information removed**] **Prior systemic therapy** Patients were permitted to have received previous systemic therapy or phototherapy; [**Confidential information removed**] *PASI score (mean)* Etanercept 25 mg: 19.1 [**Confidential information removed**] Etanercept 50 mg: 19.5 [**Confidential information removed**] Placebo: 18.6 [**Confidential information removed**]	group gives >99% power to detect this difference at the 5% level (2-sided Fisher's exact test) **Statistical analyses** [**Confidential information removed**] **ITT analysis** [**Confidential information removed**] **Comments**	Etanercept 50 mg 24 wks: [**Confidential information removed**]; 36 wks: [**Confidential information removed**] Placebo: 24 wks [**Confidential information removed**]; 36 wks: [**Confidential information removed**] **Mean (SE) PASI score** Etanercept 25 mg (*n* = 177) 24 wks: 5.8 [**Confidential information removed**]; improvement from wk 12 to 24: 2.0 [**Confidential information removed**] Etanercept 50 mg (*n* = 179) 24 wks: 5.6 [**Confidential information removed**]; improvement from wk 12 to 24: –0.1 [**Confidential information removed**] Placebo (*n* = 166) 12 wks: 18.5; 24 wks: 7.4 [**Confidential information removed**]; improvement from wk 12 to 24: 11.1 [**Confidential information removed**] **Clear or almost clear** Etanercept 25 mg 24 wks: [**Confidential information removed**]; 36 wks: [**Confidential information removed**] Etanercept 50 mg 24 wks: [**Confidential information removed**]; 36 wks: [**Confidential information removed**] Placebo 24 wks: [**Confidential information removed**]; 36 wks: [**Confidential information removed**] **DLQI** [**Confidential information removed**] **Patient assessment of psoriasis at wks 24 and 36** [**Confidential information removed**] **Adverse events** *Stage 1* Adverse events occurring in >3% of patients in any treatment group Placebo (*n* = 193) / Etanercept 25 mg (*n* = 196) / Etanercept 50 mg (*n* = 194) Exposure-adjusted rate/100 patient yrs [**Confidential information removed**] Non-infectious adverse events [**Confidential information removed**] Injection site reaction 11 (6%) / 26 (13%) / 35 (18%) [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
	Patient global score Etanercept 25 mg: 68 Etanercept 50 mg: 70 Placebo: 71 BSA involved (%) Etanercept 25 mg: 28.6 Etanercept 50 mg: 28.8 Placebo: 26.4 *Psoriatic arthritis* % (SD): Etanercept 25 mg: [**Confidential information removed**] Etanercept 50 mg: [**Confidential information removed**] Placebo: [**Confidential information removed**] DLQI Mean (SD): Etanercept 25 mg: [**Confidential information removed**] Etanercept 50 mg: [**Confidential information removed**] Placebo: [**Confidential information removed**] **Concurrent therapies** [**Confidential information removed**] **Comments** [**Confidential information removed**]; 583 treated		**Infectious adverse events including any serious infections** Placebo (*n* = 193) / Etanercept 25 mg (*n* = 196) / Etanercept 50 mg (*n* = 194) Any infection: 55 (29%) / 58 (30%) / 56 (29%) [**Confidential information removed**] Other non-infectious serious adverse events (no.) [**Confidential information removed**] **Deaths (no.)** None **Withdrawals due to adverse events** Etanercept 25 mg: 3 withdrawals (1.5%); [**Confidential information removed**] Etanercept 50 mg: 2 withdrawals (1%); [**Confidential information removed**] [**Confidential information removed**] **Positive test for anti-etanercept antibody** Etanercept 25 mg [**Confidential information removed**]; etanercept 50 mg [**Confidential information removed**]; placebo [**Confidential information removed**] **Other important adverse event results** None *Stage 2* All patients on etanercept 25 mg twice/wk Results expressed as exposure-adjusted rate/100 patient yrs [**Confidential information removed**] **Non-infectious adverse events** [**Confidential information removed**] **Infectious adverse events including any serious infections** [**Confidential information removed**] **Serious infections (no.)** [**Confidential information removed**] **Cancer** [**Confidential information removed**] **Other non-infectious serious adverse events (no.)** [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
			Deaths (no.) [**Confidential information removed**] **Withdrawals due to adverse events** [**Confidential information removed**] **Positive test for anti-etanercept antibody** [**Confidential information removed**] **Other important adverse event results** [**Confidential information removed**] **Comments** [**Confidential information removed**]
Gottlieb, 2003,[73] USA **Type of publication** Full publication **Other publications/reports** Industry trial report[150] Gaspari, 2002,[151] Abstract Gottlieb, 2002,[152] Abstract Gordon,[148] Conference poster Gottlieb,[149] Conference poster Industry submission (study no. 20021632), 2004[69] **Funding** Immunex Corp. (a subsidiary of Amgen Inc.) **Study design** Double-blind RCT, parallel Monotherapy The study was in 2 stages: Stage 1: RCT Stage 2: Follow-up after discontinuation of study treatments	**Inclusion/exclusion criteria** Patients aged at least 18 years, with active stable plaque psoriasis involving 10% or more of the BSA. Patients were excluded if they had guttate, erythrodermic or pustular psoriasis, other skin conditions; or other significant medical conditions that might interfere with evaluations of the effect of study medications on psoriasis. Patients were to have had at least one previous systemic psoriasis therapy or phototherapy. PUVA and systemic psoriasis therapy were not allowed within 4 weeks of the trial, and UVB, topical corticosteroids, vitamin A or D analogues, or anthralin were not allowed within 2 weeks of baseline measurements	**Intervention etanercept** Dose regimen: 25 mg s.c. twice a wk Length of treatment: 24 wks No. randomised: 57 No. completed: 12 wks: 53 (93%); 24 wks: 48 (84%) **Comparator placebo** Dose regimen: equivalent Length of treatment: 24 wks No. randomised: 55 No. completed: 12 wks: 40 (73%); 24 wks: 12 (22%) Stage 2: Etanercept $n = 17$ Placebo $n = 3$ **Primary outcome** PASI 75 at 12 wks **Sample size calculation** Assuming PASI 75 response rates of 10% in the placebo group and 35% in the treatment group, the sample	**PASI 75** Etanercept: 12 wks: 17/57 (30%); placebo: 12 wks: 1/55 (2%); $p < 0.001$; treatment difference: 28% (95% CI: 16 to 40%) Etanercept: 24 wks: 32/57 (56%); placebo: 24 wks: 3/55 (5%); $p < 0.001$; treatment difference 51% (95% CI: 36 to 65%) **PASI 50** Etanercept: 12 wks: 40/57 (70%); placebo: 12 wks: 6/55 (11%); $p < 0.001$ Etanercept: 24 wks: 44/57 (77%); placebo: 24 wks: 7/55 (13%); $p < 0.001$ **PASI 90** Etanercept: 12 wks: 6/57 (11%); placebo: 12 wks: 0/55 (0%); $p = 0.03$ Etanercept: 24 wks: 12/57 (21%); placebo: 24 wks: 0/55 (0%); $p < 0.001$ **Mean PASI score** Etanercept: 12 wks: [**Confidential information removed**]; Placebo: 12 wks: [**Confidential information removed**] Etanercept: 24 wks: [**Confidential information removed**]; Placebo: 24 wks: [**Confidential information removed**] **PASI** Mean (SE) improvement from baseline Etanercept: 12 wks: [**Confidential information removed**]; placebo: 12 wks: [**Confidential information removed**] Etanercept: 24 wks: 67% (4%); placebo: 24 wks: 1% (7%); $p < 0.001$ Median improvement from baseline [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
Setting Outpatient **Duration of follow-up** Stage 1: 24 wks Stage 2: [**Confidential information removed**] **Frequency of follow-up** Stage 1: baseline, 2, 4, 8, 12, 16, 20, and 24 wks Stage 2: [**Confidential information removed**] Extracted by: AK Checked by: NW	**Number randomised and treated** 112 **Age (years)** *Mean (range/SD)* Etanercept: 48.2 (25–72/ [**Confidential information removed**] Placebo: 46.5 (18–77/ [**Confidential information removed**] **Gender** Etanercept: male 58% (33/57) Placebo: male 67% (37/55) **Psoriasis history** *Duration of psoriasis (years)* Mean (SE/SD) Etanercept: mean 23 (1.6/12.1) Placebo: mean 20 (1.7/12.2) *Prior systemic therapy* Yes *Baseline PASI* *Mean (SE/SD) score at baseline:* Etanercept: 17.8 (1.1/8.5) Placebo: 19.5 (1.3/9.4) *BSA affected* Mean (SE/SD) (%): Etanercept: 30 (2.3/17.7) Placebo: 34 (3.0/21.9) *DLQI* [**Confidential information removed**]	size of 50 patient per group afforded over 80% power to detect a significant difference in the primary end-point between treatments using a 2-sided $\alpha = 0.05$ (Fisher's exact test) **Statistical analyses** The χ^2 test was used to analyse PASI response rate. For binary end-points, the χ^2 test was used to compare the two treatment groups with respect to the proportion who met criteria for psoriasis efficacy response. Fisher's exact test was substituted if more appropriate. Non-parametric tests were used for other end-points **ITT analysis** Yes. All patients who received at least one study dose were evaluated for safety and efficacy. [**Confidential information removed**] If a patient discontinued treatment before the end of the study, the last observation was carried forward. [**Confidential information removed**] **Comments**	**Physician GA** Mean (SE) improvement from baseline Etanercept: 24 wks: 46% (4%); placebo: 24 wks: –2 (4%); $p < 0.001$ **Clear or minimal** Number (%) clear or minimal for assessment of psoriasis Etanercept: 12 wks: 26 (46%); placebo: 12 wks: 1 (2%); $p < 0.0001$ Etanercept: 24 wks: 30 (53%); [**Confidential information removed**] **Patient GA** Mean (SE) improvement from baseline Etanercept: 24 wks: 62% (5%); placebo: 24 wks: 7% (5%); $p < 0.001$ **DLQI** Mean (SE) improvement from 4 wks Etanercept: 12 wks: [**Confidential information removed**]; placebo: 24 wks: [**Confidential information removed**] Etanercept: 24 wks: 64.3% (5.0%); placebo: 24 wks: 7.2% (8.0%); $p < 0.001$ **BSA affected** Mean (SE) improvement from baseline Etanercept: 24 wks: 63% (5%); placebo: 24 wks: –12% (7%); $p < 0.001$ *Target lesions* [**Confidential information removed**] **Adverse events** *N* (%) adverse events occurring in ≥5% of groups combined

	Etanercept ($n = 57$)	Placebo ($n = 55$)
Non-infectious adverse events		
Any non-infectious	[**Confidential information removed**]	
Headache	9 (16%)	7 (13%)
Bruise at injection site	6 (11%)	5 (9%)
Sinusitis	8 (14%)	4 (4%)
Pain	4 (7%)	4 (7%)
Peripheral oedema	1 (2%)	5 (9%)
Hypertension	4 (7%)	2 (4%)
Accidental injury	4 (7%)	2 (4%)
Injection site reaction	5 (9%)	0 (0%)
[**Confidential information removed**]		
[**Confidential information removed**]		

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
	Psoriatic arthritis Number of patients: Etanercept: 16 (28%) Placebo: 19 (35%) *Physician GA* Mean (SE) score: Etanercept: 2.8 (0.1) Placebo: 2.9 (0.1) *Patient GA* Mean (SE) score: Etanercept: 4.1 (0.1) Placebo: 4.2 (0.1) **Concurrent therapies** Tar compounds and steroid-free topical emollients were allowed during the study. Some topical preparations (such as lower potency corticosteroids and tar-based shampoo) were allowed to continue at stable doses during therapy on the scalp, axilla and groin **Comments** 118 patients were randomised; 112 received treatment		[**Confidential information removed**] [**Confidential information removed**] [**Confidential information removed**] [**Confidential information removed**] [**Confidential information removed**] **Infectious adverse events including any serious infections** Any infection [**Confidential information removed**] Upper respiratory tract infection 20 (35%) 11 (20%) Bronchitis [**Confidential information removed**] Cellulitis [**Confidential information removed**] Herpes simplex [**Confidential information removed**] **Serious infections (no.):** Etanercept: appendicitis: 1/57 Placebo: pharyngitis: 1/55 **Cancer** [**Confidential information removed**] **Other non-infectious serious adverse events (no.)** Etanercept: motor vehicle crash: 1/57 Placebo: stroke: 1/55; pustular psoriasis: 1/55 **Deaths (no.)** [**Confidential information removed**] **Withdrawals due to adverse events** Etanercept: 2/57 Placebo: 6/55 **Positive test for anti-etanercept antibody** No patients developed antibodies to etanercept: all samples negative for anti-etanercept antibodies **Other important adverse event results** Number of patients reporting adverse events was similar between the two groups [**Confidential information removed**] **Comments**

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
Leonardi, 2003,[71] USA **Type of publication** Full publication **Other publications/reports** Industry trial report,[140] Industry trial report,[153] Krueger,[154] Conference poster Gottlieb,[155] Conference poster Gordon,[148] Conference poster Gottlieb,[149] Conference poster Industry submission (study no. 20021639), 2004[69] **Funding** Immunex (wholly-owned subsidiary of Amgen) **Study design** Stage 1: double-blind RCT, parallel Monotherapy Stage 2: double-blind follow-up Stage 3: discontinuation of treatment (for responders, i.e. those who achieved PASI 50) or open-label etanercept (for incomplete responders, i.e. those who did not achieve PASI 50) Stage 4: retreatment **Setting** Outpatients **Duration of follow-up (wks)** Total: 72 Stage 1: 12 Stage 2: 12 Stage 3: variable duration with	**Inclusion/exclusion criteria** Aged at least 18 yrs, with active clinically stable plaque psoriasis involving ≥ 10% BSA and a PASI score of ≥ 10; previously received systemic or phototherapy for psoriasis or had been a candidate for such therapy. Patients with other forms of psoriasis or those who had previously received etanercept were excluded. Patients were excluded if they had received anti-collecting duct antibodies (anti-CDA) or interleukin-2 in the previous 6 months, other biological or other investigational therapy or PUVA, systemic corticosteroids or systemic psoriasis therapy in previous 4 wks, or UVB, topical steroids, vitamin A or D analogues or anthralin in previous 2 wks or antibiotics in previous wk **Number randomised and treated** 652 **Age (years)** *Mean age (SE/SD)* Etanercept 25 mg once a wk: 44.4 (0.9/12.0) Etanercept 25 mg twice a wk: 45.4 (1.0/13.1) Etanercept 50 mg twice a wk: 44.8 (0.8/10.8) Placebo: 45.6 (1.0/12.9)	*Stage 1* **Intervention etanercept** Dose regimen: 25 mg s.c. once a wk Length of treatment: 12 wks No. randomised: 160 No. completed: [**Confidential information removed**] (94% of total study population) **Intervention etanercept** Dose regimen: 25 mg s.c. twice a wk Length of treatment: 12 wks No. randomised: 162 No. completed: [**Confidential information removed**] (94% of total study population) **Intervention etanercept** Dose regimen: 50 mg s.c. twice a wk Length of treatment: 12 wks No. randomised: 164 No. completed: [**Confidential information removed**] (94% of total study population) **Comparator placebo** Dose regimen: equivalent Length of treatment: 12 wks No. randomised: 166 No. completed: [**Confidential information removed**] (94% of total study population) *Stage 2* Patients continued on same doses of etanercept. Those on placebo in Stage 1 switched to	*Stage 1* **PASI 75** Etanercept 25 mg once a wk 12 wks: 23/160 (14%); etanercept 25 mg twice a wk 12 wks: 55/162 (34%); etanercept 50 mg twice a wk 12 wks: 81/164 (49%); placebo 12 wks: 6/166 (4%); $p < 0.001$ for placebo vs all etanercept doses Etanercept 25 mg once a wk 24 wks: 40/160 (25%); etanercept 25 mg twice a wk 24 wks: 71/162 (44%); etanercept 50 mg twice a wk 24 wks: 97/164 (59%). [**Confidential information removed**] **PASI 50** Etanercept 25 mg once a wk 12 wks: 65/160 (41%); etanercept 25 mg twice a wk 12 wks: 94/162 (58%); etanercept 50 mg twice a wk 12 wks: 121/164 (74%); placebo 12 wks: 24/166 (14%); $p < 0.0001$ for placebo vs all etanercept doses Etanercept 25 mg once a wk 24 wks: 92/160 (58%); etanercept 25 mg twice a wk 24 wks: 113/162 (70%); etanercept 50 mg twice a wk 24 wks: 127/164 (77%). [**Confidential information removed**] **PASI 90** Etanercept 25 mg once a wk 12 wks: 5/160 (3%); etanercept 25 mg twice a wk 12 wks: 19/162 (12%); etanercept 50 mg twice a wk 12 wks: 36/164 (22%); placebo 12 wks: 1/166 (1%); $p < 0.0001$ for placebo vs two higher etanercept doses Etanercept 25 mg once a wk 24 wks: 9/160 (6%); etanercept 25 mg twice a wk 24 wks: 32/162 (20%); etanercept 50 mg twice a wk 24 wks: 49/164 (30%). [**Confidential information removed**] **Clear or almost clear** Etanercept 25 mg once a wk 12 wks: 37/160 (23%); etanercept 25 mg twice a wk 12 wks: 55/162 (34%); etanercept 50 mg twice a wk 12 wks: 81/164 (49%); placebo 12 wks: 8/166 (5%); $p < 0.0001$ for placebo vs all etanercept doses *Stage 2* Etanercept 25 mg once a wk 24 wks: 41/160 (26%); etanercept 25 mg twice a wk 24 wks: 63/162 (39%); etanercept 50 mg twice a wk 24 wks: 90/164 (55%). [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
follow-up until relapse (for responders); 48 wks (for incomplete responders) Stage 4: 24 wks or until study conclusion **Frequency of follow-up (wks)** Stage 1: 0, 2, 4, 8, 12 Stage 2: 16, 20, 24 Stages 3 and 4: 36, 48, 60 Extracted by: NFW Checked by: AK	**Gender** Etanercept 25 mg once a wk: male 74% (119/160) Etanercept 25 mg twice a wk: male 67% (109/162) Etanercept 50 mg twice a wk: male 65% (106/164) Placebo: male 63% (104/166) Total: male 67% (438/652) **Psoriasis history** *Duration of psoriasis [mean (SE/SD)] (yrs)* Etanercept 25 mg once a wk: 19.3 (0.9/11.0) Etanercept 25 mg twice a wk: 18.5 (0.9/11.2) Etanercept 50 mg twice a wk: 18.6 (0.9/11.2) Placebo: 18.4 (0.9/11.6) Total 18.7 *Prior systemic therapy [n (%)]* [**Confidential information removed**] Total 76% *BSA [mean (SE/SD)]* Etanercept 25 mg once a wk: 27.7% (1.5/18.8) Etanercept 25 mg twice a wk: 28.5% (1.6/20.2) Etanercept 50 mg twice a wk: 29.9% (1.6/19.9) Placebo: 28.8% (1.4/18.5) Total 28.7% (not stated) *PASI score [mean (SE/SD)]* Etanercept 25 mg once a wk: 718.2 (0.7/8.6)	etanercept 25 mg twice a week **No. completed 24 wks** [**Confidential information removed**] Total: 573 (88%) *Stage 3* 157 patients who had not achieved a PASI 50 by 24 wks: open-label etanercept 25 mg s.c. twice a wk 409 patients who achieved a PASI 50 by 24 wks had etanercept stopped (i.e. no treatment) *Stage 4* Of those responders who underwent treatment withdrawal in Stage 3, those whose disease relapsed (i.e. lost >50% of their initial treatment response) were retreated with their original blinded dose of etanercept (n = 297) [**Confidential information removed**] **Primary outcome** Stage 1 and Stage 2: PASI 75 at wk 12 of first phase Stage 3: duration of treatment response during withdrawal Stage 4: difference in PASI 75 at wk 12 of retreatment and PASI 75 at wk 12 of Stage 1	After 12 wks retreatment (n = 297): Etanercept 25 mg once a wk 12 wks: [**Confidential information removed**]; etanercept 25 mg twice a wk 12 wks: [**Confidential information removed**]; etanercept 50 mg twice a wk 12 wks: [**Confidential information removed**]; etanercept 25 mg twice a wk (ex-placebo) 12 wks: [**Confidential information removed**] **PASI score** Mean (SE) % improvement from baseline Etanercept 25 mg once a wk 12 wks: 40.9 (2.4); etanercept 25 mg twice a wk 12 wks: 52.6 (2.7); etanercept 50 mg twice a wk 12 wks: 64.2 (2.4); placebo 12 wks: 14.0 (2.6); $p < 0.0001$ for placebo vs all etanercept doses Etanercept 25 mg once a wk 24 wks: 50.3 (2.5); etanercept 25 mg twice a wk 24 wks: 62.1 (2.5); etanercept 50 mg twice a wk 24 wks: 71.1 (2.2). [**Confidential information removed**] **PASI Score [mean (SE)]** [**Confidential information removed**] **PASI score [median (range)]** Etanercept 25 mg once a wk 12 wks: 9.6 (0.7–70.8); etanercept 25 mg twice a wk 12 wks: 6.5 (0.0–51.9); etanercept 50 mg twice a wk 12 wks: 4.2 (0.0–48.0); placebo 12 wks: 14.4 (1.6–49.1) Etanercept 25 mg once a wk 24 wks: 7.0 (0.0–54.0); etanercept 25 mg twice a wk 24 wks: 4.8 (0.0–29.4); etanercept 50 mg twice a wk 24 wks: 3.0 (0.0–48.0). [**Confidential information removed**] **% change from baseline in total DLQI score [mean (SE)]** Etanercept 25 mg once a wk 12 wks: 47.2 (2.9); etanercept 25 mg twice a wk 12 wks: 50.8 (3.8); etanercept 50 mg twice a wk 12 wks: 61.0 (4.3); placebo 12 wks: 10.9 (4.8); $p < 0.0001$ for placebo vs all etanercept doses Etanercept 25 mg once a wk 24 wks: 54.0 (3.0); etanercept 25 mg twice a wk 24 wks: 59.4 (3.6); etanercept 50 mg twice a wk 24 wks: 73.8 (2.8). [**Confidential information removed**] **Patient global assessment** Wk 12 distribution on 6-point scale favoured all doses of etanercept over placebo ($p < 0.0001$) [**Confidential information removed**] **Responses over time** [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
	Etanercept 25 mg twice a wk: 18.5 (0.7/8.6) Etanercept 50 mg twice a wk: 18.4 (0.7/8.4) Placebo: 18.3 (0.6/7.5) Total 18.4 (not stated) *DLQI score [mean (SE/SD)]* Etanercept 25 mg once a wk: 12.2 (0.5/6.6) Etanercept 25 mg twice a wk: 12.7 (0.5/7.0) Etanercept 50 mg twice a wk: 11.3 (0.5/6.4) Placebo: 12.8 (0.6/7.3) Psoriatic arthritis Etanercept 25 mg once a wk: [**Confidential information removed**] Etanercept 25 mg twice a wk: [**Confidential information removed**] Etanercept 50 mg twice a wk: [**Confidential information removed**] Placebo: [**Confidential information removed**] Total: 22% (146/652) **Concurrent therapies** Stable doses of low or moderate potency topical steroids on scalp, axilla and groin were permitted. [**Confidential information removed**] **Comments** 672 randomised, 652 received one dose of study drug	**Sample size calculation** Sample size [**Confidential information removed**] was calculated to give 99% power to detect a difference of 25% between etanercept and placebo [**Confidential information removed**] for PASI 75 at wk 12 of Stage 1 **Statistical analyses** Pearson's χ^2 test, Fisher's exact test for binary end-points; Mantel–Haenszel for ordinal end-points and non-parametric tests for continuous end-points. Hochberg's set-up procedure for multiple comparisons was used on comparisons up to 12 wks **ITT analysis** All patients who took at least one dose of medication included in all safety and efficacy analyses. Last observation carried forward used for missing data **Comments**	*Stage 3* Duration of treatment response (time to loss of <50% PASI improvement achieved between baseline and wk 24 >50%) for all responders after withdrawal of treatment [median (75th percentile, 25th percentile)] (n = 409) [**Confidential information removed**] **Time to relapse after withdrawal of etanercept (loss of half of PASI improvement achieved by wk 24) [median (75th percentile, 25th percentile)] (n = 409)** Etanercept 25 mg once a wk (n = 85): 70 days (56, 113 days); etanercept 25 mg twice a wk (n = 107); 85 days (56, 169 days); etanercept 50 mg twice a wk (n = 122): 91 days (60, 169 days); etanercept 25 mg twice a wk (ex-placebo) (n = 95): 85 days (57, 143 days) Median time for all patients from wk 24 to study visit when relapse identified: 85 days **Time to loss of PASI 50 after withdrawal of etanercept in those with PASI 75 or better at wk 24 [Confidential information removed] (n = 252)** Etanercept 25 mg once a wk (n = 37): 85 days [**Confidential information removed**]; etanercept 25 mg twice a wk (n = 69): 87 days [**Confidential information removed**]; etanercept 50 mg twice a wk (n = 91): 112 days [**Confidential information removed**]; etanercept 25 mg twice a wk (ex-placebo): 106 days [**Confidential information removed**] Median time for all patients from wk 24 to study visit when loss of PASI 50 identified: 91 days **Rebound psoriasis** Of those patients who had received 24 wks etanercept therapy (n = 409), 1 patient (who had been in the etanercept 25 mg once a wk group) developed a PASI score of 125% or more of baseline score. [**Confidential information removed**]. No patient developed a PASI score of 150% or more of baseline score *Stage 4* [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results

Adverse events

Stage 1

At wk 12 occurring in at least 3% of patients in any group

	Placebo	Etanercept 25 mg 1/wk	Etanercept 25 mg 2/wk	Etanercept 50 mg 2/wk
	n = 166	*n* = 160	*n* = 162	*n* = 164
Non-infectious adverse events				
[Confidential information removed]				
Injection site reaction	12 (7%)	17 (11%)	28 (17%)	22 (13%)
Headache	11 (7%)	5 (3%)	19 (12%)	11 (7%)
Inject site ecchymosis	6 (4%)	11 (7%)	4 (2%)	8 (5%)
Asthenia	5 (3%)	7 (4%)	6 (4%)	3 (2%)
Myalgia	4 (2%)	3 (2%)	6 (4%)	3 (2%)
Accidental injury	7 (4%)	6 (4%)	5 (3%)	7 (4%)
[Confidential information removed]				
Sinusitis	1 (1%)	0	0	0
Nausea	2 (1%)	5 (3%)	4 (2%)	3 (2%)
Rash	4 (2%)	4 (3%)	4 (2%)	5 (3%)
Infectious adverse events including any serious infections				
[Confidential information removed]				
URT infection	19 (11%)	16 (10%)	15 (9%)	9 (5%)
[Confidential information removed]				

[Confidential information removed]

Deaths (no.)
[Confidential information removed]

Withdrawals due to adverse events
[Confidential information removed]

Positive test for anti-etanercept antibody
[Confidential information removed]

Other important adverse event results

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results

Stage 2

Adverse events from wk 13 to wk 24: occurring in at least 3% of patients in any group

	Etanercept 25 mg 2/wk (was placebo) *n* = 153	Etanercept 25 mg 1/wk *n* = 150	Etanercept 25 mg 2/wk *n* = 149	Etanercept 50 mg 2/wk *n* = 159
Non-infectious adverse events				
Any non-infectious	[**Confidential information removed**]			
Rash	0	0	2 (1%)	6 (4%)
Headache	8 (5%)	5 (3%)	8 (5%)	4 (3%)
Sinusitis	5 (3%)	3 (2%)	3 (2%)	1 (1%)
Asthenia	2 (1%)	3 (2%)	7 (5%)	2 (1%)
Myalgia	3 (2%)	5 (3%)	6 (4%)	4 (3%)
Accidental injury	6 (4%)	6 (4%)	6 (4%)	4 (3%)
[**Confidential information removed**]				
Infectious adverse events including any serious infections				
Any infectious	[**Confidential information removed**]			
URT infection	9 (6%)	8 (5%)	9 (6%)	11 (7%)

Serious infections (no.)
[**Confidential information removed**]

Cancer
[**Confidential information removed**]

Other non-infectious serious adverse events (no.)
[**Confidential information removed**]

Deaths (no.)

Withdrawals due to adverse events
Etanercept 25 mg once a wk: [**Confidential information removed**]; etanercept 25 mg twice a wk: [**Confidential information removed**]; etanercept 50 mg twice a wk: [**Confidential information removed**]; placebo: [**Confidential information removed**]

Over the 24-week study 27 patients withdrew due to adverse events

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
			Positive test for anti-etanercept antibody 8/520 etanercept patients for whom paired baseline–24 wk (or study withdrawal) samples were available had serum samples tested positive for non-neutralising anti-etanercept antibodies **Other important adverse event results** [**Confidential information removed**] *Stage 3* Adverse events at wk 60 Of the 157 treated with open-label etanercept 25 mg twice a wk in Stage 3, 72% received 48 wks therapy and 38% received 60 wks. [**Confidential information removed**] Exposure-adjusted rates of adverse events, infections and serious adverse events were similar to those in the first phase [number (exposure-adjusted event rate per 100 patient years)]: [**Confidential information removed**] **Serious adverse events** Any: [**Confidential information removed**] Serious infection: [**Confidential information removed**] **Withdrawals due to adverse events** [**Confidential information removed**] *Stage 4* [**Confidential information removed**] **Serious adverse events** [**Confidential information removed**] **Withdrawals due to adverse events** [**Confidential information removed**] **Serious adverse events** [**Confidential information removed**] **Withdrawals due to adverse events** [**Confidential information removed**] **Comments** Further subgroup analyses and further results relating to the re-treatment phase are reported in the Industry Trial Report

Data extraction tables: intervention efficacy – efalizumab

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
Gordon, 2003,[75] USA **Type of publication** Full publication **Other publications/reports** Menter, 2004,[156] Full publication Hamilton, 2003,[157] Abstract ACD2390g, 2004,[158] Industry submission **Funding** Genentech Inc. **Study design** Double-blind RCT, parallel Multicentre **Setting** Outpatient **Duration of follow-up** 12 wks **Frequency of follow-up** Baseline, 2, 4, 6, 8, 10, 12 wks Extracted by: ZK Checked by: NW	**Inclusion/exclusion criteria** Patients aged between 18 and 75 yrs with moderate to severe plaque psoriasis for at least 6 months, with at least 10% of total BSA affected, with a minimum PASI score of 12 and candidates for systemic therapy **Number randomised and treated** 556 **Age (years)** *Mean age (range)* Efalizumab: 45 (18–75) Placebo: 45 (20–75) **Gender** Efalizumab: male 68% (251/369) Placebo: male 71% (132/187) **Psoriasis history** *Duration of psoriasis (years)* Efalizumab: mean 19 (1–62) Placebo: mean 19 (1–53) *Prior systemic therapy* Efalizumab: yes 77% (283/369) Placebo: yes 74% (139/187) Baseline PASI score (range) Efalizumab: 19 (10–59) Placebo: 19 (11–50) % BSA affected (range) Efalizumab: 28 (10–95) Placebo: 27 (10–90)	**Intervention efalizumab** Dose regimen: 1 mg/kg s.c. once a wk Length of treatment: 12 wks No. randomised: 369 No. completed: 345 **Comparator placebo** Dose regimen: equivalent Length of treatment: 12 wks No. randomised: 187 No. completed: 175 **Primary outcome** PASI 75 at wk 12 **Sample size calculation** A planned sample size of 333 patients receiving efalizumab and 167 receiving placebo produced 99% power to detect a difference between assumed placebo response rate of 5% and efalizumab response rate of 25% **Statistical analyses** Dichotomous outcomes including the PASI 75 were compared using the 2-sided Fisher's exact test. Continuous data were analysed using 2-sided *t*-test or non-parametric test (Wilcoxon rank sum test) as appropriate. Hochberg–Bonferroni adjustment for multiple comparisons used for secondary end-points	**PASI 75** Efalizumab: 12 wks: 27% (98/369); placebo: 12 wks: 4% (8/187); $p < 0.001$. Treatment effect: 22.3% (95% CI 15.8 to 29.5%) **PASI 50** Efalizumab: 12 wks: 59% (216/369); placebo: 12 wks: 14% (26/187); $p < 0.001$ Mean % improvement from baseline Efalizumab: 12 wks: 52%; placebo: 12 wks: 19%; $p < 0.001$ **Clear or almost clear** Efalizumab: 12 wks: 26%; placebo: 12 wks: 3%; $p < 0.001$ **PGA** Proportion excellent or cleared Efalizumab: 12 wks: 33%; placebo: 12 wks: 5%; $p < 0.001$ **DLQI (mean % improvement)** Efalizumab: 12 wks: 47%; placebo: 12 wks: 14%; $p < 0.001$ **PSA frequency (mean % improvement)** Efalizumab 12 wks: 46.9%; placebo 12 wks: 18.4%; $p < 0.001$ **PSA severity (mean % improvement)** Efalizumab 12 wks: 47.3%; placebo 12 wks: 17.3%; $p < 0.001$ **Itching scores (mean % improvement)** Efalizumab 12 wks: 37.7%; placebo 12 wks: 11.2%; $p < 0.001$ **Adverse events** Adverse events occurring in ≥5% of all patients Efalizumab ($n = 368$) / Placebo ($n = 187$) Total: 296 (80%) / 133 (71%) Drug-exposure related: 163 (44%) / 47 (25%) **Non-infectious adverse events** Headache: 123 (33%) / 39 (21%) Chills: 44 (12%) / 10 (5%) Nausea: 39 (11%) / 13 (7%) Myalgia: 38 (10%) / 8 (4%) Pain: 37 (10%) / 9 (5%) Fever: 25 (7%) / 3 (2%)

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Study details and design	Participant details	Intervention/outcome/ analyses details	Results
	Concurrent therapies Tar and salicylic acid preparations were permitted for the scalp, and low-potency topical corticosteroids were allowed for the face, hands, feet, groin and axillae **Comments** Patients were permitted to use emollients	**ITT analysis** Yes. For primary and secondary end-points, consisting of all patients who were randomised. Safety analyses were performed on the as-treated population **Comments** After 12 wks all patients were enrolled in a separate long-term open-label extension study	Rhinitis 23 (6%) 11 (6%) Asthenia 22 (6%) 9 (5%) Diarrhoea 20 (5%) 10 (5%) Unintentional injury 17 (5%) 19 (10%) Accidental injury 17 (5%) 19 (10%) **Infectious adverse events including any serious infections** Any infection 27% 23% Infection not specified 46 (13%) 23 (12%) Pharyngitis 27 (7%) 10 (5%) Flu-like syndrome 27 (7%) 7 (4%) Herpes simplex 17 (5%) 7 (4%) Gastroenteritis 5 (1%) 10 (5%) Serious infections (no.): efalizumab: 0.5%; placebo: 0.5% Opportunistic infections: none **Cancer** 2 cases in efalizumab-treated patients (squamous cell cancer at day 2; basal cell cancer at day 77) **Other non-infectious serious adverse events (no.)** Serious adverse events: efalizumab: 2% (9/368); Placebo: 1% (1/187) **Deaths** None **Withdrawals due to adverse events** Efalizumab: 12 (3%); placebo: 2 (1%) **Positive test for anti-efalizumab antibody** Efalizumab: 8 (2%); placebo: 0 **Other important adverse event results** No clinically significant laboratory abnormalities or pattern of changes were observed during efalizumab therapy **Comments** In the industry submission, adverse events experienced by >2% patients

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
Lebwohl, 2003,[74] USA **Type of publication** Full publication **Other publications/reports** Menter, 2004,[156] Full publication Gordon, 2002,[159] Abstract ACD2059g, 2004,[160] Industry submission **Funding** Genentech Inc. **Study design** Double-blind RCT, parallel Monotherapy The study was in 3 stages: Stage 1: RCT Stage 2: Further RCT dependent on response of participants after completion of first stage Stage 3: Follow-up after discontinuation of study treatments **Setting** Outpatient **Duration of follow-up (wks)** Total: 36 Stage 1: 12 Stage 2: 12 Stage 3: 12 **Frequency of follow-up** Main assessments every 12 wks for 36 wks Extracted by: NW Checked by: AK	**Inclusion/exclusion criteria** Aged 18–70 yrs, plaque psoriasis stable for ≥3 months and PASI score ≥ 12, covering ≥ 10% BSA and candidate for systemic therapy. Patients with uncontrolled infection, cancer, hepatic or renal dysfunction or abnormal white blood cell count were excluded Stage 2: participants who had received efalizumab 1- or 2-mg dose in Stage 1 Stage 3: all patients continuing in study after Stage 2 **Number randomised and treated** Stage 1: 597 Stage 2: 434 **Age** *Mean age (SD)* Total: 46 yrs (not stated) **Gender** Total: male 65% **Psoriasis history** *Duration of psoriasis [mean (SD)]* Total: 19 yrs (not stated) *Prior systemic therapy* Total: 67% PASI score at baseline [mean (SD)] Total: 20.0 (not stated)	*Stage1* **Intervention efalizumab** Dose regimen: 1 mg/kg s.c. once a wk Length of treatment: 12 wks No. randomised: 232 No. completed: 211 **Intervention efalizumab** Dose regimen: 2 mg/kg s.c. once a wk Length of treatment: 12 wks No. randomised: 243 No. completed: 227 **Comparator placebo** Dose regimen: equivalent Length of treatment: 12 wks No. randomised: 122 No. completed: 111 *Stage 2* **Intervention efalizumab** Patients with PASI >50 at end of Stage 1 were re-randomised to two different dose frequencies Dose regimen: efalizumab s.c. 2 mg/kg once a wk Length of treatment: 12 wks No. randomised: 86 No. completed: 78 Dose regimen: efalizumab s.c. 2 mg/kg once every 2 wks Length of treatment: 12 wks No. randomised: 85 No. completed: 80	*Stage 1* **PASI 75** Efalizumab 1 mg 12 wks: 52/232 (22%); efalizumab 2 mg 12 wks: 69/243 (28%); placebo 12 wks: 6/122 (5%); $p < 0.001$ for placebo vs both efalizumab doses **PASI 50** Efalizumab 1 mg 12 wks: 120/232 (52%); efalizumab 2 mg 12 wks: 138/243 (57%); placebo 12 wks: 19/122 (16%); $p < 0.001$ for placebo vs both efalizumab doses **PASI 90** Efalizumab 1 mg 12 wks: 10/232 (4%); efalizumab 2 mg 12 wks: 15/243 (6%); placebo 12 wks: 1/122 (>1%); p = NS for placebo vs both efalizumab doses **DLQI (mean % improvement)** Efalizumab 1 mg 12 wks: 45.4%; placebo 12 wks: 12.3%; $p < 0.001$ **PSA frequency (mean % improvement)** Efalizumab 1 mg 12 wks: 41.9%; placebo 12 wks: 9.0%; $p < 0.001$ **PSA severity (mean % improvement)** Efalizumab 1 mg 12 wks: 45.1%; placebo 12 wks: 8.1%; $p < 0.001$ **Itching scores (mean % improvement)** Efalizumab 1 mg 12 wks: 43.3%; placebo 12 wks: 12.9%; $p < 0.001$ *Stage 2* ***Patients with PASI 75 at wk 12:*** **PASI 75** Efalizumab 1 mg 24 wks: 30/39 (77%); efalizumab 2 mg 24 wks: 31/40 (78%); placebo 24 wks: 8/40 (20%); $p < 0.001$ for placebo vs both efalizumab doses **PASI 50** Efalizumab 1 mg 24 wks: 35/39 (90%); efalizumab 2 mg 24 wks: 38/40 (95%); placebo 24 wks: 16/40 (40%); p = NS for placebo vs both efalizumab doses **PASI 90** Efalizumab 1 mg 24 wks: 12/39 (31%); efalizumab 2 mg 24 wks: 13/40 (32%); placebo 24 wks: 1/40 (2%); p = NS for placebo vs both efalizumab doses ***Patients with PASI 50-74 at wk 12*** **PASI 75** Efalizumab 1 mg 24 wks: 25/47 (53%); efalizumab 2 mg 24 wks: 13/45 (29%); placebo 24 wks: 2/46 (4%); $p < 0.001$ for placebo vs both efalizumab doses

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Study details and design	Participant details	Intervention/outcome/ analyses details	Results
	Concurrent therapies All patients were permitted to use Eucerin cream, tar or salicylic acid preparations for psoriasis of the scalp, limited application of low-potency corticosteroids and oral antipruritic agents. **Comments**	Patients with PASI <50 at end of Stage 1 were re-randomised to: Dose regimen: efalizumab s.c. 4 mg/kg once a wk. Length of treatment: 12 wks No. randomised: 118 No. completed: 101 **Comparator placebo** Dose regimen: equivalent Length of treatment: 12 wks No. randomised: 145 No. completed: 96 *Stage 3* No study treatment **Primary outcome** PASI 75 at 12 wks **Sample size calculation** Planned sample size was 500 patients, based on assumption of 25% response rate on efalizumab and 2% on placebo, giving 95% power at the 0.025% level **Statistical analyses** Fisher's exact test and two-sample *t*-test. Analysis of Stage 2 data was stratified by treatment response in Stage 1 **ITT analysis** Yes. Analysis included all patients randomised **Comments**	**PASI 50** Efalizumab 1 mg 24 wks: 35/47 (74%); efalizumab 2 mg 24 wks: 30/45 (67%); placebo 24 wks: 5/46 (11%); p = NS for placebo vs both efalizumab doses **PASI 90** Efalizumab 1 mg 24 wks: 1/47 (2%); efalizumab 2 mg 24 wks: 3/45 (7%); placebo 24 wks: 0 (0%); p = NS for placebo vs both efalizumab doses ***Patients with PASI <50 at wk 12*** **PASI 75** Efalizumab 4 mg 24 wks: 15/118 (13%); placebo 24 wks: 1/59 (2%); $p < 0.001$ for placebo vs both efalizumab doses **PASI 50** Efalizumab 4 mg 24 wks: 47/118 (40%); placebo 24 wks: 9/59 (15%); $p < 0.001$ for placebo vs both efalizumab doses **PASI 90** Efalizumab 4 mg 24 wks: 5/118 (4%); placebo 24 wks: 1/59 (2%); $p < 0.001$ for placebo vs both efalizumab doses *Stage 3* For wks 24–36 mean time to relapse (loss of >50% of improvement achieved in PASI score at wk 24) in those who had achieved ≥ PASI 50 was 84 days. At wk 36 approximately one-third of patients who had received continuous efalizumab had not relapsed **Adverse events** *Stage 1* Adverse events reported by ≥5% patients in any treatment group during Stage 1 Placebo (n = 122) / Efalizumab 1 mg (n = 232) / Efalizumab 2 mg (n = 243) Any: 91 (75%) / 199 (86%) / 207 (85%) Drug-exposure related: 49 (40%) / 117 (50%) **Non-infectious adverse events** Headache: 29 (24%) / 71 (31%) / 93 (38%) Nausea: 11 (9%) / 34 (15%) / 35 (14%) Chills: 3 (2%) / 38 (16%) / 31 (13%) Pain: 4 (3%) / 35 (15%) / 29 (12%) Fever: 6 (5%) / 26 (11%) / 29 (12%) Asthenia: 7 (6%) / 17 (7%) / 27 (11%)

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results

Myalgia	5 (4%)	16 (7%)	22 (9%)
Arthralgia	6 (5%)	24 (10%)	12 (5%)
Rhinitis	8 (7%)	18 (8%)	13 (5%)
Peripheral oedema	5 (4%)	14 (6%)	12 (5%)
Back pain	1 (1%)	10 (4%)	16 (7%)
Cough increased	5 (4%)	8 (3%)	13 (5%)
Vomiting	2 (2%)	12 (5%)	10 (4%)
Worsening psoriasis	2 (2%)	12 (5%)	8 (3%)
Acne	1 (1%)	14 (6%)	6 (2%)
Accidental injury	9 (7%)	11 (5%)	
Diarrhoea	11 (9%)	16 (7%)	
Rhinitis	8 (7%)	18 (8%)	
Dizziness	6 (5%)	9 (4%)	

Infectious adverse events including any serious infections

Any infection	25%	22%	NR
Infection not specified	19 (16%)	27 (12%)	43 (18%)
Pharyngitis	6 (5%)	14 (6%)	22 (9%)
Herpes simplex	5 (4%)	8 (3%)	14 (6%)

Serious infection: not reported

Cancer
Not reported

Other non-infectious serious adverse events
Placebo: 1 (1%); efalizumab 1 mg: 4 (2%); efalizumab 2 mg: 7 (3%)

Deaths
Not reported

Withdrawals due to adverse events
Placebo: 2 (2%); Efalizumab 1 mg: 9 (4%); Efalizumab 2 mg: 7 (3%)

Positive test for anti-efalizumab antibody
3/456 (0.7%) (NB: a rate of 5% reported for longer period)

Other important adverse event results

Stage 2
Adverse events for wks 12–24 were stated to be similar to wks 0–12, with fewer acute events

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Study details and design	Participant details	Intervention/outcome/ analyses details	Results
			Serious adverse events Not stated **Withdrawals due to adverse events** Adverse events leading to withdrawal were more common in patients receiving placebo *Stage 3* For treatment-free follow-up (wks 24–36) adverse events in all patients were: infection (13%); worsening psoriasis (9%); pruritis (6%); arthritis (5%). 5 efalizumab-treated patients developed anti-efalizumab antibodies; the safety profile of these patients was not different from that of the other patients **Serious adverse events** 13 patients (3%) had a serious adverse events (5 non-fatal infections and 3 psoriasis-related events). *Withdrawals due to adverse events* Not stated **Comments** In the industry submission, adverse events experienced by >2% patients

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Study details and design	Participant details	Intervention/outcome/ analyses details	Results
Papp, 2001,[79] USA and Canada **Type of publication** Full publication **Other publications/reports** None **Funding** XOMA; Genentech Inc. **Study design** Double-blind RCT, parallel Monotherapy **Setting** Outpatient (not stated) **Duration of follow-up** 20 wks **Frequency of follow-up** Not clear. Assessment of efficacy at wk 8 (1 week after last infusion)	**Inclusion/exclusion criteria** Chronic moderate to severe plaque psoriasis, with a minimum PASI of 12 and affecting ≥10% BSA. Psoriasis diagnosed for ≥6 months and stable for ≥3 months. Aged 18–70 yrs and weighed 120 kg or less. Systemic (including UVB and PUVA) therapies stopped ≥28 days before trial and topical therapy stopped ≥14 days before trial. Patients with guttate, pustular or erthrodermic psoriasis were excluded **Number randomised and treated** 145 **Age (years)** *Mean age (SD)* Efalizumab 0.1 mg: 43.2 (14.6) Efalizumab 0.3 mg: 44.5 (12.9) Placebo: 42.3 (12.3) *Median (range)* Efalizumab 0.1 mg : 42 (21–72) Efalizumab 0.3 mg: 44 (21–69) Placebo: 42 (21–66) **Gender** Efalizumab 0.1 mg: male 73% Efalizumab 0.3 mg: male 63% Placebo: male 67% **Psoriasis history** *Duration of psoriasis [mean (SD)] (years)* Efalizumab 0.1 mg: 19.2 (10.4)	**Intervention efalizumab** Dose regimen: 0.1 mg/kg i.v. infusion once a wk; Length of treatment: 8 wks No. randomised: 22; No. completed: 18 **Intervention efalizumab** Dose regimen: 0.3 mg/kg i.v. infusion once a wk. Length of treatment: 8 wks No. randomised: 75 No. completed: 71 **Comparator placebo** Dose regimen: equivalent Length of treatment: 8 wks No. randomised: 48 (47 treated) No. completed: 41 **Primary outcome** Proportion achieving change in PGA to ≥ 'fair' indicating a 25% improvement at day 56 (1 week after final i.v. infusion) **Sample size calculation** Not stated **Statistical analysis** Fisher's exact test (two-sided) Wilcoxon rank sum test **ITT analysis** Yes. All patients randomised included in analysis. **Comments**	**No. (%) with at least 'fair' improvement in PGA** Efalizumab 0.1 mg: 11/22 (50%) Efalizumab 0.3 mg : 53/75 (71%) ($p = 0.0004$ vs placebo) Placebo: 18/48 (38%) **No. (%) with at least 'good' improvement in PGA** Efalizumab 0.1 mg: 5/22 (23%) Efalizumab 0.3 mg: 38/75 (51%) ($p = 0.002$ vs placebo) Placebo: 7/48 (15%) **No. (%) with 'excellent' improvement in PGA** Efalizumab 0.1 mg: 1/22 (5%) Efalizumab 0.3 mg: 19/75 (25%); $p = 0.0003$ vs placebo Placebo: 1/48 (2%) **No. (%) with clearance** No patients on any treatment achieved clearance of their psoriasis **Mean (SD) PASI score at Day 56** Efalizumab 0.1 mg: 14.2 (8.9) Efalizumab 0.3 mg: 10.9 (8.4); $p < 0.0001$ vs placebo Placebo: 13.9 (7.5) **Median change in PASI score from baseline to day 56** Efalizumab 0.1 mg: not stated Efalizumab 0.3 mg: –7.1; $p < 0.0001$ vs placebo Placebo: –1.8 **Adverse events** Adverse events reported by ≥10% patients in any group **Non-infectious adverse events** Headache: 9 (41%) / 31 (41%) / 15 (32%) Fever: 4 (18%) / 26 (35%) / 8 (17%) Chills: 2 (9%) / 21 (28%) / 2 (4%) Asthenia: 3 (14%) / 10 (13%) / 8 (17%) Nausea: 4 (18%) / 18 (24%) / 7 (15%) Vomiting: 0 (0%) / 8 (11%) / 0 (0%) Dizziness: 3 (14%) / 7 (9%) / 4 (9%) Urinary abnormality: 3 (14%) / 4 (5%) / 5 (11%) Efalizumab 0.1 mg/kg ($n = 22$); Efalizumab 0.3 mg/kg ($n = 75$); Placebo ($n = 47$)

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Study details and design	Participant details	Intervention/outcome/ analyses details	Results
	Efalizumab 0.3 mg: 22.8 (12.6) Placebo: 17.8 (10.0) *Prior systemic therapy* Efalizumab 0.1 mg: 77% Efalizumab 0.3 mg: 81% Placebo: 85% Note in this study systemic included ciclosporin, methotrexate, UVB and PUVA *PASI score at baseline [mean (SD)]* Efalizumab 0.1 mg: 18.2 (6.7) Efalizumab 0.3 mg: 19.1 (7.3) Placebo: 16.2 (4.4) **Concurrent therapies** Not stated **Comments**		**Infectious adverse events including any serious infections** Any infection: not reported Serious infection: not reported **Cancer** One efalizumab 0.1 mg/kg patient developed breast cancer 9 months after treatment; not considered study drug related. **Other non-infectious serious adverse events** Ten serious adverse events reported overall: breakdown by treatment group not reported. Most not related to study drug. One patient on efalizumab 0.3 mg/kg reported unilateral hearing loss that resolved 140 days after start of treatment: not considered drug related **Deaths** None **Withdrawals due to adverse events** None **Positive test for anti-efalizumab antibody** 1/19 (5%) patients treated with 0.1 mg/kg; 10/70 (14%) patients treated with 0.3 mg/kg; none on placebo **Other important adverse event results** Adverse events more common in the efalizumab 0.3 mg/kg group compared with placebo were headache, fever, psoriasis, chills, nausea, infection, pain, vomiting, pharyngitis, flu syndrome and back pain; most were mild

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Results
ACD2058g, 2004[76] **Type of publication** Industry submission (based on clinical trial data on file with Serono) **Other publications/reports** Menter, 2004,[156] Full publication Gordon, 2002,[159] Abstract **Funding** Serono **Study design** Double-blind RCT, parallel Monotherapy The study was in 2 stages: Stage 1: RCT Stage 2: continued treatment or re-treatment following relapse for non-responders **Setting** Not stated **Duration of follow-up** Stage 1: 12 wks Stage 2: 12 wks **Frequency of follow-up** Assessment at 12 wks Extracted by: AK Checked by: NW	**Inclusion/exclusion criteria** Adults with moderate to severe plaque psoriasis who had had prior systemic therapy or were candidates for systemic therapy. Patients had to have a minimum PASI score of 12 and ≥10% BSA. Patients had to have been diagnosed ≥6 months and have been clinically stable for ≥3 months **Number randomised and treated** 498 **Age (years)** Mean age Efalizumab: 45.5 Placebo: 41.7 **Gender** Not stated **Psoriasis history** Not stated **Prior systemic therapy** Not stated **Other** Not stated **Concurrent therapies** Not stated **Comments**	**Intervention efalizumab** Dose regimen: 1 mg/kg s.c. once a wk Length of treatment: 12 wks No. randomised: 162 No. completed: 149 **Intervention efalizumab** Dose regimen: 2 mg/kg s.c. once a wk Length of treatment: 12 wks No. randomised: 166 No. completed: 145 **Comparator placebo** Dose regimen: not stated Length of treatment: 12 wks No. randomised: 170 No. completed: 151 **Primary outcome** Not stated **Sample size calculation** Not stated **Statistical analyses** Not stated **ITT analysis** Yes. Included all patients randomised **Comments**	**PASI 50** Efalizumab 1 mg 12 wks: 99/162 (61%); placebo 12 wks: 25/170 (14.7%); $p < 0.001$ **DLQI (mean % improvement)** Efalizumab 1 mg 12 wks: 47.0%; placebo 12 wks: 16.1%; $p < 0.001$ **PSA frequency (mean % improvement)** Efalizumab 1 mg 12 wks: 43.4%; placebo 12 wks: 13.5%; $p < 0.001$ **PSA severity (mean % improvement)** Efalizumab 1 mg 12 wks: 45.2%; placebo 12 wks: 14.1%; $p < 0.001$ **Itching scores (mean % improvement)** Efalizumab 1 mg 12 wks: 45.3%; placebo 12 wks: 8.5%; $p < 0.001$ **Adverse events** *Stage 1* Adverse events reported by ≥5% of patients treated with efalizumab |	Efalizumab 1 mg (n = 162)	Placebo (n = 170)
	At least 1 adverse event	135 (83%)	130 (77%)
	Drug-exposure related	75 (46%)	58 (34%)
	Non-infectious adverse events		
	Headache	57 (35%)	51 (30%)
	Chills	20 (12%)	10 (6%)
	Fever	12 (7%)	9 (5%)
	Pain	21 (13%)	16 (9%)
	Accidental injury	17 (11%)	6 (4%)
	Asthenia	16 (10%)	17 (10%)
	Nausea	14 (9%)	16 (9%)
	Diarrhoea	12 (7%)	12 (7%)
	Myalgia	13 (8%)	8 (5%)
	Sinusitis	12 (7%)	6 (4%)
	Rhinitis	13 (8%)	14 (8%)
	Pruritis	8 (5%)	11 (7%)
	Peripheral oedema	9 (6%)	5 (3%)
	Back pain	10 (6%)	5 (3%)
	Cough increased	5 (3%)	8 (5%)
	Worsening psoriasis	8 (5%)	4 (2%)
	Dizziness	11 (7%)	8 (5%)
	Hearing loss	12 (7%)	5 (3%)

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Study details and design	Participant details	Intervention/outcome/ analyses details	Results
			Infectious adverse events including any serious infections Any infection 27% 23% Infection not specified 23 (14%) 23 (14%) Pharyngitis 9 (6%) 14 (8%) Herpes simplex 10 (6%) 10 (6%) Serious infections: not stated **Cancer** Not reported **Other non-infectious serious adverse events** Not reported **Withdrawals due to adverse events** Efalizumab: 6 (3.7%); placebo: 6 (3.5%) **Deaths** None **Positive test for anti-efalizumab antibodies** 2/314 (0.6%) **Other important adverse event results** *Stage 2* During re-exposure to efalizumab, the proportion of patients with ≥1 adverse event was ~15% less than that observed during the initial 12-wk period **Comments** PASI 75, overall, lesion severity, PGA and median time to relapse after withdrawal were reported to be trial outcomes, but no data were reported for these

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Study details and design	Participant details	Intervention/outcome/ analyses details	Results
ACD2600g, 2004[77] **Type of publication** Industry submission (based on clinical trial data on file with Serono) **Other publications/reports** FDA website and SPC **Funding** Not stated **Study design** Double-blind RCT, parallel Monotherapy **Setting** Not stated **Duration of follow-up** 12 wks **Frequency of follow-up** Assessment at 12 wks Extracted by: AK Checked by: NW	**Inclusion/exclusion criteria** Adults with moderate to severe plaque psoriasis who had had prior systemic therapy or were candidates for systemic therapy. [**Confidential information removed**] **Number randomised and treated** 686 **Age (years)** *Mean age* Efalizumab: 45.6 Placebo: 46.4 **Gender** Not stated **Psoriasis history** Not stated **Prior systemic therapy** Not stated **Other** Not stated **Concurrent therapies** Not stated **Comments**	**Intervention efalizumab** Dose regimen: 1 mg/kg s.c. once a wk Length of treatment: 12 wks No. randomised: 450 No. completed: 421 **Comparator placebo** Dose regimen: not stated Length of treatment: 12 wks No. randomised: 236 No. completed: 218 **Primary outcome** Not stated **Sample size calculation** Not stated **Statistical analyses** Not stated **ITT analysis** Yes. Included all patients randomised **Comments**	**PASI 50** Efalizumab 12 wks: 234/450 (52%); placebo 12 wks: 33/263 (12.5%); $p < 0.001$ [**Confidential information removed**] **Adverse events** [**Confidential information removed**] **Infectious adverse events including any serious infections** [**Confidential information removed**] **Cancer** [**Confidential information removed**] **Other non-infectious serious adverse events** [**Confidential information removed**] **Deaths** [**Confidential information removed**] **Withdrawals due to adverse events** [**Confidential information removed**] **Positive test for anti-efalizumab antibodies** [**Confidential information removed**] **Other important adverse event results** [**Confidential information removed**] **Comments** [**Confidential information removed**]

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Study details and design	Participant details	Intervention/outcome/ analyses details	Results
IMP24011, 2004[78] **Type of publication** Industry submission (based on clinical trial data on file with Serono) **Other publications/reports** SPC **Funding** Serono **Study design** Double-blind RCT, parallel Monotherapy **Setting** Not stated **Duration of follow-up** 12 wks **Frequency of follow-up** Not stated Extracted by: AK Checked by: NW	**Inclusion/exclusion criteria** Adults with moderate to severe plaque psoriasis who had had prior systemic therapy or were candidates for systemic therapy. [**Confidential information removed**] **Number randomised and treated** 793 **Age (years)** [**Confidential information removed**] **Gender** [**Confidential information removed**] **Psoriasis history** [**Confidential information removed**] **Prior systemic therapy** [**Confidential information removed**] **Other** [**Confidential information removed**] **Concurrent therapies** [**Confidential information removed**] **Comments**	**Intervention efalizumab** Dose regimen: 1 mg/kg s.c. once a wk Length of treatment: 12 wks No. randomised: 529 No. completed: [**Confidential information removed**] **Comparator placebo** Dose regimen: not stated Length of treatment: 12 wks No. randomised: 264 No. completed: [**Confidential information removed**] **Primary outcome** Not stated **Sample size calculation** [**Confidential information removed**] **Statistical analyses** [**Confidential information removed**] **ITT analysis** [**Confidential information removed**] **Comments** PASI 75 was reported to be a trial outcome, but no data were reported for this	**PASI 50** [**Confidential information removed**] **PASI 75** Efalizumab 12 wks: 163/529 (31.0%); placebo 12 wks:11/264 (4%) **Adverse events** [**Confidential information removed**] **Cancer** [**Confidential information removed**] **Other non-infectious serious adverse events** [**Confidential information removed**] **Deaths** [**Confidential information removed**] **Withdrawals due to adverse events** [**Confidential information removed**] **Positive test for anti-efalizumab antibodies** [**Confidential information removed**] **Other important adverse event results** [**Confidential information removed**] **Comments** [**Confidential information removed**]

Appendix 5

Data extraction tables: intervention adverse events

Data extraction tables: intervention adverse events – etanercept

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Bathon, 2000,[98] USA **Genovese, 2002,[161] USA** **Type of publication** Full publication **Other publications/reports** Bathon, 2003,[162] Full publication **Funding** Immunex **Study design** Stage 1: double-blind RCT Stage 2: open-label follow-up **Duration of follow-up** Stage 1: 12 months Stage 2: 12 months **Study objective** To compare the efficacy and safety of etanercept and methotrexate in patients with early rheumatoid arthritis Extracted by: AK Checked by: NW	**Indication** Early rheumatoid arthritis **Inclusion criteria** Patients ≥18 yrs of age who had had rheumatoid arthritis for no more than 3 yrs, had not been treated with methotrexate and had no other important concurrent illness. Patients were required to have positive rheumatoid factor or at least 3 bone erosions of the hand, wrists or feet, at least 10 swollen joints and at least 12 tender or painful joints. Disease-modifying anti-rheumatic drugs (DMARDs) were discontinued at least 4 weeks before the study began **Total no. of participants** Stage 1: 632 Stage 2: 512 **Age (years)** Etanercept 10 mg: mean 50.0 (SD 13, range 19–84) Etanercept 25 mg: mean 51.0 (SD 13, range 21–82) **Gender** Etanercept 10 mg: male 25% Etanercept 25 mg: male 26% **Concurrent therapies** All patients received 1 mg folic acid per day. Other drugs	**Intervention etanercept** Dose regimen: 10 mg s.c. twice a wk Duration/frequency of treatment: 24 months No. of participants: Stage 1: 208; Stage 2: 166 **Intervention etanercept** Dose regimen: 25 mg s.c. twice a wk Duration/frequency of treatment: 12 months No. of participants: Stage 1: 207; Stage 2: 177 **Comparators** Methotrexate (Stage 1 $n = 217$; Stage 2 $n = 169$): 2.5 mg oral three times a wk titrated to 2.5 mg oral eight times a wk after 8 wks **Assessment** Adverse events were graded on a scale derived from the Common Toxicity Criteria for the National Cancer Institute. Patients were assessed every 3 months for adverse events **Comments** Patients who discontinued either study drug received standard care and continued to be evaluated for the duration of the study	**STAGE 1 (MONTHS 0–12)** **Non-infectious adverse events occurring in ≥10% patients in any etanercept group (no. of patients)** Etanercept 10 mg $n = 208$ / Etanercept 25 mg $n = 207$ Low peripheral lymphocyte count: (56%) / Not reported Injection site reaction: 63 (30%) / 77 (37%) Headache: 52 (25%) / 46 (22%) Nausea: 29 (14%) / 35 (17%) Sporadic neutropenia: Not reported / (16%) Rhinitis: 36 (17%) / 31 (15%) Diarrhoea: 26 (12%) / 30 (14%) Bleeding at injection site: 30 (14%) / 29 (14%) Asthenia: 19 (9%) / 27 (13%) Flu-like syndrome: 20 (10%) / 26 (13%) Rash: 33 (16%) / 25 (12%) Dyspepsia: 21 (10%) / 25 (12%) Dizziness: 10 (5%) / 24 (12%) Back pain: 12 (6%) / 22 (11%) Abdominal pain: 23 (11%) / 20 (10%) Sinusitis: 28 (13%) / 20 (10%) **Other non-infectious adverse events (no. of patients)** Etanercept 10 mg: grade 3 neutropenia 1 Etanercept 25 mg: grade 3 neutropenia 2 **Infectious adverse events including any serious infections occurring in ≥10% patients in any etanercept group (no. of patients)** Etanercept 10 mg / Etanercept 25 mg URT infection: 57 (27%) / 72 (35%) Skin infection: 22 (11%) / 28 (14%) All types of infection occurred at a rate of 1.5 events per patient year across the two etanercept groups Infection requiring hospitalisation or i.v. antibiotics occurred in <3% of patients There were no opportunistic infections The rate of serious infections was similar to that in months 13–24

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
	permitted were stable doses of NSAIDs, prednisdone (≤ 10 mg a day), glucocorticoids **Comments**		**Cancer (no. of patients)** Breast cancer: Etanercept 10 mg 1; Etanercept 25 mg 0 Lung cancer: 1; 0 Carcinoid lung cancer: 0; 1 Hodgkin's disease: 0; 1 Prostate cancer: 0; 1 **Other non-infectious serious adverse events** Not reported **Deaths (no.)** Metastatic lung cancer: Etanercept 10 mg 1; Etanercept 25 mg 0 Non-infectious complications from dissection of pre-existing aortic aneurysm: 0; 1 **Withdrawals due to adverse events (no.)** Etanercept 10 mg: 2 (10.6%); etanercept 25 mg: 5 (4.8%) **Positive test for anti-etanercept antibody** <3% of etanercept patients were positive. The positives tests were not associated with adverse events **Other important adverse event results** Not reported **STAGE 2 (MONTHS 13–24)** **Non-infectious adverse events** Not reported **Infectious adverse events including any serious infections (no. of patients)** Cellulitis: Etanercept 10 mg *n* = 166: 1; Etanercept 25 mg *n* = 177: 1 Bronchitis: 1; 0 Pneumonia: 1; 0 Cystitis: 0; 2 There were no tuberculosis infections

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results

Cancer (no. of patients)
Etanercept 10 mg: 1; etanercept 25 mg: 1

Other non-infectious serious adverse events (no. of patients)
Not reported

Deaths
There were no deaths

Withdrawals due to adverse events (no. of patients)
Etanercept 10 mg: 2; etanercept 25 mg: 5

Positive test for anti-etanercept antibody
Not reported

Other important adverse event results
Not reported

STAGE 1 AND 2 COMBINED (MONTHS 0–24)
Non-infectious adverse events occurring in >10% patients in any group (no. of patients)

	Etanercept 10 mg *n* = 208	Etanercept 25 mg *n* = 207
Low peripheral lymphocyte count	Not reported	Not reported
Injection site reaction	66 (32%)	81 (39%)
Headache	56 (27%)	51 (25%)
Nausea	30 (14%)	42 (20%)
Rash	40 (19%)	37 (18%)
Rhinitis	41 (20%)	37 (18%)
Diarrhoea	28 (14%)	35 (17%)
Asthenia	25 (12%)	33 (16%)
Bleeding at injection site	31 (15%)	32 (16%)
Sporadic neutropenia	Not reported	Not reported
Dyspepsia	33 (16%)	31 (15%)
Dizziness	15 (7%)	30 (15%)
Abdominal pain	26 (13%)	26 (13%)
Back pain	17 (8%)	25 (12%)
Accidental injury	24 (12%)	23 (11%)
Pain	17 (8%)	22 (11%)
Ecchymosis	19 (9%)	23 (11%)
Vomiting	7 (3%)	20 (10%)

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results

Hypertension	23 (11%)	18 (9%)
Peripheral oedema	23 (11%)	14 (7%)

Infectious adverse events including any serious infections occurring in >10% patients in any etanercept group (no. of patients)
Not reported

There were no opportunistic infections

Infection requiring hospitalisation or i.v. antibiotics (no. of patients)
Etanercept 10 mg: 5 (2.4%); etanercept 25 mg: 7 (3.4%)

Cancer (no. of patients)
Etanercept 10 mg: 3; etanercept 25 mg: 4

Other serious non-infectious adverse events
Not reported

Deaths (no.)
See Stage 1 (months 0–12) data

Withdrawals due to adverse events (no.)
Etanercept 10 mg: 11 (6.6%); etanercept 25 mg: 15 (7.3%)

Positive test for anti-etanercept antibody
14 (3.5%) etanercept patients were positive: etanercept 10 mg: 6 (2.9%) patients; etanercept 25 mg: 8 (3.9%) patients. The positive tests were not associated with adverse events

Other important adverse event results
Not reported

Comments
Withdrawal data reported for Stages 1 and 2 combined (months 0–24) do not tally with withdrawal data reported for Stage 1 (months 0–12). Using Stage 1 data (months 0–12) and Stage 2 data (months 13–24), withdrawal figures tally to etanercept 10 mg: 24 (11.5%); etanercept 25 mg: 15 (7.2%)

The reporting of infection and serious adverse events across the different time periods and different publications was inconsistent

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Davis, 2003,[92] USA, Canada and Europe **Type of publication** Full publication **Other publications/reports** None **Funding** Immunex Corp. **Study design** Double-blind placebo-controlled RCT **Duration of follow-up** 24 wks **Study objective** To determine the safety and efficacy of etanercept in adults with moderate to severe ankylosing spondylitis Extracted by: AK Checked by: NW	**Indication** Ankylosing spondylitis **Inclusion criteria** Patients aged between 18 and 70 years with ankylosing spondylitis. Patients were excluded if they had complete ankylosis (fusion) of the spine, had previously received TNF inhibitor therapy, had serious infection within 4 wks of starting the study, were pregnant or received DMARDs (except for hydroxychloroquine, sulfasalazine, or methotrexate) within 4 wks of starting **Total no. of participants** 277 **Age (years)** Etanercept: mean 42.1 (range 24–70) Placebo: mean 41.9 (range 16–65) **Gender** Etanercept: male 76% (n = 105) Placebo: male 76% (n = 105) **Concurrent therapies** Hydroxychloroquine, sulfasalazine, methotrexate, NSAIDs and prednisone, analgesics were permitted **Comments**	**Intervention etanercept** Dose regimen: 25 mg s.c. twice a wk Duration/frequency of treatment: 24 wks No. of participants: 138 **Comparators** Placebo (n=139): equivalent **Assessment** All patients who were randomised and received at least one dose of study drug were evaluated for adverse events, which were graded on a scale derived from the Common Toxicity Criteria for the National Cancer Institute. Patient diaries were used to record any adverse events. Study staff reviewed the diary with the patient at each visit **Comments**	**Non-infectious adverse events occurring in ≥5% patients (no. of patients)** Placebo / Etanercept Injection site reaction: 13 (9%) / 41 (30%) Injection site bruising: 23 (17%) / 29 (21%) Headache: 16 (12%) / 19 (14%) Accidental injury: 6 (4%) / 17 (12%) Diarrhoea: 13 (9%) / 11 (8%) Rash: 9 (6%) / 11 (8%) Rhinitis: 9 (6%) / 8 (6%) Abdominal pain: 7 (5%) / 8 (6%) Dizziness: 3 (2%) / 8 (6%) Flu-like syndrome: 10 (7%) / 5 (4%) **Infectious adverse events including any serious infections occurring in ≥5% patients (no. of patients)** Placebo / Etanercept URT infection: 16 (12%) / 28 (20%) There were no opportunistic or tuberculosis infections **Serious infections (no. of patients)** Etanercept: wound infection after cat bite 1; placebo: viral infection 1 **Cancer** Not reported **Other non-infectious serious adverse events (no. of patients)** Placebo / Etanercept Chest pain: 1 Accidental injury: 2 Suicide attempt: 1 Lymphadenopathy: / 1 Staphylococcal cellulitis after spider bite: 1 Fever with injection site reaction: / 1 Ulcerative colitis: / 1 Intestinal obstruction due to adhesions: / 1 Bone fracture after trauma: / 3 **Deaths** Not reported

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
			Withdrawals due to adverse events (no.) Placebo: Total 1 Etanercept: Total 7; Fever with injection site reaction 1; Ulcerative colitis 1; Intestinal obstruction due to adhesions 1; Bone fracture after trauma 2; Gastrointestinal haemorrhage secondary to haemorrhoids 1; Ileitis secondary to Crohn's disease 1 **Positive test for anti-etanercept antibody** 3 etanercept patients tested positive for non-neutralising anti-etanercept antibodies **Other important adverse event results** Not reported **Comments**
Geborek, 2002,[96] Sweden **Type of publication** Full publication **Other publications/reports** None **Funding** Not stated **Study design** Prospective study **Duration of follow-up** 2 yrs **Study objective** To apply a clinical protocol adapted to monitor new treatments in rheumatoid arthritis to evaluate tolerability and efficacy of etanercept,	**Indication** Rheumatoid arthritis **Inclusion criteria** Patients who had failed on at least two DMARDs, including methotrexate, who started on treatment with etanercept, infliximab or leflunomide **Total no. of participants** 369 **Age** Etanercept: mean 54.0 **Gender** Etanercept: male 22% **Concurrent therapies** Prednisolone, systemic glucocorticoid, DMARDs	**Intervention etanercept** Dose regimen: 25 mg s.c. twice a wk Duration/frequency of treatment: up to 2 years No. of participants: 166 **Comparators** Infliximab (n = 135): 3 mg/kg infusion at start, wks 2, 6, 12 and thereafter every 8th wk. Later the dose could be individually tailored and increased. Leflunomide (n = 103): 100 mg oral days 1–3 and thereafter 20 mg a day. **Assessment** For assessment, the patient was included in the new	**Non-infectious adverse events** Not reported **Infectious adverse events including any serious infections** Not reported **Serious infections (no.)** Etanercept: bacterial infection 3 (days 130, 150, 270) **Cancer** Not reported **Other non-infectious serious adverse events (no.)** Etanercept: Myocardial infarction 4, days 41, 63, 130, 501; Uterine cervical carcinoma 2, days 160, 413; Acute myeloic leukaemia 1, day 440; General malaise 1, day 350; Leucopenia 1, day 91; Bell's paralysis 1, day 130; Cutaneous vasculitis 1, day 368; Discoid lupus 1, day 69

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
infliximab and leflunomide under post-marketing conditions Extracted by: AK Checked by: NW	**Comments**	treatment group when starting on a new regimen. If restarted on one treatment after a pause, the patient was considered to have continued to receive the original therapeutic regimen **Comments** All adverse events were recorded using WHO terminology Patients were allowed to switch between etanercept, infliximab and leflunomide if withdrawn from any of the three treatments. 33 patients tried two treatments and one tried all three	**Deaths (no.)** Etanercept Gastroenteritis 1, day 180 Immunocytoma of breast 1, day 220 Myocardial infarction 1, day 413 **Withdrawals due to adverse events** Etanercept: adverse reactions were the main cause of withdrawal throughout the study. **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** The total no. of observational years for etanercept was 232.8 **Graded side effects per 100 yrs (no.)** Etanercept Fatal 1.3 (*n* = 3) Life-threatening 0 (*n* = 0) Serious 7 (*n* = 15) Moderate 16 (*n* = 36) Mild 27 (*n* = 61) Not graded 2 (*n* = 5) **Comments**

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Klareskog, 2004,[93] Europe, Australia, UK and USA **Type of publication** Full publication **Other publications/reports** Industry submission (TEMPO trial), 2004[69] **Funding** Wyeth Research **Study design** Double-blind RCT **Duration of follow-up** 52 weeks **Study objective** To assess combination treatment with etanercept and methotrexate versus the monotherapies in patients with rheumatoid arthritis Extracted by: AK Checked by: NW	**Indication** Rheumatoid arthritis **Inclusion criteria** Patients aged ≥ 18 years with disease duration of 6 months to 20 years with active adult-onset rheumatoid arthritis (defined as ≥ 10 swollen and ≥ 12 painful joints). Patients had to have had a less than satisfactory response to ≥ 1 DMARD other than methotrexate. Patients previously treated with methotrexate were included provided that they had not had clinically important toxic effects or lack of response and had not been treated with methotrexate within 6 months of enrolment **Total no. of participants** 682 **Age (years)** Etanercept: mean 53.2 (SD 13.8) **Gender** Etanercept: male 23% **Concurrent therapies** NSAIDs, corticosteroids. All patients received 5 mg folic acid supplement twice a week **Comments**	**Intervention etanercept** Dose regimen: 25 mg s.c. twice a wk and oral placebo once a wk Duration/frequency of treatment: 52 wks No. of participants: 223 **Comparators** Methotrexate (n = 228): 7.5 escalated to 20 mg oral once a wk and placebo s.c. twice a wk Combination (n = 231): etanercept 25 mg s.c. twice a wk combined with methotrexate oral once a wk **Assessment** Treatment-emergent adverse events were defined as either an adverse event that was not present at baseline or an event present at baseline that worsened during the study. A serious infection was defined as need for treatment with parenteral antibiotics or admission **Comments**	**Non-infectious adverse events** Treatment-emergent adverse events occurring in ≥ 10% patients Etanercept Any adverse event 192 (86%) Abdominal pain 26 (12%) Accidental injury 19 (9%) Asthenia 23 (10%) Back pain 28 (13%) Cough increased 14 (6%) Diarrhoea 23 (10%) Headache 34 (15%) Injection site reaction 46 (21%) Nausea 22 (10%) Rash 16 (7%) Vomiting 7 (3%) **Infectious adverse events including any serious infections** Etanercept: all infections 131 (59%); serious infections 10 (4%) **Cancer** Etanercept: basal cell carcinoma 1; breast cancer 1; rectal cancer 1; melanoma 1 **Other non-infectious serious adverse events (no. of patients)** Etanercept: total 25 (11%) **Deaths (no.)** Etanercept: heart failure and suspected sepsis 1 **Withdrawals due to adverse events** Etanercept: 25 **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** Not reported **Comments**

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Mease, 2004,[94] USA **Type of publication** Full publication **Other publications/reports** Industry trial report[163] Industry trial report[164] Industry expert report[165] Ory, 2002,[166] Abstract **Funding** Immunex Corporation **Study design** Stage 1: double-blind placebo controlled RCT Stage 2: maintenance period (blinded) Stage 3: open-label follow-up **Duration of follow-up** Stage 1: 24 wks Stage 2: <24 wks Stage 3: 48 wks **Study objective** To evaluate the safety, efficacy, and effect on radiographic progression of etanercept in patients with psoriatic arthritis Extracted by: AK Checked by: NW	**Indication** Psoriatic arthritis **Inclusion criteria** Patients between 18 and 70 yrs of age with active psoriatic arthritis and stable plaque psoriasis (target lesion >2 cm diameter) with >3 swollen joints and >3 painful/tender points with at least one of the following subtypes of psoriatic arthritis: DIP involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis or ankylosing spondylitis-like. Arthritis had to have demonstrated an inadequate response to NSAID therapy **Total no. of participants** Stage 1: 205 [**Confidential information removed**] Stage 3: 168 **Age** Stage 1: Total: mean [**Confidential information removed**] (range 18–76) Etanercept: mean 47.6 (range 18–76) Placebo: mean 47.3 (range 21–73) **Gender** *Stage 1* Etanercept: male 57% (n = 58)	**Intervention etanercept** *Stage 1* Dose regimen: 25 mg s.c. twice a wk Duration/frequency of treatment: 24 wks No. of participants: 101 *Stage 2* After completing Stage 1, patients could chose to continue on their blinded study treatment in this maintenance period until all patients had completed 24 wks of study treatment and the database was locked Dose regimen: 25 mg s.c. twice a wk Duration/frequency of treatment: [**Confidential information removed**] *Stage 3* After the database was locked all patients who completed 12 wks of study drug in Stage 1 [**Confidential information removed**] were eligible to enter a 48-week open label extension Dose regimen: 25 mg s.c. twice a wk Duration/frequency of treatment: 48 wks No. of participants: 168 (87 previously on etanercept; 81 Stage 1 previously on placebo)	**STAGE 1 (24-WK DOUBLE-BLIND RCT)** **Non-infectious adverse events occurring in >5% patients in any group (no. of patients)** Etanercept / Placebo Any adverse event: 65 (64%) / 69 (66%) Injection site reaction: 36 (36%) / 9 (9%) Injection site ecchymosis: 12 (12%) / 11 (11%) Accidental injury: 8 (8%) / 5 (5%) Headache: 8 (8%) / 5 (5%) Sinusitis: 6 (6%) / 8 (8%) Rash: 5 (5%) / 7 (7%) Cough increase: 4 (4%) / 6 (6%) Dizziness: 4 (4%) / 5 (5%) Nausea: 2 (2%) / 7 (7%) Rhinitis: 1 (1%) / 7 (7%) Diarrhoea: 1 (1%) / 6 (6%) Dyspepsia: 1 (1%) / 6 (6%) Immunisation reaction: 0 (0%) / 6 (6%) Pruritus: 1 (1%) / 5 (5%) **Infectious adverse events including any serious infections occurring in >5% patients in any group (no. of patients)** Etanercept / Placebo Any infection: 40 (40%) / 45 (43%) Upper respiratory infection: 21 (21%) / 24 (23%) Urinary tract infection: 6 (6%) / 6 (6%) **Infections that required hospitalisation or use of intravenous antibiotics (no. of patients)** Etanercept: 0 Placebo: gastroenteritis 1 **Cancer** None **Other non-infectious serious adverse events** Etanercept: total 4 (4 patients); chest pain 1; renal calculus 1; multiple sclerosis 1; synscope 1 Placebo: total 8 (4 patients); angina pectoris 1; gastroenteritis 1; gastritis 1; atrial fibrillation 1; gastrointestinal haemorrhage 1; heart failure 1; perforated large intestine 1; surgery complications for perforated bowel (intraperitoneal haemorrhage 1

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
	Placebo: male 45% (n = 47) **Concurrent therapies** Methotrexate, NSAIDs, corticosteroids, topical preparations (for scalp, axilla or groin only) **Comments**	[**Confidential information removed**] **Comparators** *Stage 1* Placebo (n = 104): equivalent *Stage 2* Placebo [**Confidential information removed**]: equivalent **Assessment** All patients who were randomised and received at least one dose of study drug were evaluated for adverse events. [**Confidential information removed**] **Comments**	**Deaths (no.)** Etanercept: 0 Placebo: total 1; surgery complications for perforated bowel (intraperitoneal haemorrhage) 1 **Withdrawals due to adverse events** Etanercept: total 1; elevated liver enzymes 1 Placebo: total 1; increased psoriasis 1 **Positive test for anti-etanercept antibody** All samples were negative for anti-etanercept antibodies **Other important adverse event results** [**Confidential information removed**] **STAGE 2 (<24-WK MAINTENANCE PERIOD)** **Non-infectious adverse events** [**Confidential information removed**] **Infectious adverse events including any serious infections** [**Confidential information removed**] **Cancer** [**Confidential information removed**] **Other non-infectious serious adverse events** [**Confidential information removed**] **Deaths (no.)** [**Confidential information removed**] **Withdrawals due to adverse events (no. of patients)** [**Confidential information removed**] **Positive test for anti-etanercept antibody** [**Confidential information removed**] **Other important adverse event results** [**Confidential information removed**] **STAGE 3 (48-WK OPEN-LABEL FOLLOW-UP)** **Non-infectious adverse events** [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
			Infectious adverse events including any serious infections **[Confidential information removed]** **Cancer** **[Confidential information removed]** **Other non-infectious serious adverse events** **[Confidential information removed]** **Deaths (no.)** **[Confidential information removed]** **Withdrawals due to adverse events (no.)** **[Confidential information removed]** **Positive test for anti-etanercept antibody** **[Confidential information removed]** **Other important adverse event results** **[Confidential information removed]** **STAGE 2 AND STAGE 3 COMBINED** **Non-infectious adverse events** **[Confidential information removed]** **Infectious adverse events including any serious infections** **[Confidential information removed]** **Cancer** **[Confidential information removed]** **Other non-infectious serious adverse events** **[Confidential information removed]** **Deaths (no.)** **[Confidential information removed]** **Withdrawals due to adverse events (no.)** **[Confidential information removed]** **Positive test for anti-etanercept antibody** **[Confidential information removed]** **Other important adverse event results** **[Confidential information removed]** **Comments** **[Confidential information removed]**

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Moreland, 1999,[97] USA **Type of publication** Full publication **Other publications/reports** None **Funding** Immunex Corp. **Study design** Double-blind RCT **Duration of follow-up** 26 wks **Study objective** To establish the benefit of etanercept in the treatment of rheumatoid arthritis over time with simplified dosing Extracted by: ZK Checked by: NW	**Indication** Rheumatoid arthritis **Inclusion criteria** Patients were adults aged ≥ 18 yrs with active rheumatoid arthritis that had an inadequate response to one of any four DMARDs. Use of DMARDs stopped at least 4 wks prior to study **Total no. of participants** 234 **Age (years)** Etanercept (10 mg): mean 53 Etanercept (25 mg): mean 53 Placebo: mean 51 **Gender** Etanercept (10 mg): male 16% Etanercept (25 mg): male 26% Placebo: male 24% **Concurrent therapies** Oral corticosteroids, NSAIDs and analgesics (except 24 h before joint examinations) were permitted **Comments**	**Intervention etanercept** Dose regimen: 10 mg s.c. twice a wk Duration/frequency of treatment: 26 wks No. of participants: 76 **Intervention etanercept** Dose regimen: 25 mg s.c. twice a wk Duration/frequency of treatment: 26 wks No. of participants: 78 **Comparators** Placebo (n = 80): equivalent **Assessment** Not reported **Comments**	**Non-infectious adverse events (no. of events per patient-year) occurring in ≥10% of patients** Placebo / Etanercept 10 mg / Etanercept 25 mg Injection-site reaction: 0.79 (13%) / 7.39 (43%) / 11.76 (49%) Headache: 0.65 (10%) / 0.81 (20%) / 0.46 (14%) Sinusitis: 0.42 (11%) / 0.26 (11%) / 0.34 (12%) Rhinitis: 0.54 (11%) / 0.36 (12%) / 0.37 (10%) Diarrhoea: 0.28 (6%) / 0.33 (11%) / 0.18 (5%) **Infectious adverse events including any serious adverse events (no.) occurring in ≥10% of patients** Placebo / Etanercept 10 mg / Etanercept 25 mg URT infection: 0.93 (16%) / 0.85 (29%) / 1.11 (33%) **Cancer** Not reported **Other non-infectious serious adverse events** Not reported **Deaths** Not reported **Withdrawals due to adverse events (no.)** Etanercept 10 mg: injection-site reactions 1 Etanercept 25 mg: total 0 **Positive test for anti-etanercept antibody** 1 etanercept 10 mg patient tested positive for non-neutralising anti-etanercept antibodies at 3 and 4 months **Other important adverse events** Not reported **Comments**

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Phillips, 2002,[100] **Type of publication** Full publication **Other publications/reports** None **Funding** National Institutes of Health grants and Arthritis Foundation Investigator Award **Study design** Retrospective review of medical records **Duration of follow-up** 6 mths **Study objective** To investigate the long-term safety and tolerability of etanercept in patients with systemic rheumatic diseases. Extracted by: ZK Checked by: NW	**Indication** *Rheumatic diseases* Rheumatoid arthritis 49 (66%) Juvenile rheumatoid arthritis 25 (14%) Psoriatic arthritis 17 (9%) Ankylosing spondylitis 4 (2%) Dermatomyositis, Stills disease or undifferentiated inflammatory arthritis (9%) **Inclusion criteria** Patients receiving 25 mg etanercept twice weekly **Total no. of participants** 168 **Age (years)** mean 52.8 (SD 15.6) **Gender** Etanercept: male 19% **Concurrent therapies** Methotrexate (56%) Other DMARDs (8%) Corticosteroids (62%) **Comments**	**Intervention etanercept** Dose regimen: 25 mg twice a wk Duration of treatment: median 10 months (range 1–19) No. of participants: 180 **Assessment** Not reported **Comments** Medically important or serious adverse events defined as those requiring i.v. antibiotics or hospitalisation The records of 180 patients were reviewed but as 12 patients were lost to follow-up during the period of the study, only 168 patients were included in the final calculations	**Minor non-infectious adverse events (no. of patients)** Injection site reactions 6 Chest pain 5 Skin rash 14 Depression 5 **Infectious adverse events including any serious infections (no. of patients)** URT infection/cough/sinusitis: 16 **Serious infections (no. of patients)** Acute cholecystitis 1 Septic wrist 1 Arthroplastic hip infection 1 Bacteraemia 1 Psoas abscess/internal perforation 1 **Cancer** None **Other non-infectious serious adverse events** 5 (2.9%) patients experienced serious adverse events **Deaths (no.)** Total 2 (both infection related) **Withdrawals due to adverse events (no.)** Total 10; minor adverse event 6; serious infection 4 **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** 91 (54%) of patients experienced an adverse event; 86 (51%) patients experienced a minor adverse event **Comments**

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Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Willis, 2001,[99] Europe **Type of publication** Abstract (interim analysis) **Other publications/reports** Wajdula, 2000,[167] Abstract **Funding** Wyeth-Ayerst **Study design** Open-label study **Duration of follow-up** 1–2 yrs **Study objective** To evaluate the long-term safety and efficacy of etanercept in patients who completed prior double-blind studies comparing etanercept to placebo Extracted by: AK Checked by: NW	**Indication** Rheumatoid arthritis **Inclusion criteria** Patients with inadequate responses to DMARDs **Total no. of participants** 549 **Age** Not stated **Gender** Not stated **Concurrent therapies** Not stated **Comments**	**Intervention etanercept** Dose regimen: 25 mg s.c. twice a wk Duration/frequency of treatment: 1–2 yrs No. of participants: 549 [479 (87%) completed 1-year follow-up, 94 (17%) completed 2 year follow-up)] **Comparators** None **Assessment** Not stated **Comments**	**Non-infectious adverse events** The most frequent adverse events were injection site reactions **Infectious adverse events including any serious infections** The most frequent adverse events were URT infections Rate of serious infections remained unchanged over the course of the study **Cancer** Rate of malignancies remained unchanged over the course of the study **Other non-infectious serious adverse events** Not stated **Deaths** Not stated **Withdrawals due to adverse events** The rate of withdrawal for tolerance-related reasons was 8% **Positive test for anti-etanercept antibody** Not stated **Other important adverse event results** Not stated **Comments**

Data extraction tables: intervention adverse events – efalizumab

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Gottlieb, 2004,[95] USA **Type of publication** Conference poster **Other publications/reports** Gottlieb, 2003,[168] Abstract Gottlieb, 2002,[169] Abstract ACD2243g, 2004,[170] Industry submission **Funding** Genentech, Inc. **Study design** Open-label study of efalizumab. All patients received efalizumab. For first 12 weeks patients were randomised to receive concomitant corticosteroids or not **Duration of follow-up** 36 months **Study objective** To evaluate the efficacy, safety and tolerability of long-term continuous efalizumab therapy in patients who respond to an initial 12-wk course of efalizumab **Note**: No data available for this study except for the long-term adverse events data extracted here. No data on relative efficacy or adverse events with or without corticosteroids Extracted by: NW Checked by: AK	**Indication** Moderate to severe plaque psoriasis **Inclusion criteria** Patients with moderate to severe plaque psoriasis were entered into a 12-wk period of efalizumab treatment. Those who achieved at least PASI 50 or PGA of mild, minimal or clear were entered into long-term treatment with efalizumab **Total no. of participants** 339 **Age (years)** Efalizumab: mean 43.6 (range 19–73) **Gender** Efalizumab: male 64.9% (n = 220) **Concurrent therapies** During the initial 12 wks, half the patients were randomised to receive concomitant topical steroids. During the long-term follow-up patients were permitted to receive topical therapy or UVB therapy	**Intervention efalizumab** Dose regimen: initial 3 months 2 mg/kg/wk s.c.; subsequent 33 months 1 mg/kg/wk s.c. **Duration/frequency of treatment** 36 months **No. of participants** 339 initial 3 months; 290 subsequent 33 months **Comparators** None **Assessment** Not reported **Comments** Safety analyses were conducted on the as-treated population (i.e. only patients remaining in the study)	**Non-infectious adverse events** Non-infectious adverse events that occurred in at least 5% of patients during any 12-week period of the follow-up phase included accidental injury, increased cough, rhinitis and sinusitis **Infectious adverse events including any serious infections** Infectious adverse events that occurred in at least 5% of patients during any 12-wk period of the follow-up phase included non-specific infections, mostly colds and urinary infections. The average frequency of non-specific infection per 3-month period over the 30-month follow-up ranged from 8.8 to 15.9% of patients. That for infection-related adverse events ranged from 18.0 to 30.1% of patients **Cancer** The average frequency of skin cancer per 3-month period over the 30-month follow-up ranged from 0 to 3.3% of patients **Other non-infectious serious adverse events** The average frequency of serious adverse events per 3-month period over the 30-month follow-up ranged from 1.0 to 5.5% of patients **Deaths** Not reported **Withdrawals due to adverse events** The average frequency of withdrawals due to adverse events per 3-month period over the 30-month follow-up was 3.1% of patients or less **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** Clinically significant, including serious, adverse events remained generally stable between each 3-month period

Appendix 6
Adverse effects

Adverse effects of etanercept

Information from standard reference texts

The adverse effects of etanercept summarised from standard reference sources[63,65,80,81] are listed below.

Adverse events that are frequent and requiring medical attention are infection, respiratory tract infection and varicella infection. Adverse events that are frequent but only require medical attention if they continue or are bothersome are abdominal pain, headache, injection site reaction, nausea and vomiting, pharyngitis, rhinitis and sinusitis. Adverse events that are less frequent but requiring medical attention are abdominal abscess, septic arthritis, bronchitis, cellulitis, cholecystitis, hypertension, hypotension, pneumonia, pylonephritis, sepsis and development of new positive antinuclear antibodies (ANA) or anti-double-stranded DNA antibodies. Adverse events that are rare but requiring medical attention are aplastic anaemia, generalised anaemia, central nervous system effects suggestive of multiple sclerosis (MS), transverse myelitis or other demyelinating conditions, leucopenia, optic neuritis, pancytopenia, neutropenia, seizures, thrombocytopenia and tuberculosis. Adverse events that are less frequent or rare and only require medical attention if they continue or are bothersome are anorexia, asthenia, cough, cutaneous vasculitis, diarrhoea, dry eyes, dry mouth, dyspepsia, fatigue, foot abscess, joint pain, leg ulcer, ocular inflammation, generalised pain, skin rash and subcutaneous nodules.

Serious adverse events reported with etanercept include malignancies, asthma, infections, heart failure, myocardial infarction, myocardial ischaemia, chest pain, syncope, cerebral ischaemia, hypertension, hypotension, cholecystitis, pancreatitis, gastrointestinal haemorrhage, bursitis, confusion, depression, dyspnoea, abnormal healing, renal insufficiency, kidney calculus, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, thrombophlebitis, liver damage, leucopenia, paresis, paresthesia, vertigo, allergic alveolitis, angioedema, scleritis, bone fracture, lymphadenopathy, ulcerative colitis and intestinal obstruction.

Other side-effects include hypersensitivity reactions (including angioedema, bronchospasm, urticaria, and anaphylaxis), worsening heart failure, fever, depression, lupus erythematosus-like syndrome and pruritus. Other effects reported for etanercept are oesophagitis, pancreatitis, gastrointestinal haemorrhage, myocardial or cerebral ischaemia, venous thromboembolism, dyspnoea, bone fracture, renal impairment, polymyositis, bursitis, lymphadenopathy.

This list of adverse effects appears very comprehensive but provides only limited information on the significance and frequency of individual events.

Information from existing reviews of etanercept

In addition to the standard reference texts, a large number of articles and reviews have been published regarding the adverse effects of etanercept.[82–91] To date the main areas of concern relate to the potential of etanercept to increase the risk of infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease.

Infections

Like other treatments for rheumatoid arthritis, psoriasis or psoriatic arthritis, etanercept is an immunosuppressant and all carry a risk of rendering the patient susceptible to infection. The most frequently occurring infections associated with etanercept and other anti-TNF agents are URT infections. These are generally not serious, that is, they do not require hospitalisation or intravenous antibiotics. The US Food and Drug Administration (FDA) review in August 2001[171] reported that of an estimated 82,000 patients treated worldwide with etanercept there had been 13,000 MedWatch reports, 2782 (21%) of which were of infections.

Mycobacterium tuberculosis infection [tuberculosis (TB)] is a major concern with anti-TNF agents. This is because TNF is important for controlling

M. tuberculosis infection within the body. About 95% of those infected will contain the organism via an effective cell-mediated immune response. Exposure to anti-TNF agents may enable reactivation of latent infection. The number of cases with infliximab has been estimated as 24.4 per 100,000 compared to a rate of 6.2 cases per 100,000 in patients with rheumatoid arthritis. Data reviewed by the FDA in August 2001[171] indicated that the risk of TB with etanercept seems lower than with infliximab. However, differences in incidences may reflect different background prevalence and there may be other confounding factors; the relative risk of TB with infliximab and etanercept is difficult to quantify. The review concluded that testing for TB prior to etanercept therapy was not warranted but that caution was required and physicians need to be alert to the possibility of TB infections in patients treated with etanercept.

Other infections which may be of significance are *Listeria monocytogenes, Streptococcus pneumonias, Aspergillus fumigatus, Histoplasma capsulatum, Cryptococus neoformans, Pneumocystis jiroveci (carinii)*, *Coccidiodes immitis* and opportunistic infections.

Congestive heart failure

The pharmacology of anti-TNFs suggested the possibility that these agents would have beneficial effects in patients with congestive heart failure (CHF). Two fairly large randomised double-blind placebo-controlled trials found no evidence of efficacy for etanercept. However, one trial found a trend towards a higher mortality with etanercept and this appeared to be dose related. These findings were not substantiated by the second trial and therefore the risk of increased mortality in patients with CHF from etanercept cannot be considered definitive.

Malignancy

There is no real indication that etanercept is associated with an increase in solid tumours over the background rate. There is some concern regarding the incidence of lymphoma, which has been reported for etanercept. Lymphomas are more common in patients with rheumatoid arthritis and there is uncertainty whether this is related to the disorder or to the treatments used for rheumatoid arthritis. Most commonly associated with anti-TNF therapy is Hodgkin's lymphoma, with an apparent time to onset of 10–21 months. It is not known if this is worse than the incidence associated with other disease modifying anti-rheumatic drugs (DMARDS).

Development of antibodies

Treatment with etanercept has been associated with the development of antibodies in some patients: non-neutralising antibodies, anti-nuclear antibodies and anti-double-stranded DNA antibodies. Generally, the development of these antibodies has not been found to be clinically significant, but there have been some reports of symptoms consistent with lupus-like syndrome.

Lupus-like syndromes

Reports of a lupus-like rash associated with positive antibodies appear to represent a real but very rare side-effect of etanercept therapy. None of the cases were associated with systemic features of systemic lupus erythematosus (SLE) or with a definite diagnosis of SLE.

Demyelinating disease

Concerns were established after several spontaneous reports of demyelinating disease associated with etanercept: some of new cases of MS and others of exacerbations of existing MS. The pharmacology of anti-TNFs suggests a possible therapeutic role in MS, but an RCT of an anti-TNF drug (not etanercept) found an adverse effect of therapy. This finding was reflected in the experience of two patients with MS treated with infliximab. The FDA review[171] concluded that although the evidence is not conclusive, 'TNF agents as a class, may worsen MS in some patients. Caution is clearly warranted in treating patients with pre-existing demyelinating syndromes or in continuing etanercept therapy in patients who develop a demyelinating syndrome.'

Seizures

There have been reports of seizures or convulsions in patients treated with etanercept. However, the association with etanercept therapy is not clear: the condition of some patients with pre-existing seizures was not exacerbated by etanercept therapy.

Haematological adverse effects

There have been rare reports of aplastic anaemia and cases of pancytopenia. Although the cases of aplastic anaemia represent a rare event, the rate is higher than would have been expected. This increased rate may reflect the higher prevalence in patients with rheumatoid arthritis. All the cases of pancytopenia were confounded by other factors and the association with etanercept is very unclear.

Intestinal perforation

There have been several cases of intestinal perforation reported for etanercept. The FDA

review[171] concluded that the incidence did not appear to be in excess of the background incidence and that evidence for an association with etanercept was not strong.

Against this background information on the adverse effects profile of etanercept, we reviewed systematically all long-term (longer than 24 weeks) studies of at least 100 patients for further information on the adverse effects of etanercept.

Adverse events for etanercept: data from included studies

From the selection of trials for inclusion in the efficacy evaluation of etanercept, three RCTs of etanercept in psoriasis provided data on the adverse effects of etanercept in psoriasis.[71–73] Although these trials do not meet the selection criteria for studies to be included in the adverse effects part of the review, they are included in order that the data on both the harms and the benefits reported in the trials of efficacy are considered in this review.

In addition to the RCTs of efficacy, nine clinical studies that provided data on the adverse events of etanercept were identified.[92–100] Details of all studies are presented in the data extraction tables [see the section 'Data extraction tables: intervention adverse events – etanercept' in Appendix 5 (p. 148)]. Each of these nine studies had included at least 100 patients and provided at least 24 weeks' data. Five of these studies were of patients treated with etanercept for rheumatoid arthritis, one was of patients with psoriasis, one was of patients with psoriatic arthritis, one was of patients with ankylosing spondylitis and one was of patients with either rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis.

Overall, there are data available on the adverse effects of etanercept over 12 weeks, 24 weeks (6 months), 1 year and 2 years or more.

Adverse effects of etanercept over 12 weeks

Note: because one of the selection criteria for studies to be included in the evaluation of adverse effects was that trials should be at least 24 weeks long, only the data from the trials of efficacy in psoriasis are included in this summary of 12-week data.

Two RCTs of etanercept in psoriasis[71,72] provided data on the adverse effects of etanercept over a 12-week period (*Table 64*). Both trials compared etanercept 25 mg twice weekly and etanercept 50 mg twice weekly with placebo. One trial contained approximately 160 patients per arm and the other contained approximately 190 patients per arm, giving patient totals of 358 for etanercept 25 mg, 358 for etanercept 50 mg and 359 for placebo.

Withdrawals due to adverse events occurred in 1–3% of patients on etanercept and 1–2% of patients on placebo. Neither trial reported the total number of patients reporting an adverse event: non-infectious and infectious adverse events were reported separately. Headache was commonly reported in all groups. Details of the proportion of patients who reported any non-infectious adverse event and also the rate of injection site ecchymosis cannot be presented owing to commercial confidentiality.

The reported rate of infections was up to 30% in all treatment groups. This finding was similar for URT infections which occurred in at least 5% of all patients. Other non-serious infections were reported by some etanercept patients.

Adverse effects of etanercept over 24 weeks (6 months)

Six studies provided data on the adverse effects of etanercept given for a period of 24 weeks (6 months) (*Table 65*).[71,73,92,94,97,100] Two were of patients with psoriasis and one each of patients with psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and any rheumatic disease. Four of these studies were placebo-controlled double-blind RCTs and one was also a double-blind RCT but provided no placebo data. The sixth study was an uncontrolled retrospective case series.

The total number of patients reporting an adverse event was not reported in any of the studies. Patients with psoriasis were studied in one placebo-controlled double-blind RCT[73] and one double-blind RCT but with no placebo data.[71] In the one double-blind RCT of patients treated for psoriatic arthritis, non-infectious adverse events occurred in 64% of patients treated with etanercept 25 mg twice weekly compared with 66% treated with placebo.[94]

Individual adverse events reported by 5% or more of etanercept-treated patients in at least one of the studies are listed in *Table 21*. In the placebo-controlled RCTs, injection site reaction was reported in 9–49% of etanercept-treated patients compared with 0–13% of placebo-treated patients. In the placebo-controlled trial of psoriasis patients, sinusitis was more common in

TABLE 64 *Pooled adverse events data – etanercept 12 weeks follow-up*[a]

	Leonardi, 2004[71] (DB-RCT in psoriasis – 12-week data)			Elewski, 2003[72] (DB-RCT in psoriasis – 12-week data)		
	Etanercept 25 mg *n* = 162	**Etanercept 50 mg *n* = 164**	**Placebo *n* = 166**	**Etanercept 25 mg *n* = 196**	**Etanercept 50 mg *n* = 194**	**Placebo *n* = 193**
Non-infectious adverse events						
Occurring in	≥5% of patients	≥5% of patients		>5% of patients	>5% of patients	
Any non-infectious adverse event			[**Confidential information removed**]			
Injection site reaction	28 (17%)	22 (13%)	12 (7%)	26 (13%)	35 (18%)	11 (6%)
Headache	19 (12%)	11 (7%)	11 (7%)	[**Confidential information removed**]	[**Confidential information removed**]	[**Confidential information removed**]
Inject site ecchymosis	4 (2%)	8 (5%)	6 (4%)	[**Confidential information removed**]	[**Confidential information removed**]	[**Confidential information removed**]
Accidental injury	5 (3%)	7 (4%)	7 (4%)	[**Confidential information removed**]	[**Confidential information removed**]	[**Confidential information removed**]
Infectious adverse events including any serious infections						
Any infectious	[**Confidential information removed**]	[**Confidential information removed**]	[**Confidential information removed**]	58 (30%)	56 (29%)	55 (29%)
URT infection	15 (9%)	9 (5%)	19 (11%)	[**Confidential information removed**]	[**Confidential information removed**]	[**Confidential information removed**]
[**Confidential information removed**]				[**Confidential information removed**]		
Serious infections (no.)	[**Confidential information removed**]	[**Confidential information removed**]	[**Confidential information removed**]	1	0	1
Cancer				[**Confidential information removed**]		
Other non-infectious serious adverse events (no.)	[**Confidential information removed**]	[**Confidential information removed**]	[**Confidential information removed**]	2	3	1
Deaths (no.)	[**Confidential information removed**]	[**Confidential information removed**]	0	0	0	0
Withdrawals due to adverse events	[**Confidential information removed**]	[**Confidential information removed**]	[**Confidential information removed**]	3 (1%)	2 (1%)	2 (1%)
Positive test for anti-etanercept antibody	NA	NA	NA	[**Confidential information removed**]	[**Confidential information removed**]	NA
Other important adverse event results						

DB-RCT, double-blind randomised controlled trial; NA, not applicable.

[a] Where rate is given as <3%, <5% or <10%, the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut-off level.

TABLE 65 *Pooled adverse events data – etanercept 24 weeks (6 months) follow-up*[a]

	Davis, 2003[92] (DB-RCT ankylosing spondylitis – 24 wks)		Gottlieb, 2003[72] (DB-RCT psoriasis – 24 wks)		Mease, 2004[94] (DB-RCT psoriatic arthritis – 24 wks)		Moreland, 1999[97] (DB-RCT rheumatoid arthritis – 26 wks)		Phillips, 2002[100] (uncontrolled case series rheumatoid disease – 6 months)	Leonardi, 2003[71] (DB-RCT psoriasis – 13-24 wks)	
	Etanercept 25 mg *n* = 138 No. pts (%)	Placebo *n* = 139 No. pts (%)	Etanercept 25 mg *n* = 57 No. pts (%)	Placebo *n* = 55 No. pts (%)	Etanercept 25 mg *n* = 101 No. pts (%)	Placebo *n* = 104 No. pts (%)	Etanercept 25 mg *n* = 78 No. events/ pt-yr	Placebo *n* = 80 No. events/ pt-yr	Etanercept 25 mg *n* = 168 No. pts (%)	Etanercept 25 mg *n* = 149 No. pts (%)	Etanercept 50 mg *n* = 159 No. pts (%)
Non-infectious adverse events (no. of patients)											
Occurring in	>5% of patients		>5% of patients		>5% of patients		≥10% of patients			>5% of patients	>5% of patients
Any non-infectious adverse event	NR	NR	[Confidential information removed]	[Confidential information removed]	65 (64%)	69 (66%)	NR	NR	NR	[Confidential information removed]	[Confidential information removed]
Abdominal pain	8 (6%)	7 (5%)	[Confidential information removed]	[Confidential information removed]	<5%	<5%	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Accidental injury	17 (12%)	6 (4%)	4 (7%)	2 (4%)	8 (8%)	5 (5%)	<10%	<10%	NR	<3%	<3%
Asthenia	<5%	<5%	[Confidential information removed]	[Confidential information removed]	<5%	<5%	<10%	<10%	NR	7 (5%)	2 (1%)
Cellulitis	<5%	<5%	[Confidential information removed]	[Confidential information removed]	<5%	<5%	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Diarrhoea	11 (8%)	13 (9%)	[Confidential information removed]	[Confidential information removed]	1 (1%)	6 (6%)	0.18 (5%)	0.28 (6%)	NR	[Confidential information removed]	[Confidential information removed]
Dizziness	8 (6%)	3 (2%)	[Confidential information removed]	[Confidential information removed]	4 (4%)	5 (5%)	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Headache	19 (14%)	16 (12%)	9 (16%)	7 (13%)	8 (8%)	5 (5%)	0.46 (14%)	0.65 (10%)	NR	8 (5%)	4 (3%)
Hypertension	<5%	<5%	4 (7%)	2 (4%)	<5%	<5%	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]

continued

TABLE 65 *Pooled adverse events data – etanercept 24 weeks (6 months) follow-up[a] (cont'd)*

	Davis, 2003[92] (DB-RCT ankylosing spondylitis – 24 wks)		Gottlieb, 2003[72] (DB-RCT psoriasis – 24 wks)		Mease, 2004[94] (DB-RCT psoriatic arthritis – 24 wks)		Moreland,[97] 1999 (DB-RCT rheumatoid arthritis – 26 wks)		Phillips, 2002[100] (uncontrolled case series rheumatoid disease – 6 months)	Leonardi, 2003[71] (DB-RCT psoriasis – 13-24 wks)	
	Etanercept 25 mg *n* = 138 No. pts (%)	Placebo *n* = 139 No. pts (%)	Etanercept 25 mg *n* = 57 No. pts (%)	Placebo *n* = 55 No. pts (%)	Etanercept 25 mg *n* = 101 No. pts (%)	Placebo *n* = 104 No. pts (%)	Etanercept 25 mg *n* = 78 No. events/ pt-yr	Placebo *n* = 80 No. events/ pt-yr	Etanercept 25 mg *n* = 168 No. pts (%)	Etanercept 25 mg *n* = 149 No. pts (%)	Etanercept 50 mg *n* = 159 No. pts (%)
Injection site reaction	41 (30%)	13 (9%)	5 (9%)	0 (0%)	36 (36%)	9 (9%)	11.76 (49%)	0.79 (13%)	6 (3.6%)	<3%	<3%
Injection site bruising/ ecchymosis	29 (21%)	23 (17%)	6 (11%) [Confidential information removed]	5 (9%) [Confidential information removed]	12 (12%)	11 (11%)	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Pain	<5%	<5%	4 (7%)	4 (7%)	<5%	<5%	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Psoriasis	<5%	<5%	[Confidential information removed]	[Confidential information removed]	<5%	<5%	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Rash	11 (8%)	9 (6%)	[Confidential information removed]	[Confidential information removed]	5 (5%)	7 (7%)	<10%	<10%	14 (8.3%)	<3%	<3%
Rhinitis	8 (6%)	9 (6%)	[Confidential information removed]	[Confidential information removed]	1 (1%)	7 (7%)	0.37 (10%)	0.54 (11%)	NR	[Confidential information removed]	[Confidential information removed]
Sinusitis	<5%	<5%	8 (14%)	4 (4%)	6 (6%)	8 (8%)	0.34 (12%)	0.42 (11%)	NR	<3%	<3%
Infectious adverse events including any serious infections (no. of patients) occurring in >5% of patients											
Any infectious adverse event	NR	NR	[Confidential information removed]	[Confidential information removed]	40 (40%)	45 (43%)	NR	NR	NR	[Confidential information removed]	[Confidential information removed]
URT infection	28 (20%)	16 (12%)	20 (35%)	11 (20%)	21 (21%)	24 (23%)	1.11 (33%)	0.93 (16%)	16 (9.5%)	9 (6%)	11 (7%)

continued

TABLE 65 *Pooled adverse events data – etanercept 24 weeks (6 months) follow-up[a] (cont'd)*

	Davis, 2003[92] (DB-RCT ankylosing spondylitis – 24 wks)		Gottlieb, 2003[72] (DB-RCT psoriasis – 24 wks)		Mease, 2004[94] (DB-RCT psoriatic arthritis – 24 wks)		Moreland, 1999[97] (DB-RCT rheumatoid arthritis – 26 wks)		Phillips, 2002[100] (uncontrolled case series rheumatoid disease – 6 months)	Leonardi, 2003[71] (DB-RCT psoriasis – 13-24 wks)	
	Etanercept 25 mg *n* = 138 No. pts (%)	Placebo *n* = 139 No. pts (%)	Etanercept 25 mg *n* = 57 No. pts (%)	Placebo *n* = 55 No. pts (%)	Etanercept 25 mg *n* = 101 No. pts (%)	Placebo *n* = 104 No. pts (%)	Etanercept 25 mg *n* = 78 No. events/ pt-yr	Placebo *n* = 80 No. events/ pt-yr	Etanercept 25 mg *n* = 168 No. pts (%)	Etanercept 25 mg *n* = 149 No. pts (%)	Etanercept 50 mg *n* = 159 No. pts (%)
Urinary tract infection	<5%	<5%	[Confidential information removed]	[Confidential information removed]	6 (6%)	6 (6%)	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Herpes simplex	<5%	<5%	[Confidential information removed]	[Confidential information removed]	<5%	<5%	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Bronchitis	<5%	<5%	[Confidential information removed]	[Confidential information removed]	<5%	<5%	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Opportunistic or tuberculosis infections (no. of patients)	0	0	NR	NR	NR	NR	NR	NR	NR	<3%	<3%
Serious infections (no. of patients)	1	1	1	1	0	1	NR	NR	5 (3.0%)	[Confidential information removed]	[Confidential information removed]
Cancer	NR	NR	NR	NR	0	0	NR	NR	0	[Confidential information removed]	[Confidential information removed]
Other non-infectious serious adverse events (no. of patients)	8	4	1	2	[Confidential information removed]	[Confidential information removed]	NR	NR	5 (3.0%)	[Confidential information removed]	[Confidential information removed]
Deaths (no.)	NR	NR	0	0	0	1	NR	NR	2 (1.2%)	NR	NR

continued

TABLE 65 *Pooled adverse events data – etanercept 24 weeks (6 months) follow-up[a] (cont'd)*

	Davis, 2003[92] (DB-RCT ankylosing spondylitis – 24 wks)		**Gottlieb, 2003[72] (DB-RCT psoriasis – 24 wks)**		**Mease, 2004[94] (DB-RCT psoriatic arthritis – 24 wks)**		**Moreland, 1999[97] (DB-RCT rheumatoid arthritis – 26 wks)**		**Phillips, 2002[100] (uncontrolled case series rheumatoid disease – 6 months)**	**Leonardi, 2003[71] (DB-RCT psoriasis – 13-24 wks)**	
	Etanercept 25 mg *n* = 138 No. pts (%)	**Placebo *n* = 139 No. pts (%)**	**Etanercept 25 mg *n* = 57 No. pts (%)**	**Placebo *n* = 55 No. pts (%)**	**Etanercept 25 mg *n* = 101 No. pts (%)**	**Placebo *n* = 104 No. pts (%)**	**Etanercept 25 mg *n* = 78 No. events/ pt-yr**	**Placebo *n* = 80 No. events/ pt-yr**	**Etanercept 25 mg *n* = 168 No. pts (%)**	**Etanercept 25 mg *n* = 149 No. pts (%)**	**Etanercept 50 mg *n* = 159 No. pts (%)**
Withdrawals due to adverse events (no. of patients)	7 (5%)	1 (1%)	2 (3.5%)	6 (11%)	1 (1%)	1 (1%)	0	0	10 (5.6%)	[Confidential information removed]	[Confidential information removed]
Positive test for anti-etanercept antibody	3	0	NR	NR	0	0	0	0	NR	NR	NR
Other important adverse event results	NR	NR			[Confidential information removed]	[Confidential information removed]	NR	NR	91 (54%) of patients experienced an adverse event; 86 (51%) patients experienced a minor adverse event		

NR, not reported.

[a] Where rate is given as <3%, <5% or <10%, the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut-off level.

etanercept-treated patients than placebo-treated patients.

The proportion of patients suffering an infection during treatment with etanercept 25 mg was reported in three double-blind RCTs: two placebo controlled and one in which the control was etanercept 50 mg. For reasons of commercial confidentiality, only the results from one trial relating to proportion of patients suffering infection can be presented here: the trial in psoriatic arthritis found the rate on active treatment and placebo to be the same (40 and 43%). URT infections appeared to be more common in etanercept-treated patients than in placebo-treated patients. Of the four trials that reported placebo-controlled data, only the one on psoriatic arthritis did not report a higher rate in the active treatment group.

Serious infections were reported by fewer than 1% of patients in any group in the controlled trials. The case series of 149 patients reported a rate of 3%.

Serious adverse events were uncommon and reported approximately equally on active and placebo treatments.

Withdrawals due to adverse events were not consistently higher in etanercept-treated patients compared with placebo; the highest rate reported was 5.6% in the uncontrolled case series.

In the one study that reported it, the proportion of patients developing anti-etanercept antibodies by 24 weeks was 2%.

The RCT comparison between etanercept 25 mg and etanercept 50 mg twice weekly found no increase in adverse events associated with the higher dose.[71]

Adverse effects of etanercept over 12 months (1 year)

Data from two double-blind RCTs of patients suffering from rheumatoid arthritis were available for the adverse events of etanercept 25 mg over 12 months of treatment.[93,98] Unfortunately, in both of these RCTs the control was methotrexate and therefore comparative placebo data were not available. The most common adverse events (those reported by ≥10% of patients in at least one of these trials) are listed in *Table 66*. One study reported the proportion of patients experiencing any adverse event (86%)[93] and the same study reported a rate of 59% for any infection. Injection site reaction was the most commonly reported adverse event in both trials. Neutropenia was reported in one of these long-term trials; this adverse effect has not been seen in trials of shorter duration. URT infection was common (35% reported in one trial[98]) and skin infections were reported in 14% of patients.[98] These findings are reflected by an uncontrolled open-label follow-up study of etanercept in patients with rheumatoid arthritis.[99] Serious infections occurred in 4% of patients in one RCT[93] and in 3% in the other RCT.[98] Opportunistic infections were not reported for any of the studies. Cases of cancer were reported at rates of <1 to 2% across these studies; one of the uncontrolled open-label follow-up studies reported that the rate of malignancy had not changed over the course of the study.[99]

Other serious adverse events, reported in one of the RCTs, occurred at a rate of 11%. The rate of withdrawals reported by these three 1-year studies in rheumatoid arthritis varied: 11 and 2% in the two RCTs[93,98] and 8% in the uncontrolled open-label follow-up study.[99] Two studies reported the proportion of patients developing anti-etanercept antibodies as 3 and 6%.

One-year data for etanercept in psoriasis patients were available from one uncontrolled follow-up study.[72] [**Confidential information removed**].

Adverse effects of etanercept over 2 years or more

Three studies provided data on the adverse effects of etanercept over a period of 2 years or more.[94,96,98] Of these, two were open-label follow-up of RCTs and one was an uncontrolled observational study. Two were of patients with rheumatoid arthritis and one was of patients with psoriatic arthritis. The results from these studies are summarised in *Table 67*.

The long-term data on psoriatic arthritis patients come from an extension of an RCT,[94] but the details cannot be presented here owing to commercial confidentiality. Furthermore, data on serious adverse effects were not reported for this study.

Even with these long-term data, the information relating to serious adverse events, particularly serious infections and cancer, are sparse. Serious infection and opportunistic infections are not reported.

Two-year data from two studies, one in patients with rheumatoid arthritis and one in patients with

TABLE 66 *Pooled adverse events data – etanercept 1 year follow-up*[a]

	Klareskog 2004[93] (rheumatoid arthritis DB-RCT – 52 weeks)	**Bathon 2000[98] (rheumatoid arthritis DB-RCT 1 year – 52 weeks)**	**Elewski 2004[69,72] (psoriasis open-label follow-up – 48 weeks)**	**Willis 2001[99] (rheumatoid arthritis open-label follow-up – ~1 year)**
	Etanercept 25 mg *n* = 223	**Etanercept 25 mg *n* = 207**	**Etanercept 25 mg (177 on placebo and 190 on 50-mg dose for first 12 weeks) *n* = 557**	**Etanercept 25 mg *n* = 549**
			[**Confidential information removed**]	
Any adverse event	192 (86%)			
Non-infectious adverse events				
Occurring in	≥5%	≥10% of patients		
Any non-infectious adverse event	NR	NR	[**Confidential information removed**]	The most frequent adverse events were injection site reactions
Abdominal pain	26 (12%)	20 (10%)		
Accidental injury	19 (9%)	<10%	[**Confidential information removed**]	
Asthenia	23 (10%)	27 (13%)		
Back pain	28 (13%)	22 (11%)		
Cough increased	14 (6%)	<10%		
Diarrhoea	23 (10%)	30 (14%)		
Dizziness	<5%	24 (12%)		
Dyspepsia	<5%	25 (12%)		
Headache	34 (15%)	46 (22%)	[**Confidential information removed**]	
Flu-like syndrome	<5%	26 (13%)		
Injection site reaction	46 (21%)	77 (37%)		
injection site ecchymosis	<5%	29 (14%)	[**Confidential information removed**]	
Low peripheral lymphocyte count	<5%	NR (56% for lower dose)		
Migraine			[**Confidential information removed**]	
Nausea	22 (10%)	35 (17%)		
Neutropenia sporadic	<5%	(16%)		
Rhinitis	<5%	31 (15%)		
Rash	16 (7%)	25 (12%)		
Sinusitis	<5%	20 (10%)		

continued

TABLE 66 *Pooled adverse events data – etanercept 1 year follow-up[a] (cont'd)*

	Klareskog 2004[93] (rheumatoid arthritis DB-RCT – 52 weeks)	**Bathon 2000[98] (rheumatoid arthritis DB-RCT 1 year – 52 weeks)**	**Elewski 2004[69,72] (psoriasis open-label follow-up – 48 weeks)**	**Willis 2001[99] (rheumatoid arthritis open-label follow-up – ~1 year)**
	Etanercept 25 mg *n* = 223	**Etanercept 25 mg *n* = 207**	**Etanercept 25 mg (177 on placebo and 190 on 50-mg dose for first 12 weeks) *n* = 557**	**Etanercept 25 mg *n* = 549**
Infectious adverse events including any serious infections				
Occurring in	≥ 10% of patients	≥ 10% of patients		
Any infection	131 (59%)	NR	[**Confidential information removed**]	The most frequent adverse events were URT infections
URT infection		72 (35%)		
Skin infection		28 (14%)		
Serious infections	10 (4%)	<3%	[**Confidential information removed**]	Rate of serious infections remained unchanged over the course of the study
Opportunistic infections	NR	0		NR
Cancer	4	3	[**Confidential information removed**]	Rate of malignancies have remained unchanged over the course of the study
Other non-infectious serious adverse events (no. of patients)	25 (11%)	NR	[**Confidential information removed**]	NR
Deaths (no.)	1	1	[**Confidential information removed**]	NR
Withdrawals due to adverse events	25	5	[**Confidential information removed**]	The rate of withdrawal for tolerance-related reasons was 8%
Positive test for anti-etanercept antibody	NR	<3%	[**Confidential information removed**]	NR
Other important adverse event results		All types of infection occurred at a rate of 1.5 events per patient-year. The rate of serious infections was similar to that in months 13–24		NR

[a] Where rate is given as <3%, <5% or <10%, the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut-off level.

TABLE 67 *Pooled adverse events data – etanercept 2 years or more follow-up*[a]

	Bathon 2000[98] (rheumatoid arthritis, open-label follow-up – 2 years)	**Mease 2004[94] (psoriatic arthritis, open-label follow-up – 96 weeks)**	**Geborek 2002[96] (rheumatoid arthritis, open-label follow-up – 2 years)**
	Etanercept 25 mg *n* = 207	**Etanercept 25 mg [Confidential information removed]**	**Etanercept 25 mg *n* = 166**
Non-infectious adverse events			NR
Occurring in	≥ 10% of patients	**[Confidential information removed]**	
Any non-infectious adverse event	NR	**[Confidential information removed]**	
Injection site reaction	81 (39%)	**[Confidential information removed]**	
Ecchymosis (injection site)	23 (11%)	**[Confidential information removed]**	
Bleeding at injection site	32 (16%)	**[Confidential information removed]**	
Accidental injury	23 (11%)	**[Confidential information removed]**	
Headache	51 (25%)	**[Confidential information removed]**	
Back pain	25 (12%)	**[Confidential information removed]**	
Hypertension	< 10%	**[Confidential information removed]**	
Nausea	42 (20%)	**[Confidential information removed]**	
Rash	37 (18%)	**[Confidential information removed]**	
Rhinitis	37 (18%)	**[Confidential information removed]**	
Diarrhoea	35 (17%)	**[Confidential information removed]**	
Asthenia	33 (16%)	**[Confidential information removed]**	
Sporadic neutropenia	> 10%	**[Confidential information removed]**	
Dyspepsia	31 (15%)	**[Confidential information removed]**	
Dizziness	30 (15%)	**[Confidential information removed]**	
Abdominal pain	26 (13%)	**[Confidential information removed]**	
Pain	22 (11%)	**[Confidential information removed]**	
Vomiting	20 (10%)	**[Confidential information removed]**	
Low peripheral lymphocyte count	≥ 10%	**[Confidential information removed]**	
Infectious adverse events including any serious infections			NR
Occurring in	> 10% of patients	**[Confidential information removed]**	
Any infection	NR	**[Confidential information removed]**	
URT infection	NR	**[Confidential information removed]**	
Flu-like syndrome	NR	**[Confidential information removed]**	
Sinusitis	NR	**[Confidential information removed]**	
Pharyngitis	NR	**[Confidential information removed]**	
Serious infections	7 (3.4%)	**[Confidential information removed]**	3
Opportunistic infections	0		NR

continued

TABLE 67 *Pooled adverse events data – etanercept 2 years or more follow-up[a] (cont'd)*

	Bathon 2000[98] (rheumatoid arthritis, open-label follow-up – 2 years)	Mease 2004[94] (psoriatic arthritis, open-label follow-up – 96 weeks)	Geborek 2002[96] (rheumatoid arthritis, open-label follow-up – 2 years)
	Etanercept 25 mg *n* = 207	**Etanercept 25 mg [Confidential information removed]**	**Etanercept 25 mg *n* = 166**
Cancer	4	[**Confidential information removed**]	NR (at least one)
Other serious non-infectious adverse events	NR	[**Confidential information removed**]	8
Deaths (no.)	1	[**Confidential information removed**]	3
Withdrawals due to adverse events (no.)	15 (7.3%)	[**Confidential information removed**]	
Positive test for anti-etanercept antibody	8 (3.9%)	[**Confidential information removed**]	NR
Other important adverse event results		[**Confidential information removed**]	The total no. of observational years for etanercept was 232.8 Graded side-effects per 100 years (no.): Fatal 1.3 (*n* = 3) (included above) Life-threatening 0 (*n* = 0) Serious 7 (*n* = 15) Moderate 16 (*n* = 36) Mild 27 (*n* = 61) Not graded 2 (*n* = 5)

[a] Where rate is given as <3%, <5% or <10%, the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut-off level.

psoriatic arthritis,[94,98] provide information on the relative rates of adverse events in the two populations. Injection site reaction is the most common non-infectious adverse event in both trials. Other adverse events reported include headache, nausea, rash, diarrhoea and rhinitis The reported differences may reflect differences in the underlying disease or the concomitant medication taken by the two populations.

In the one study that reported it, the proportion of patients developing anti-etanercept antibodies was 3.9%.

Summary of adverse events data for etanercept

Data were available for 2 years or more of etanercept treatment but most of the long-term data are from patients with rheumatoid arthritis. Furthermore, published long-term data are poorly reported and therefore of limited value. For patients with psoriasis, data are only available for up to 6 months. From the clinical trial data reviewed, it can be seen that the most common adverse effect of etanercept is injection site reaction; this includes ecchymosis, bruising or bleeding at the injection site. The rate of infections with etanercept is high but not necessarily higher than that on placebo. With longer term use, neurological adverse events are reported and haematological effects such as neutropenia appear. However, it is unclear how treatment related such affects are. Data regarding anti-etanercept antibodies are also scarce, with few studies reporting them. The rates reported indicated that up to 6% of patients might develop antibodies. As identified from earlier reviews, the main areas of concern relate to the potential of etanercept to increase the risk of serious infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease. These serious events are uncommon and not readily identified from the published reports of clinical trials.

Adverse effects of efalizumab

Information from standard reference texts

The information included in the Summary of Product Characteristics for efalizumab (Raptiva) is summarised below.

The most frequent symptomatic adverse events reported during efalizumab therapy were mild to moderate dose-related acute flu-like symptoms including headache, fever, chills, nausea and myalgia. In large placebo-controlled clinical studies, these reactions were observed in approximately 41% of efalizumab-treated patients and 24% of placebo-treated patients over 12 weeks of treatment. After initiation of therapy, these reactions were generally less frequent and occurred at similar rates to those seen in the placebo group from the third and subsequent weekly injections. Antibodies to efalizumab were detected in only 6% of patients. In this small number of patients, no differences were observed in pharmacokinetics, pharmacodynamics, clinically noteworthy adverse events or clinical efficacy.

Those adverse events that were very common (i.e. occurred in more than one in 10 patients) in the total population studied clinically with efalizumab were leuc ocytosis, lymphocytosis and flu-like symptoms (fever, headaches, chills, nausea and myalgia). Common adverse events (i.e. occurred in between one in 10 and one in 100 patients) were psoriasis, arthralgia, psoriatic arthritis (exacerbation/flare), hypersensitivity reactions, back pain, asthenia, elevation of alkaline phosphatase and elevation of alanine aminotransferase. Uncommon adverse events (i.e. occurred in between one in 100 and one in 1000 patients) were thrombocytopenia, urticaria and injection site reactions. No rare (between one in 1000 and one in 10,000 patients) or very rare (less than one in 10,000) reactions were reported.

Infections were common in efalizumab-treated patients; however, in placebo-controlled trials this rate was not higher than with placebo treatment.

Analysis following long-term use in a cohort of 158 patients with moderate to severe psoriasis receiving efalizumab 1 mg/kg/week for 108 weeks did not show any noteworthy differences in frequency of adverse events compared with 12 weeks of exposure to efalizumab. Safety data beyond 12 weeks in the target population were not yet available.

Therapies affecting the immune system have been associated with an increased rate of malignancies. In placebo-controlled clinical trials, the overall incidences of malignancy (the majority of which were non-melanoma skin cancers) were similar in efalizumab- and in placebo-treated patients. In addition, the incidences of specific tumours in efalizumab patients were in line with those observed in control psoriasis populations. Among psoriasis patients who received efalizumab at any

dose, the overall incidence of malignancies of any kind was 1.7 per 100 patient-years for efalizumab-treated patients compared with 1.6 per 100 patient-years for placebo-treated patients. Experience with efalizumab has not shown evidence of risk of developing malignancy exceeding that expected in the psoriasis population.

Information from existing reviews of efalizumab

Little has been published on the adverse effects of efalizumab. Two overviews[101,102] summarise the clinical trials data. These data are evaluated as part of the systematic review below and are therefore not discussed further here.

Adverse events for efalizumab: data from included studies

In addition to the five trials already identified for the assessment of the efficacy of efalizumab,[74–78] there was one long-term follow-up study[95] that provided information on the adverse effects of efalizumab subcutaneous injection. One trial of an intravenous formulation of efalizumab was also found.[79] Details of all studies are presented in the data extraction tables [see the section 'Data extraction tables: intervention adverse events – efalizumab' in Appendix 5 (p. 162)]. All studies of efalizumab were in psoriasis patients; no data from studies of other indications met the inclusion criteria.

The five trials were all double-blind placebo-controlled RCTs conducted in patients with plaque psoriasis. All five trials evaluated efalizumab at a dose of 1 mg/kg administered subcutaneously once a week. One trial also evaluated a higher dose of 2 mg/kg, administered once a week.[74] All five trials provided adverse events data for a 12-week treatment period. In addition, two trials[74,76] provided data for a further 12 weeks in selected patients (number not reported) and one of these trials[74] provided data for a treatment-free follow-up period of 12 weeks (171 with efalizumab and 158 with placebo).

Adverse effects of efalizumab over 12 weeks

These data are summarised in *Table 68*. Across the trials the proportion of patients reporting at least one adverse event during treatment was high on both efalizumab 1 mg/kg (up to 86%) and on placebo (up to 77%). Headache was the most commonly reported non-infectious adverse event in all five trials, with up to 35% of patients in at least one trial reporting headache with efalizumab 1 mg/kg. In all five trials the proportion of patients reporting headache in the placebo group was lower. Chills was the next most common adverse event (up to 16% of patients) and in all but one trial the rate in the efalizumab group was double that in the placebo group (range 2–6%). Nausea, myalgia, pain and fever were reported by some patients in all or almost all trials and the rates were generally higher in the groups who received active rather than placebo treatment. Rhinitis, asthenia, diarrhoea and accidental injury were also reported commonly but the rates in the placebo-treated groups were approximately equal to those in the efalizumab-treated groups.

No specific infection was reported more commonly with efalizumab than with placebo. Unfortunately, the rate of serious infections was not reported, so whether or not there is any tendency for efalizumab to increase these relatively rare events cannot be discerned from these trial data.

The rate of serious adverse events with efalizumab was low at around 2%, but again data are sparse, with only two trials reporting them.[74,75] There were no deaths associated with 12 weeks of efalizumab treatment and most trials did not report cancer data.

Withdrawals due to adverse events were at a rate of around 4% on efalizumab compared with around 2% on placebo.

Rates of around 1% or higher were reported for patients who developed anti-efalizumab antibodies.

The adverse events reported for the 2 mg/kg dose of efalizumab over 12 weeks reflect those reported with the 1 mg/kg dose and do not appear to occur with any greater frequency.[74] However, some data were not reported and it may be that rates of infection or serious adverse effects are higher with the higher dose.

Adverse effects of efalizumab over 24 weeks

Two trials[74,76] evaluated 24 weeks of efalizumab treatment but for both the level of detail available from the available reports is very limited and these are not presented in a table. These trials reported that adverse events were similar to or less than for the initial 12-week period and one trial[74] reported that adverse events leading to withdrawal were more common in patients receiving placebo. Unfortunately, one of these trials evaluated only the higher dose of efalizumab for the second 12 weeks,[74] and in the other it is unclear which dose was studied.[76] Furthermore, the total number

TABLE 68 *Pooled adverse events data – efalizumab 12 weeks follow-up*

	Gordon, 2003[75] DB-RCT, psoriasis 12 wks		**IMP24011, 2004[78]** [Confidential information removed]		**ACD2600g, 2004[77]** [Confidential information removed]		**ACD2058g, 2004[76] DB-RCT, psoriasis 12 weeks**		**Lebwohl, 2003[74] DB-RCT, psoriasis 12 weeks**		
	Efalizumab 1 mg *n* = 368)	**Placebo *n* = 187**	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	**Efalizumab 1 mg *n* = 162**	**Placebo *n* = 170**	**Efalizumab 1 mg *n* = 232**	**Efalizumab 2 mg *n* = 243**	**Placebo *n* = 122**
Adverse events occurring in	≥5% of all patients		[Confidential information removed]		[Confidential information removed]		≥5% of efalizumab patients		≥5% patients in any treatment group		
Total	296 (80%)	133 (71%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	135 (83%)	130 (77%)	199 (86%)	207 (85%)	91 (75%)
Drug-exposure related	163 (44%)	47 (25%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	75 (46%)	58 (34%)	117 (50%)	NR	49 (40%)
Non-infectious adverse events											
Headache	123 (33%)	39 (21%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	57 (35%)	51 (30%)	71 (31%)	93 (38%)	29 (24%)
Chills	44 (12%)	10 (5%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	20 (12%)	10 (6%)	38 (16%)	31 (13%)	3 (2%)
Nausea	39 (11%)	13 (7%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	14 (9%)	16 (9%)	34 (15%)	35 (14%)	11 (9%)
Myalgia	38 (10%)	8 (4%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	13 (8%)	8 (5%)	16 (7%)	22 (9%)	5 (4%)
Pain	37 (10%)	9 (5%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	21 (13%)	16 (9%)	35 (15%)	29 (12%)	4 (3%)
Fever	25 (7%)	3 (2%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	12 (7%)	9 (5%)	26 (11%)	29 (12%)	6 (5%)

continued

TABLE 68 *Pooled adverse events data – efalizumab 12 weeks follow-up (cont'd)*

	Gordon, 2003[75] DB-RCT, psoriasis 12 wks		IMP24011, 2004[78] [Confidential information removed]		ACD2600g, 2004[77] [Confidential information removed]		ACD2058g, 2004[76] DB-RCT, psoriasis 12 weeks		Lebwohl, 2003[74] DB-RCT, psoriasis 12 weeks		
	Efalizumab 1 mg *n* = 368)	**Placebo *n* = 187**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**Efalizumab 1 mg *n* = 162**	**Placebo *n* = 170**	**Efalizumab 1 mg *n* = 232**	**Efalizumab 2 mg *n* = 243**	**Placebo *n* = 122**
Rhinitis	23 (6%)	11 (6%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	13 (8%)	14 (8%)	18 (8%)	13 (5%)	8 (7%)
Asthenia	22 (6%)	9 (5%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	16 (10%)	17 (10%)	17 (7%)	27 (11%)	7 (6%)
Diarrhoea	20 (5%)	10 (5%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	12 (7%)	12 (7%)	16 (7%)		11 (9%)
Accidental injury	17 (5%)	19 (10%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	17 (11%)	6 (4%)	11 (5%)		9 (7%)
Sinusitis	<5%	<5%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	12 (7%)	6 (4%)	<5%	<5%	
Pruritis	<5%	<5%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	8 (5%)	11 (7%)	<5%	<5%	
Peripheral oedema	<5%	<5%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	9 (6%)	5 (3%)	14 (6%)	12 (5%)	5 (4%)
Back pain	<5%	<5%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	10 (6%)	5 (3%)	10 (4%)	16 (7%)	1 (1%)
Cough increased	<5%	<5%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	5 (3%)	8 (5%)	8 (3%)	13 (5%)	5 (4%)
Worsening psoriasis	<5%	<5%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	8 (5%)	4 (2%)	12 (5%)	8 (3%)	2 (2%)

continued

TABLE 68 *Pooled adverse events data – efalizumab 12 weeks follow-up (cont'd)*

	Gordon, 2003[75] DB-RCT, psoriasis 12 wks		**IMP24011, 2004[78] [Confidential information removed]**		**ACD2600g, 2004[77] [Confidential information removed]**		**ACD2058g, 2004[76] DB-RCT, psoriasis 12 weeks**		**Lebwohl, 2003[74] DB-RCT, psoriasis 12 weeks**		
	Efalizumab 1 mg *n* = 368)	**Placebo *n* = 187**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**Efalizumab 1 mg *n* = 162**	**Placebo *n* = 170**	**Efalizumab 1 mg *n* = 232**	**Efalizumab 2 mg *n* = 243**	**Placebo *n* = 122**
Dizziness	<5%	<5%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	11 (7%)	8 (5%)	9 (4%)		6 (5%)
Hearing loss	<5%	<5%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	12 (7%)	5 (3%)	24 (10%)	12 (5%)	6 (5%)
Anthralgia	<5%	NR	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	<5%	NR	12 (5%)	10 (4%)	2 (2%)
Vomiting	<5%	NR	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	<5%	NR	14 (6%)	6 (2%)	1 (1%)
Acne	<5%	NR	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	<5%	NR			
Infectious adverse events including any serious infections											
Any infection	27%	23%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	27%	23%	22%	NR	25%
Infection not specified	46 (13%)	23 (12%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	23 (14%)	23 (14%)	27 (12%)	43 (18%)	19 (16%)
Pharyngitis	27 (7%)	10 (5%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	9 (6%)	14 (8%)	14 (6%)	22 (9%)	6 (5%)
Flu-like syndrome	27 (7%)	7 (4%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	<5%	NR	<5%	<5%	<5%
Herpes simplex	17 (5%)	7 (4%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	10 (6%)	10 (6%)	8 (3%)	14 (6%)	5 (4%)

continued

TABLE 68 *Pooled adverse events data – efalizumab 12 weeks follow-up (cont'd)*

	Gordon, 2003[75] DB-RCT, psoriasis 12 wks		**IMP24011, 2004[78]** [Confidential information removed]		**ACD2600g, 2004[77]** [Confidential information removed]		**ACD2058g, 2004[76] DB-RCT, psoriasis 12 weeks**		**Lebwohl, 2003[74] DB-RCT, psoriasis 12 weeks**		
	Efalizumab 1 mg *n* = 368)	**Placebo *n* = 187**	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	**Efalizumab 1 mg *n* = 162**	**Placebo *n* = 170**	**Efalizumab 1 mg *n* = 232**	**Efalizumab 2 mg *n* = 243**	**Placebo *n* = 122**
Gastroenteritis	5 (1%)	10 (5%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	<5%	NR	<5%	<5%	<5%
Serious infections	0.5%	0.5%	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	NR	NR	NR	NR	NR
Cancer	2	0	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	NR	NR	NR	NR	NR
Other non-infectious serious adverse events	2% (9/368)	1% (1/187)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	NR	NR	4 (2%)	7 (3%)	1 (1%)
Deaths	0	0	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	0	0	NR	NR	NR
Withdrawals due to adverse events	12 (3%)	2 (1%)	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]	6 (3.7%)	6 (3.5%)	9 (4%)	7 (3%)	2 (2%)
Positive test for anti-efalizumab antibody	8 (2%)	0	[Confidential information removed]	[Confidential information removed]	[Confidential information removed]		2/314 (0.6%)	NR	3/456 (0.7%)	NR	NR

of patients treated with efalizumab was only 171 in one trial[74] and not reported in the other.[76] For treatment-free follow-up (weeks 24–36), adverse events in all patients were infection (13%), worsening psoriasis (9%), pruritis (6%) and arthritis (5%). Five efalizumab-treated patients developed anti-efalizumab antibodies; the safety profile of these patients was not different from that of the other patients. Thirteen patients (3%) had a serious adverse event (five non-fatal infections and three psoriasis-related events).

One trial of an intravenous formulation of efalizumab in which 97 patients were randomised to 0.1 or 0.3 mg/kg efalizumab and 45 were randomised to placebo followed patients for 20 weeks. The findings of this trial reflected those for the subcutaneous formulation.[79] Details can be found in the data extraction tables [see the section 'Data extraction tables: intervention adverse event – efalizumab' in Appendix 5 (p. 162)].

Adverse effects of efalizumab over 1 year or more

One long-term study provided data on 339 patients who had responded to efalizumab and who were then followed for up to 3 years.[95] This study reported the data in terms of 12-week periods during the whole follow-up period. The results are summarised in *Table 69*. These data indicated that the clinically significant adverse events were non-specific infections (mostly colds and URT infections), accidental injury, increased cough, rhinitis and sinusitis.

The rate of serious adverse events per 3-month period ranged from 1 to 5.5% over the whole study period. The average frequency of skin cancer per 3-month period ranged from 0 to 3.3%, the higher figure representing 1-month's atypical high rate. Withdrawals during any period of the follow-up were at a rate of 3.4% or less. The authors state that 'Clinically significant including serious adverse events remained generally stable between each 3-month period'.

Summary of adverse events data for efalizumab

The available data for 12 weeks of treatment with efalizumab demonstrate a very high rate of adverse events, but this rate is not higher than that reported on placebo. The events that are more commonly reported with efalizumab than with placebo are headache, chills and, in some trials but at a lower rate, nausea, myalgia, pain and fever. The rate of infection is also high, but again, the rate is no higher than on placebo. Unfortunately, data for serious infections are not reported and therefore the relative incidence of these cannot be evaluated. Similarly, few data on serious adverse events with efalizumab are available. Overall, withdrawal rates due to adverse events are low at 4%, compared with around 2% on placebo. One to **[Confidential information removed]** of patients treated with efalizumab for 12 weeks developed antibodies, but this did not appear to be associated with any increased risk of adverse events. The rate of adverse events on a higher dose of efalizumab (2 mg/kg) did not appear to be higher than that on the 1 mg/kg dose, but this higher dose was tested in only one trial and so firm conclusions cannot be drawn. The available published reports of the efalizumab trials did not reveal leucocytosis and lymphocytosis as common adverse consequences of therapy.

Longer term data for efalizumab are not readily available; those trials that were conducted have been reported in summary form only. Overall, the adverse events over longer periods up to 3 years appear to reflect those over 12 weeks and to remain stable.

In summary, the publicly available information for efalizumab indicates that the drug is well tolerated over a 12-week period; however, few data for any longer term treatment are available for evaluation.

TABLE 69 *Pooled adverse events data – efalizumab 1 year or more follow-up*[a]

	Gottlieb, 2004[95] (psoriasis, open-label follow-up – 3 years)
	Etanercept 25 mg ***n*** **= 339**
Non-infectious adverse events	Non-infectious adverse events that occurred in at least 5% of patients during any 12-week period of the follow-up phase included accidental injury, increased cough, rhinitis and sinusitis
Any non-infectious adverse event	
Injection site reaction	
Ecchymosis (injection site)	
Bleeding at injection site	
Accidental injury	
Headache	
Back pain	
Hypertension	
Nausea	
Rash	
Rhinitis	
Diarrhoea	
Asthenia	
Sporadic neutropenia	
Dyspepsia	
Dizziness	
Abdominal pain	
Pain	
Vomiting	
Low peripheral lymphocyte count	
Infectious adverse events including any serious infections	Infectious adverse events that occurred in at least 5% of patients during any 12-week period of the follow-up phase included non-specific infections, mostly colds and urinary tract infections. The average frequency of non-specific infection per 3-month period over the 30-month follow-up ranged from 8.8 to 15.9% of patients. That for infection-related adverse events ranged from 18.0 to 30.1% of patients
Any infection	
URT infection	
Flu-like syndrome	
Sinusitis	
Pharyngitis	
Serious infection	
Opportunistic infections	NR
Cancer	The average frequency of skin cancer per 3-month period over the 30-month follow-up ranged from 0 to 3.3% of patients
Other serious non-infectious adverse events	The average frequency of serious adverse events per 3-month period over the 30-month follow-up ranged from 1.0 to 5.5% of patients
Deaths (no.)	NR
Withdrawals due to adverse events	The average frequency of withdrawals due to adverse events per 3-month period over the 30-month follow-up was 3.1% of patients or less
Positive test for anti-etanercept antibody	NR
Other important adverse event results	Clinically significant, including serious, adverse events remained generally stable between each 3-month period

[a] Where rate is given as <3%, <5% or <10%, the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut-off level.

Appendix 7

Data extraction tables: efficacy of other treatments for moderate to severe psoriasis

Data for included and excluded studies are given in *Tables 70* and *71*, respectively.

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis*

Study details	Participants	Treatment	Outcomes and results
Ellis, 1991[103] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** >25% **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 85	**Treatment** Ciclosporin 3 mg/kg/day *n* = 25 Ciclosporin 5 mg/kg/day *n* = 20 Ciclosporin 7.5 mg/kg/day *n* = 15 **Comparator** Placebo equivalent Number of patients *n* = 25 **Duration of treatment** 8 wks **Outcome measure** % clear/almost clear Mean PASI (from graph) PGA	**% clear/almost clear** Ciclosporin 3 mg/kg/day 36% Ciclosporin 5 mg/kg/day 65% Ciclosporin 7 mg/kg/day 80% Placebo 0% **mean PASI (from graph)** Ciclosporin 3 mg/kg/day 6.2 (range 4–7) Ciclosporin 5 mg/kg/day 6.5 (range 5–7) Ciclosporin 7 mg/kg/day 6.5 (range 6–7) Placebo 6.1 (range 5–7) **Physician GA** Ciclosporin 3 mg/kg/day (wk 0) mean 6.2; (wk 8) mean 3.8 (SE 0.4) Ciclosporin 5 mg/kg/day (wk 0) mean 6.5; (wk 8) mean 2.7 (SE 0.3) Ciclosporin 7 mg/kg/day (wk 0) mean 6.5; (wk 8) mean 1.9 (SE 0.2) Placebo (wk 0) mean 6.1; (wk 8) mean 5.9 (SE 0.2)
Guenther, 1991[104] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** NS **Minimum BSA included** ≥25 **Minimum PASI included** ≥12 **Adult?** Yes **Number of participants** *n* = 23	**Treatment** Ciclosporin 5 mg/kg/day Number of patients *n* = 12 **Comparator** Placebo equivalent Number of patients *n* = 11 **Duration of treatment** 10 wks **Outcome measure** PASI 50/PSI 50 Mean PASI score	**PASI 50/PSI 50** Ciclosporin wk 4: 9/12; placebo: 0/11 Ciclosporin wk 6: 11/12; placebo: 0/11 Ciclosporin wk 10: 12/12; placebo: 1/11 **Mean PASI** Ciclosporin wk 0: 23 (*n* = 12); placebo 21 (*n* = 11) Ciclosporin wk 10: 2 (*n* = 11); placebo 16 (*n* = 3)

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Meffert, 1997[105] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** NS **Minimum PASI included** 8–25 **Adult?** Yes **Number of participants** *n* = 128	**Treatment** Ciclosporin 1.25 mg/kg/day Number of patients *n* = 41 Ciclosporin 2.5 mg/kg/day Number of patients *n* = 44 **Comparator** Placebo equivalent *n* = 43 **Duration of treatment** 10 wks **Outcome measure** PASI 75 PASI 50 Mean PASI Reduction in PASI (from graph)	**PASI 75** Ciclosporin 1.25 mg/kg/day (*n* = 41): 10% Ciclosporin 2.5 mg/kg/day (*n* = 44): 29% Placebo (*n* = 43): 5% **PASI 50** Ciclosporin 1.25 mg/kg/day (*n* = 41): 21% Ciclosporin 2.5 mg/kg/day (*n* = 44): 58% Placebo (*n* = 43): 10% **Mean PASI** Ciclosporin 1.25 mg/kg/day wk 0 (*n* = 40): mean 16.7 (5.7 SD) Ciclosporin 1.25 mg/kg/day wk 10 (*n* = 40): mean 11.8 (6.8 SD) Ciclosporin 2.5 mg/kg/day wk 0 (*n* = 41): mean 15.1 (5.0 SD) Ciclosporin 2.5 mg/kg/day wk 10 (*n* = 41): mean 7.6 (6.2 SD) Placebo wk 0 (*n* = 39): mean 15.6 (5.1 SD) Placebo wk 10 (*n* = 39): mean 14.9 (7.9 SD) **Reduction in PASI** Ciclosporin 1.25 mg/kg/day wk 1 (*n* = 41): mean 4.3 (9.8 SD) Ciclosporin 1.25 mg/kg/day wk 3 (*n* = 41): mean 11.7 (22.3 SD) Ciclosporin 1.25 mg/kg/day wk 6 (*n* = 41): mean 22.1 (29 SD) Ciclosporin 1.25 mg/kg/day wk 10 (*n* = 41): mean 27.2 (34.6 SD) Ciclosporin 2.5 mg/kg/day wk 1 (*n* = 44): mean 10.2 (15.3 SD) Ciclosporin 2.5 mg/kg/day wk 3 (*n* = 44): mean 22.9 (26.3 SD) Ciclosporin 2.5 mg/kg/day wk 6 (*n* = 44): mean 39.3 (28.8 SD) Ciclosporin 2.5 mg/kg/day wk 10 (*n* = 44): mean 51 (30.9 SD) Placebo wk 1 (*n* = 43): mean 3.2 (6.5 SD) Placebo wk 3 (*n* = 43): mean 7.3 (19.2 SD) Placebo wk 6 (*n* = 43): mean 11 (28 SD) Placebo wk 10 (*n* = 43): mean 5.9 (36.1 SD)

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
van Joost, 1988[106] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** NS **Minimum PASI included** >20 **Adult?** Yes **Number of participants** *n* = 20	**Treatment** Ciclosporin 5.5 mg/kg/day (mean dose) Number of patients *n* = 10 **Comparator** Placebo equivalent Number of patients *n* = 10 **Duration of treatment** 4 wks **Outcome measure** PASI 75 PASI 50 (from graph) Reduction in PASI	**PASI 75** Ciclosporin: 7/10 Placebo: 0/10 **PASI 50/PSI 50** Ciclosporin: 9/10 Placebo: 0/10 **Reduction in PASI** Ciclosporin (*n* = 10): mean 72% Placebo (*n* = 10): mean 3%
Dogan, 1999[115] **Study design** RCT Whole body	**Psoriasis type** NS **Resistant to topicals/require systemics?** Yes **Minimum BSA included** ≥15% **Minimum PASI included** Pretreatment PASI mean 12 **Adult?** Yes **Number of participants** *n* = 50	**Treatment** Acitretin 50 mg/day for 15 days, 25 mg/day thereafter plus PUVA (oral psoralen) 3/wk Note: the average UVA dose was 52.4 J/cm and the average number of UVA sessions was 13 Number of patients *n* = 20 **Comparator** PUVA 3/wk [10 patients used oral psoralen (average UVA dose 187.7 J/cm and average number of UVA sessions 31), 20 used bath psoralen (average UVA dose 44.6 J/cm and average number of UVA sessions 20.4)] Number of patients *n* = 30 **Duration of treatment** Maximum of 3 months (or until clearance of psoriasis) **Outcome measure** PASI 50/PSI 50 % clear/almost clear (defined as 80–100% improvement in PASI)	**PASI 50/PSI 50** Acitretin plus PUVA 20/20 (100%) PUVA 29/30 (97%) Note: bath PUVA 20/20 (100%) but oral PUVA 9/10 (90%) **% clear/almost clear** Acitretin plus PUVA 6/20 (30%) PUVA 25/30 (83%) Note: bath PUVA 19/20 (95%) but oral PUVA 6/10 (60%)

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Goldfarb, 1988[109] **Study design** RCT Whole body	**Psoriasis type** NS **Resistant to topicals/require systemics?** NS **Minimum BSA included** >10% **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 38	**Treatment** Acitretin 10 mg Acitretin 25 mg Acitretin 50 mg Acitretin 75 mg Number of patients *n* = 26 **Comparator** Placebo equivalent Number of patients *n* = 12 **Duration of treatment** 8 wks **Outcome measure** PGS (0–6) 0 = absent or clear, 6 = severe Physician improvement ratings (worse, unchanged, fair, good, excellent)	**Physician GA** Acitretin 10 mg (*n* = 5): mean 0 (0 SE) Acitretin 25 mg (*n* = 5): mean 1 (0.3 SE) Acitretin 50 mg (*n* = 11): mean 1.6 (0.04 SE) Acitretin 75 mg (*n* = 5): mean 3 (0.8 SE) Placebo (*n* = 12): mean 0.5 (0.3 SE) **Improvement** Acitretin 10 mg (*n* = 5): 2 worse, 3 unchanged Acitretin 25 mg (*n* = 5): 1 worse, 4 fair Acitretin 50 mg (*n* = 11): 6 fair, 3 good, 2 excellent Acitretin 75 mg (*n* = 5): 1 fair, 2 good, 2 excellent Placebo (*n* = 12): 5 worse, 1 unchanged, 5 fair, 1 excellent
Lassus, 1987[110] **Study design** RCT Whole body	**Psoriasis type** Plaque, erythrodermic, pustular **Resistant to topicals/require systemics?** NS **Minimum BSA included** NS **Minimum PASI included** NS **Adult?** NS **Number of participants** *n* = 80	**Treatment** Acitretin 10 mg Acitretin 25 mg Acitretin 50 mg Number of patients *n* = 60 **Comparator** Placebo equivalent Number of patients *n* = 20 **Duration of treatment** 8 wks **Outcome measure** Need for topicals % reduction in PASI (data not extractable from graph)	**Need for topicals** Acitretin 10 mg (*n* = 20): 6 Acitretin 25 mg (*n* = 20): 7 Acitretin 50 mg (*n* = 20): 4 Placebo (*n* = 20): 12

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Saurat, 1988[112] **Study design** RCT Whole body	**Psoriasis type** Plaque, erythrodermic **Resistant to topicals/require systemics?** NS **Minimum BSA included** >20% **Minimum PASI included** NS **Adult?** NS **Number of participants** *n* = 58	**Treatment** Acitretin 50 mg/day + PUVA Etretinate 50 mg/day + PUVA Number of patients *n* = 38 **Comparator** PUVA + placebo Number of patients *n* = 20 **Duration of treatment** 12 wks **Outcome measure** Remission (equal to PASI 90), days to clear (mean)	**PASI 90** Acitretin (*n* = 20): 17 Placebo (*n* = 22): 16 **Clearance** Acitretin wk 6 (*n* = 18): 8 Acitretin wk 8 (*n* = 18): 16 Acitretin wk 10 (*n* = 18): 17 Acitretin wk 12 (*n* = 18): 17 Etretinate wk 6 (*n* = 20): 5 Etretinate wk 8 (*n* = 20): 11 Etretinate wk 10 (*n* = 20): 13 Etretinate wk 12 (*n* = 20): 16 Placebo wk 6 (*n* = 20): 3 Placebo wk 8 (*n* = 20): 7 Placebo wk 10 (*n* = 20): 13 Placebo wk 12 (*n* = 20): 16 **Days to clearance** Acitretin wk 6 (*n* = 18): mean 47.8 (2.3 SE) Etretinate wk 6 (*n* = 20): mean 57.8 (4.4 SE) Placebo wk 6 (*n* = 20): mean 65.4 (4.1 SE)
Sommerburg, 1993[113] **Study design** RCT Whole body	**Psoriasis type** Plaque, guttate or nummularis **Resistant to topicals/require systemics?** NS **Minimum BSA included** NS **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 88	**Treatment** Acitretin 25 mg/day + PUVA (3–5/wk) Number of patients *n* = 44 **Comparator** PUVA (3–5/wk) + placebo Number of patients *n* = 44 **Duration of treatment** 8 wks **Outcome measure** Physician assessment (complete remission, marked improvement, slight improvement, no change, exacerbation) ≥75% decrease in PSI Reduction in PSI (score points/%)	**Clearance** Acitretin + PUVA (*n* = 44): 28 Placebo (*n* = 44): 19 **Improvement** Acitretin + PUVA (*n* = 44): 9 marked improvement, 1 slight improvement, 1 no change, 1 exacerbation Placebo (*n* = 44): 11 marked improvement, 7 slight improvement, 2 no change, 4 exacerbation **>75% decrease in PSI** Acitretin + PUVA (*n* = 44): 34 Placebo (*n* = 44): 26 **Reduction in PSI** Acitretin + PUVA (*n* = 44): median 24 Placebo (*n* = 44): median 21

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Tanew, 1991[114] **Study design** RCT Whole body	**Psoriasis type** Plaque, guttate or erythrodermic **Resistant to topicals/require systemics?** NS **Minimum BSA included** >20% **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 42	**Treatment** PUVA 4/wk+ acitretin 1 mg/kg a day Number of patients *n* = 22 **Comparator** PUVA 4/wk + placebo Number of patients *n* = 20 **Duration of treatment** 11 wks or until complete clearance **Outcome measure** 90% clearance	**Clearance** PUVA + acitretin (*n* = 30): 22 Placebo (*n* = 30): 20
van de Kerkhof, 1998[116] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** NS **Minimum PASI included** NS (mean (SD): treatment 17.8 (8.9); control 17.4 (SD 8.6)) **Adult?** Yes **Number of participants** *n* = 135	**Treatment** Acitretin 20–70 mg/day + calcipotriol 2/day Number of patients *n* = 76 **Comparator** Acitretin 20–70 mg/day + placebo Number of patients *n* = 59 **Duration of treatment** 12 wks **Outcome measure** Reduction in PASI score (from graph) Investigator/patient assessment (clear or marked improvement, moderate or slight improvement, unchanged or worse)	**Reduction in PASI** Acitretin + calcipotriol (*n* = 76): mean 13.2 Acitretin + placebo (*n* = 59): mean 8.8 **Mean PASI** Acitretin + calcipotriol: (0 wks) mean 17.8 (8.9 SE); (12 wks) mean 3.75 Acitretin + placebo: (0 wks) mean 17.4 (8.6 SE); (12 wks) mean 6.25 **Degree of improvement** Acitretin + calcipotriol (*n* = 76): 51 clear or marked improvement; 25 moderate or slight improvement; 26 unchanged or worse Acitretin + placebo (*n* = 59): 24 clear or marked improvement; 33 moderate or slight improvement, 29 unchanged or worse

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Altmeyer, 1994[125] **Study design** RCT Whole body	**Psoriasis type** Plaque, guttate or erythrodermic **Resistant to topicals/require systemics?** NS **Minimum BSA included** >10% **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 100	**Treatment** Fumaderm 105 escalating to 1290 mg/day Number of patients *n* = 49 **Comparator** Placebo equivalent Number of patients *n* = 51 **Duration of treatment** 16 wks **Outcome measure** Physician's assessment: complete remission (PASI 95), good improvement (PASI 70–95%), moderate improvement (PASI 30–69%), slight improvement (PASI <30%), no change (PASI 0%), deterioration (PASI <0%) Mean PASI (from graph)	**Mean PASI** Fumaderm (16 wks): 10.77 Placebo (16 wks): 23 **Physician's assessment** Fumaderm (16 wks): 12 complete remission, 15 good improvement, 3 moderate improvement, 5 slight change, 9 no change, 5 deterioration Placebo (16 wks): 1 complete remission. 3 good improvement, 2 moderate improvement, 3 slight change, 25 no change, 17 deterioration
Nieboer, 1989[172] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** NS **Minimum BSA included** >10% **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 80	**Treatment** MEFAE-Na 240 mg/day Number of patients *n* = 19 DMFAE 240 mg/day Number of patients *n* = 22 **Comparator** Placebo equivalent Number of patients *n* = 19, *n* = 20 **Duration of treatment** 4 months **Outcome measure** Improvement measured by psoriasis severity score (0–17) including PSI 50 Psoriasis severity score (0 = absence of symptoms, 5 = >50% BSA involved)	**PSI 50** MEFAE-Na: 1/19; placebo: 2/19 DMFAE: 6/22; placebo: 0/20 **Improvement** MEFAE-Na: 1 >50% improvement, 6 25–50% improvement, 9 <25% improvement Placebo: 2 >50% improvement, 5 25–50% improvement, 8 <25% improvement DMFAE: 6 >50% improvement, 6 25–50% improvement, 4 <25% improvement Placebo: 0 >50% improvement, 1 25–50% improvement, 12 <25% improvement

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Nugteren-Huying, 1990[126] **Study design** RCT Whole body	**Psoriasis type** NS **Resistant to topicals/require systemics?** NS **Minimum BSA included** >10 % **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 32	**Treatment** Fumarates (DMFAE 120 mg, MEFAE-Ca 87 mg, MEFAE-Mg 5 mg, MEFAE-Zn 3 mg) Number of patients *n* = 12 Fumarates (OHFAE 284 mg; MEFAE-Mg 5 mg; MEFAE-Zn 3 mg) Number of patients *n* = 10 **Comparator** Placebo Number of patients *n* = 10 **Duration of treatment** 16 wks **Outcome measure** Clearance % BSA (no data)	**Clearance** DMFAE, MEFAE-Ca, MEFAE-Mg, MEFAE-Zn: 6 clear, 3 improved OHFAE, MEFAE-Mg, MEFAE-Zn: 0 clear, 0 improved Placebo: 0 clear, 0 improved
Nieboer, 1990[173] **Study design** RCT Whole body	**Psoriasis type** Plaque, macular or guttate **Resistant to topicals/require systemics?** NS **Minimum BSA included** >10% **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 45	**Treatment** Fumarates (DMFAE-EC 120–480 mg) Number of patients *n* = 22 **Comparator** Fumarates (FAC-EC 120 mg 1–4 tablets/day) Number of patients *n* = 23 **Duration of treatment** 4 months **Outcome measure** Improvement measured by psoriasis severity score (0–17; % of baseline score calculated to find proportion with 50% improvement)	**PASI 50/PSI 50** DMFAE-EC: 10/22 (45%) FAC-EC: 12/23 (52%) **Clearance** DMFAE-EC: 4/22 FAC-EC: 4/23 **Failure** DMFAE-EC: 5/22 (22%) FAC-EC: 1/23 (4%)

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Chaudari, 2001[123] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** >5% **Minimum PASI included** NS (mean baseline PASI: treatment 5 mg/kg 22.1; mean treatment 10 mg/kg 26.6; control 20.3 **Adult?** Yes **Number of participants** *n* = 33	**Treatment** Infliximab 5 mg/kg Number of patients *n* = 11 Infliximab 10 mg/kg Number of patients *n* = 11 **Comparator** Placebo Number of patients *n* = 11 **Duration of treatment** 10 wks **Outcome measure** PASI 75 Mean PASI PGA (good = 50–74% clearing with moderate improvement; excellent = 75–90% clearing with striking improvement; clear = 100% clearing; fair = 25–49% clearing with slight improvement; poor = 0–24% clearing with little or no change; worse	**PASI 75** Infliximab 5 mg/kg: 9/11 (82%) Infliximab 10 mg/kg: 8/11 (73%) Placebo: 2/11 (18%) **PASI 50/PSI 50** Infliximab 5 mg/kg: 9/11 Infliximab 10 mg/kg: 10/11 Placebo: 2/11 **Mean PASI** Infliximab 5 mg/kg (wk 0): 22.1; (wk 10) 3.8 Infliximab 10 mg/kg (wk 0): 26.6; (wk 10) 5.9 Placebo (wk 0): 20.3; (wk 10) 17.5 **Improvement** Infliximab 5 mg/kg: 9 clear or excellent, 0 good Infliximab 10 mg/kg: 7 clear or excellent, 3 good; 91% Placebo: 1 clear or excellent, 1 good; 18%

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Gottlieb, 2004[124] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** ≥ 10% **Minimum PASI included** ≥ 12% **Adult?** Yes **Number of participants** *n* = 249	**Treatment** Infliximab 3 mg/kg at wks 0. 2 and 6 Number of patients *n* = 99 Infliximab 5 mg/kg at wks 0. 2 and 6 Number of patients *n* = 99 **Comparator** Placebo Number of patients *n* = 51 **Duration of treatment** Assessment at 10 wks **Outcome measure** PASI 90 PASI 75 PASI 50 PGA assessment of scaling, erythema and induration based on a 6-point scale (0 = not present, 1 = minimally present, 2 = mild, 3 = moderate, 4 = marked, 5 = severe); median change from baseline in DLQI; median DLQI scores	**PASI 90** Infliximab 3 mg/kg: 45 (45.5%) Infliximab 5 mg/kg: 57 (57.6%) Placebo: 1 (2%) **PASI 75** Infliximab 3 mg/kg: 71 (71.7%) Infliximab 5 mg/kg: 87 (87.9%) Placebo: 3 (5.9%) **PASI 50** Infliximab 3 mg/kg: 83 (83.8%) Infliximab 5 mg/kg: 96 (97%) Placebo: 11 (21.6%) **Improvement** Infliximab 3 mg/kg: 71 (71.7%) minimal or cleared; 87 (87.9%) mild, minimal or cleared Infliximab 5 mg/kg: 89 (89.9%) minimal or cleared; 97 (98.0%) mild, minimal or cleared Placebo: 5 (9.8%) minimal or cleared; 23 (45.1%) mild, minimal or cleared
Sandhu, 2003[107] **Study design** RCT Whole body	**Psoriasis type** Plaque and erythrodermic **Resistant to topicals/require systemics?** NS **Minimum BSA included** >40% **Minimum PASI included** NS (mean baseline PASI: treatment 29.6, control 27.6) **Adult?** Yes **Number of participants** *n* = 30	**Treatment** Methotrexate 0.5 mg/kg/day (~35 mg/wk) Number of patients *n* = 15 **Comparator** Ciclosporin 3–4 mg/kg/day Number of patients *n* = 15 **Duration of treatment** 12 wks **Outcome measure** PASI 75 PASI 50 Mean PASI Reduction in PASI Clearance	**PASI 75** Methotrexate: 15 Ciclosporin: 14 **PASI 50** Methotrexate: 15 Ciclosporin: 15 **Mean PASI** Methotrexate (wk 0): 27.6 (2.3 SE); (wk 12) 0.4 (0.2 SE) Ciclosporin (wk 0): 29.6 (2.1 SE); (wk 12) 4.3 (1.7 SE) **Reduction in PASI** Methotrexate (wk 2): 35%; (wk12) 98.5% Ciclosporin (wk2): 15%; (wk12) 85.6% **Clearance** Methotrexate: 13/15 Ciclosporin: 6/15

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Heydendael, 2003[108] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** NS **Minimum PASI included** >8 **Adult?** Yes **Number of participants** *n* = 85	**Treatment** Methotrexate 15–22.5 mg/wk Number of patients *n* = 43 **Comparator** Ciclosporin 3–5 mg/kg/day Number of patients *n* = 42 **Duration of treatment** 16 wks **Outcome measure** PASI 90 PASI 75 Mean PASI PGA (score 0–10, 0 = worst, 10 = clearance) SF-36	**PASI 09** Methotrexate: 17/43 Ciclosporin: 14/42 **PASI 75** Methotrexate: 26/43 Ciclosporin: 30/42 **Mean PASI** Methotrexate (wk 0): 13.4 (3.2 SD); (wk 16) 5 (0.7 SD) Ciclosporin (wk 0): 14 (6.6 SD); (wk 16) 3.8 (0.5 SD) **Reduction in PASI** Methotrexate: 64% Ciclosporin: 74% **Physician GA** Methotrexate: mean 7 (0.38 SE) Ciclosporin: mean 4.8 (0.29 SE) **SF-36** Methotrexate: physical mean 52 (1.7 SE), mental mean 51 (1.4 SE) Ciclosporin: physical mean 53 (1.4 SE), mental mean 51 (1.4 SE)
Rim, 2003[117] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** NS **Minimum BSA included** >5% **Minimum PASI included** NS (mean baseline PASI: treatment 21.6, control 24.3) **Adult?** Yes **Number of participants** *n* = 60	**Treatment** Acitretin 10–40 mg/day + calcipotriol 50 mg twice daily Number of patients *n* = 40 **Comparator** Acitretin 10–40 mg/day Number of patients *n* = 20 **Duration of treatment** 12 wks (and 52 wks) **Outcome measure** Clearance Improvement Failure Definitions unclear	**Clearance** Acitretin + calcipotriol (12 wks): 16/40 (40%); (52 wks) 24/40 Acitretin (12 wks): 3/20 (15%); (52 wks) 8/20 **Improvement** Acitretin + calcipotriol: 15/40 (38%) Acitretin: 13/20 (65%) **Failure** Acitretin + calcipotriol: 9/40 (22.5%) Acitretin: 4/20 (20%)

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Gordon, 1999[119] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** NS **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 100	**Treatment** PUVA (oral) 2/wk Number of patients *n* = 49 **Comparator** NBUVB 2/wk Number of patients *n* = 51 **Duration of treatment** Until clearance of plaques of psoriasis at all sites above the knee **Outcome measure** Clearance No. exposures to clearance Still clear after 3 and 6 months	**Clearance** PUVA: 41/49; (6 months) 17/49 NBUVB: 32/51; (6 months) 7/51 **No. of exposures to clearance** PUVA: median 16.7 NBUVB: median 25.3 (95% CI 1.24 to 1.86)
Markham, 2003[120] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** NS **Minimum BSA included** >8% **Minimum PASI included** Baseline range 11–19 **Adult?** Yes **Number of participants** *n* = 54	**Treatment** NBUVB 3/wk Number of patients *n* = 29 **Comparator** PUVA (oral methoxsalen) 2/wk Number of patients *n* = 25 **Duration of treatment** Until patients were completely clear **Outcome measure** No. of treatments to clear Days to clear Duration of remission (days) Remission	**Clearance** NBUVB (3 months): 23/29; (6 months) 16/29; (9 months) 23/29; (12 months) 7/29 PUVA (3 months): 18/25; (9 months) 18/25; (12 months) 10/25 **Days to clear** NBUVB (*n* = 24): median 67 (95% CI 47.9 to 81.7) PUVA (*n* = 21): median 66 (95% CI 52.0 to 92.6) **No. of exposures to clearance** NBUVB (*n* = 24): median 25.5 (95% CI 18.0 to 32.5) PUVA (*n* = 21): median 19 (14.6 to 25.0) **Duration of remission (days)** NBUVB (*n* = 24): median 288.5 (95% CI 170.6 to 365.0) PUVA (*n* = 21): median 231 (95% CI 162.7 to 365.0)

continued

TABLE 70 *Included studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Caca-Biljanovska, 2002[111] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** NS **Minimum BSA included** NS (>30%) **Minimum PASI included** NS (mean baseline PASI: treatment 24.06 (SD 3.62); control 24.56 (SD 3.40) **Adult?** Yes **Number of participants** *n* = 40	**Treatment** PUVA 4/wk for 6 wks + 2/wk for 2 wks Number of patients *n* = 20 **Comparator** Acitretin 30 mg/day as an initial dose Number of patients *n* = 20 **Duration of treatment** 8 wks **Outcome measure** Mean PASI scores at 2, 4, 6 and 8 weeks Clearing	**Mean PASI** PUVA (wk 0): mean 24.06 (SE 3.62); (wk 8) mean 1.69 (SE 1.55) Acitretin (wk 0): mean 24.56 (SE 3.5); (wk 8) mean 0.9 (SE 1.07) **Clearance** PUVA: 7/20 Acitretin: 10/20 **Improvement** PUVA: 7 clear; 3 moderate; 10 considerable Acitretin: 10 clear; 2 moderate; 8 considerable
Dawe, 2003[121] **Study design** RCT Half body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** NS **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 56	**Treatment** NBUVB 3/wk Number of patients *n* = 28 **Comparator** PUVA (bath trimethoxypsoralen) 2/wk Number of patients *n* = 28 **Duration of treatment** Until clearance/MRA, or a maximum of 30 treatments **Outcome measure** Clearance/MRA Time to clearance/MRA (values not given) No. of exposures to clearance/MRA Median decrease in psoriasis severity score (scaling, erythema, induration)	**Reduction in PASI** NBUVB: mean 20 PUVA: mean 17.5 **Clearance** NBUVB: 18/28 PUVA: 15/28 **Days to clear** NBUVB (*n* = 18): median 62 PUVA (*n* = 18): median 74 **No. exposures to clearance** NBUVB (*n* = 18): median 24.5 PUVA (*n* = 18): median 19 (95% CI 1.5 to 5.5)

DMFAE, dimethylfumaric acid ester; MEFAE-Ca, -Mg, -Na, Zn, calcium, magnesium, sodium, zinc salts of monoethylfumaric acid ester; MRA, minimal residual activity; NS, not stated; OHFAE, octyl hydrogen fumaric acid ester.

TABLE 71 *Excluded studies of other treatments for moderate to severe psoriasis*

Study details	Participants	Treatment	Outcomes and results
Engst, 1989[174] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** NS **Minimum PASI included** >20 **Adult?** NS **Number of participants** *n* = 12	**Treatment** Ciclosporin 5 mg/kg/day. Number of patients *n* = 6 **Comparator** Placebo equivalent Number of patients *n* = 6 **Duration of treatment** 4 wks **Outcome measure** PASI 75	**PASI 75** Ciclosporin (*n* = 6): 3 Placebo (*n* = 6): 1
Kingston, 1987[175] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** NS **Minimum BSA included** >20% **Minimum PASI included** NS **Adult?** Yes **Number of participants** NS	**Treatment** Acitretin 10 mg Acitretin 50 mg Acitretin 75 mg Number of patients NS **Comparator** Placebo Number of patients NS **Duration of treatment** 8 wks **Outcome measure** Excellent (>75% clearance), good (50–75%), minimal (<50%). No placebo data	NS

continued

TABLE 71 *Excluded studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Madhok, 1987[176] **Study design** RCT Whole body	**Psoriasis type** Plaque, pustular **Resistant to topicals/require systemics?** NS **Minimum BSA included** >15% **Minimum PASI included** NS **Adult?** Yes **Number of participants** NS	**Treatment** Acitretin 25 mg Acitretin 50 mg Number of patients NS **Comparator** Placebo equivalent Number of patients NS **Duration of treatment** 8 wks **Outcome measure** NS	NS
Olsen, 1989[177] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** NS **Minimum BSA included** >10% **Minimum PASI included** NS **Adult?** Yes **Number of participants** NS	**Treatment** Acitretin 25 mg Acitretin 50 mg Number of patients NS **Comparator** Placebo Number of patients NS **Duration of treatment** 8 wks **Outcome measure** Assessment of severity of erythema, thickness and pustules, but no placebo data	NS

continued

TABLE 71 *Excluded studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Van Weelden, 1990[118] **Study design** RCT Half body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** NS **Minimum BSA included** NS **Minimum PASI included** NS **Adult?** Yes **Number of participants** NS	**Treatment** PUVA 2/wk Number of patients NS **Comparator** NBUVB 2/wk NS **Duration of treatment** 4 wks or until the comparisons of the symmetrical body sides gave the same difference two times in a row **Outcome measure** Overall, impression (not extractable)	Overall, impression (not extractable)
Storbeck, 1993[122] **Study design** RCT Half body	**Psoriasis type** Plaque, guttate or erythroderma **Resistant to topicals/require systemics?** NS **Minimum BSA included** NS **Minimum PASI included** NS **Adult?** Yes (17–66 years) **Number of participants** NS	**Treatment** NBUVB 3–5/wk + dithranol or BBUVB 3–5/wk + dithranol Number of patients NS **Comparator** NBUVB 3–5/wk or BBUVB 3–5/wk Number of patients NS **Duration of treatment** Treatment continued until patient stopped complying **Outcome measure** PASI (not extractable)	PASI (not extractable)

continued

TABLE 71 *Excluded studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Williams, 1985[178] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** NS **Minimum BSA included** >30 **Minimum PASI included** NS **Adult?** Yes **Number of participants** NS	**Treatment** PUVA 2/wk Number of patients NS **Comparator** UVB + tar (4/day) 5/wk (Goeckerman) Number of patients NS **Duration of treatment** NS **Outcome measure** Considerable improvement/clear on 6-point scale % reduction of percentage body coverage by psoriasis (no data) No. of treatments to achieve 90% improvement (no data)	NS
Leavell, 1970[179] **Study design** RCT Whole body Cross-over trial	**Psoriasis type** Severe recalcitrant psoriasis **Resistant to topicals/require systemics?** NS **Minimum BSA included** NS **Minimum PASI included** NS **Adult?** Yes **Number of participants** $n = 24$	**Treatment** Hydroxycarbamide 0.5 g 2/day Number of patients $n = 12$ **Comparator** Placebo equivalent Number of patients $n = 12$ **Duration of treatment** 8 wks **Outcome measure** Physician and patient subjective impression of improvement on 3-point scale (progression of disease, no change, improvement)	**Improvement** Hydroxycarbamide ($n = 12$): physician: 7 improvement, 3 no change; patient: 9 improvement, 1 increased disease Placebo ($n = 12$): physician: 1 improvement, 7 no change, 2 increased disease; patient: 1 improvement, 5 no change, 4 increased disease

continued

TABLE 71 *Excluded studies of other treatments for moderate to severe psoriasis (cont'd)*

Study details	Participants	Treatment	Outcomes and results
Ellis, 1986[180] **Study design** RCT Whole body	**Psoriasis type** Plaque **Resistant to topicals/require systemics?** Yes **Minimum BSA included** >20% **Minimum PASI included** NS **Adult?** Yes **Number of participants** *n* = 21	**Treatment** Ciclosporin 14 mg/kg/day Number of patients *n* = 11 **Comparator** Placebo equivalent Number of patients *n* = 10 **Duration of treatment** 4 wks **Outcome measure** PGA of improvement (clear = 100%; marked improvement = 51–99% better; moderate improvement = 11–50% better; minimal/no change = 0–10% better; worse)	**PASI 50/PSI 50** Ciclosporin: 8/11 Placebo: 0/10 **Clearance** Ciclosporin: 2/11 Placebo: 0/10 **Improvement** Ciclosporin: 2 clearance, 6 marked improvement, 2 moderate improvement, 1 minimal Placebo: 10 minimal or no change

Appendix 8

Detailed methods for mixed treatment comparison

Ordered probit model

With this method, the ordered probit model is designed to model a discrete dependent variable that takes ordered multinomial outcomes, for example $y = 0, 1, 2, 3, \ldots$. The ordered probit model can be expressed in terms of an underlying latent variable y^*. This could be interpreted as the individual's underlying percentage reduction in PASI score from baseline. The higher the value of y^*, the more likely they are to report a higher category of PASI response. For trials reporting the PASI 50, 75 and 90 end-points, subjects may be in one of four mutually exclusive categories; no response, PASI 50 to PASI 75 response, PASI 75 to PASI 90 response and PASI 90 and greater response. Hence the range of y^* values is divided into four intervals corresponding to these categories. The threshold values (c) correspond to the cut-offs where an individual moves from reporting one category to another. The lowest value is set at minus infinity, the highest value is set at plus infinity and the upper bound on the first interval (c_{50}) set to zero. The remaining thresholds (c_{75} and c_{90}) were estimated based on the data. The treatment effects are introduced by making the latent variable, y^*, a linear function of the treatment effect and intercept and a normally distributed error term. For trials reporting other patterns of end-points, the appropriate mutually exclusive categories were modelled; for instance, if a trial only reported the PASI 90 end-point, patients may be in one of two mutually exclusive categories (no response and PASI 90 or greater response).

The model was implemented as a Bayesian hierarchical model. The likelihood takes the form

$$\prod_j p_{j,m(j)}{}^{n}{}_{j}$$

$$p_{j,1} = \Phi\,(y^*_j)$$
$$p_{j,2} = \Phi\,(y^*_j + c_{75}) - \Phi\,(y^*_j)$$
$$p_{j,3} = \Phi\,(y^*_j + c_{90}) - \Phi\,(y^*_j + c_{75})$$
$$p_{j,4} = 1 - \Phi\,(y^*_j + c_{90})$$
$$p_{j,5} = 1 - \Phi\,(y^*_j + c_{75})$$
$$p_{j,6} = 1 - \Phi\,(y^*_j)$$
$$p_{j,7} = \Phi\,(y^*_j + c_{75})$$

$$y^*_j = \mu_{s(j)} + \beta^{t(j)}_{s(j)}$$
$$\mu_{s(j)} = N(\mu,\ 1/\tau_\mu)$$
$$\beta_{s(j)}{}^{t} = N(\beta_t,\ 1/\tau_\beta)$$

where:
n_j is the number of subjects in the mth category represented by the jth datapoint;
$p_{j,m(j)}$ is the probability of observing subjects in the mth category represented by the jth data point;
$p_{j,1}$ is the probability of observing subjects not having a PASI 50 response for the jth data point;
$p_{j,2}$ is the probability of observing subjects having between a PASI 50 and a PASI 75 response for the jth data point;
$p_{j,3}$ is the probability of observing subjects having between a PASI 75 and a PASI 90 response for the jth data point;
$p_{j,4}$ is the probability of observing subjects having between a PASI 90 response for the jth data point;
$p_{j,5}$ is the probability of observing subjects having a PASI 75 response for the jth data point;
$p_{j,6}$ is the probability of observing subjects having a PASI 50 response for the jth data point;
$p_{j,7}$ is the probability of observing subjects having less than a PASI 75 response for the jth data point;
$\mu_{s(j)}$ is the intercept for the kth study represented by the jth data point;
$\beta^{t(j)}_{s(j)}$ is the treatment coefficient for the tth treatment and sth study represented by the jth data point;
$\beta.^{1}$ is constrained to zero;
Φ is the standard normal cumulative density function (CDF).

The following vague priors were defined:
$c_{75} \sim U(0,\ 10)$
$c_{90} \sim U(c_{75},\ c_{75} + 10)$

$$\beta^t \sim N\left(\frac{1}{0.001}\right)$$

$$\mu \sim N\left(\frac{1}{0.001}\right)$$

$sd \sim U(0,\ 10)$
$\tau_\mu = 1/sd^2$
$sd_{tx} \sim U(0,\ 10)$
$\tau_\beta = 1/sd_{tx}{}^2$

The predicted mean probabilities of PASI 50 response for the *t*th treatment were estimated as follows:

$$P_t^{\text{PASI 50}} = 1 - \Phi(\mu - \beta^t)$$

and PASI 75 as:

$$P_t^{\text{PASI 75}} = 1 - \Phi(\mu + \beta^t + c_{75})$$

and PASI 90 as:

$$P_t^{\text{PASI 90}} = 1 - \Phi(\mu + \beta^t + c_{90})$$

The meta-analysis then provided estimates for response rates for each of the treatments based on all observed comparisons adjusting for (implicit) variation in placebo response rates on the log-odds scale. These estimates of response rates were used in the cost-effectiveness model. The meta-analysis was conducted using WinBUGS version 1.4.[133] A burn-in period of 50,000 simulations was used to allow convergence followed by 100,000 simulations for estimation. As a degree of auto-correlation was observed in some of the model parameters, the model was 'thinned' so every 10th simulation was retained. Caterpillar plots of the estimated parameters were checked to ensure that the model converged satisfactorily. A range of initial values was also tested. A comparison of predicted probabilities with the original data indicated a reasonable fit for the model. The deviance for the random effects was 6975 and deviance information criteria (DIC) 7004.[181] A fixed treatment effects model was also tried, but was found to fit the data less well, deviance 6990, DIC 7025. The WinBUGS code is reproduced in the next section.

Code used for mixed treatment comparison and economic modelling

All code is in WinBUGS and R.

Random **EFFECTS MODEL**

```
model
        {
        # this just has to be large enough to ensure all phi[j]'s > 0
        C <- 1

        #random effect baseline, equates to placebo/PASI50 endpoint
        for (s in 1:nStudies)
                {
                mu[s]~dnorm(muMean,muTau)
                }

        #define mean treatment effects - beta[Tx]
        #define random treatment effect variates - randBeta[ Tx]
        for (t in 2:nTx)
                {
        beta[t] ~ dnorm(0,.001)
                for (s in 1:nStudies)
                        {
                        randBeta[s,t]~dnorm(beta[t],txTau)
                        }
                }

        #treatment effect (and variance) is zero for placebo.
        beta[1] <- 0
for (s in 1:nStudies)
                {
                randBeta[s,1]<-0
                }

        #Model data
        for (j in 1:nObs)
                {
                #study baseline and treatment effect -random treatment effects model
                base[j] <- mu[study[j]] + randBeta[study[j],Tx[j]]
```

```
        #fixed treatment effects version
        #base[j] <- mu[study[j]] + beta[Tx[j]]

        #probability of <50  percent reduction in PASI
        pOutcome[1,j] <-  phi(base[j])

        #probability of 50-75  percent reduction in PASI
        pOutcome[2,j] <-  phi(base[j]+c75) - phi(base[j])

        #probability of 75-90  percent reduction in PASI
        pOutcome[3,j] <-  phi(base[j]+ c90) - phi(base[j]+c75)

        #probability of >=90  percent reduction in PASI
        pOutcome[4,j] <-  1-phi(base[j]+c90)

        #probability of >=75  percent reduction in PASI
        pOutcome[5,j] <-  1-phi(base[j]+c75)

        #probability of >=50  percent reduction in PASI
        pOutcome[6,j] <-  1-phi(base[j])

        #probability of <75 (clearance)  percent reduction in PASI
        pOutcome[7,j] <-  phi(base[j]+c75)

        #probability of >=75 (clearance) percent reduction in PASI
        pOutcome[8,j] <-  1-phi(base[j]+c75)

        #probability of <75 percent reduction in PASI
        pOutcome[9,j] <-  phi(base[j]+c75)

        #Likelihood function, probability of endpoint to the power of number of observations
L[j]<- pow(pOutcome[outcome[j],j],n[j])

        #use zeroes trick as described in winbugs manual
        logL[j]<- log(L[j])
        zeros[j] <- 0
        phi[j] <- -logL[j] + C
        zeros[j] ~ dpois(phi[j])

        predictedP[j] <- pOutcome[outcome[j],j]
        }

#predicted treatment effects in terms of absolute probabilities and Relative Risks
for (t in 1:nTx)
        {
        predictedTX50[t] <- 1-phi(muMean + beta[t])
        rr50[t] <- predictedTX50[t] /predictedTX50[1]

        predictedTX75[t] <- 1-phi(muMean + c75 + beta[t])
        rr75[t] <- predictedTX75[t] /predictedTX75[1]

        predictedTX90[t] <- 1-phi(muMean + c90 + beta[t])
        rr90[t] <- predictedTX90[t] /predictedTX90[1]
        }


#priors for ordered probit cut points
c75 ~ dunif(0,10)
c90inc ~ dunif(0,10)
c90 <- c75+c90inc

#prior for random baseline effect mean and precision
        muMean ~ dnorm(0,.001)
        muTau <- 1/(sd*sd)
        sd ~ dunif(0,10)
```

```
        #prior for random treatment effect precision
                txTau <- 1/(txSd*txSd)
                txSd ~ dunif(0,10)

        }


list(mu = c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,
0, 0, 0), beta = c(NA, 0, 0, 0, 0, 0, 0), c75 = 0.5, c90inc = 1)
```

[**Confidential information removed**]

```
#load libraries and set up functions

#set current path to location of excel sheet
setwd(currentPath)

#method of moments parameterisation of the gamma distribution
gamma <- function(N,min,max)
        {
        mean <- (min+max)/2
        sd <-   (max-min)/1.96
        shape <- (mean/sd)^2
        scale <- mean/sd^2
        if(sd>0) return(rgamma(N,shape,scale))
        else return(rep(mean,N))
        }


#check if packages already available - ifnot load from ZIP files in wd
if(!"ellipse"%in%.packages(all=TRUE)) (install.packages("ellipse_0.2-12.zip", .libPaths()[1], CRAN = NULL))
if(!"R2WinBUGS"%in%.packages(all=TRUE)) (install.packages("R2WinBUGS_0.2-2.zip", .libPaths()[1], CRAN = NULL))

#load packages
library(ellipse)
library(R2WinBUGS)

#function to call winbus code
genSamps <- function(data,inits,n.iter,n.burnin,n.thin,bugs.file,parameters.to.save,winDebug)
        {
        sims <- bugs(
                data=data,
                inits=inits,
                parameters.to.save=parameters.to.save,
                model.file=bugs.file,
                n.chains=1,
                debug=winDebug,
                n.iter = n.iter,
                n.burnin = n.burnin,
                n.thin=n.thin
                )

        return(sims)
        }

#select valid comparators from excel sheet
comparators <- comparators[comparators!=""]

#select valid lambda values
ceRange <- ceRange[1:which.max(ceRange)]

#coerce ce labels into matrix
ceLabels <- cbind(numeric(),ceRange)
```

```
#number of valid datapoints
nObs <- sum(outcome>0)

#select valid outcome codes
outcome <- outcome[1:nObs]

#select valid studies
study <- Study[1:nObs]

#select valid treatments
Tx <- Tx[1:nObs]

#select valid n's
n <- n[1:nObs]

#generate list of study names
studyNames <-as.character(unique(study))

#generate list of study codes
studyCodeList <- 1:length(studyNames)

#number of unique studies
nStudies <- length(studyCodeList)

#code studies
studyCode <- studyCodeList[match(study,studyNames)]

#list of unique treatments
txNames <-as.character(unique(Tx))

#generate list of tx codes
txCodeList <- 1:length(txNames)

#number of unique treatments
nTx <- length(txCodeList)

#code treatments
txCode <- txCodeList[match(Tx,txNames)]

#only run winbugs code is flag is set
if (runWin==1)
        {
        #run winbugs
        probInits <- list(list(mu=rep(0,nStudies),beta=c(NA,rep(0,(nTx-1))),c75=0.5,c90inc=1))
        probBugsData <-
list(study=studyCode,Tx=txCode,outcome=outcome,n=n,nObs=nObs,nTx=nTx,nStudies=nStudies)
        probParameters.to.save <-
c("predictedP","predictedTX50","predictedTX75","predictedTX90","rr50","rr75","rr90","beta","txSd","sd","c75","c90")
        probX <-
genSamps(probBugsData,inits=probInits,n.iter=nThin*(nSims+nBurnin),n.burnin=nBurnin*nThin,n.thin=nThin,bugs.file=
probWinSource,parameters.to.save=probParameters.to.save,winDebug=winDebug)

        #extract predicted probabilities,mean and CI
        probPredictedP <- cbind(probX$summary[1:nObs,1],NA)
        probPredictedTX50 <- probX$summary[(nObs+1):(nObs+nTx),c(1,3,7)]
        probPredictedTX75 <- probX$summary[(nObs+nTx+1):(nObs+nTx*2),c(1,3,7)]
        probPredictedTX90 <- probX$summary[(nObs+nTx*2+1):(nObs+nTx*3),c(1,3,7)]

        #extract relative risks
        rrTX50 <- probX$summary[(nObs+nTx*3+1):(nObs+nTx*4),c(1,3,7)]
        rrTX75 <- probX$summary[(nObs+nTx*4+1):(nObs+nTx*5),c(1,3,7)]
        rrTX90 <- probX$summary[(nObs+nTx*5+1):(nObs+nTx*6),c(1,3,7)]

        #extract DIC and deviance
        probDeviance <- probX$summary[length(probX$summary[,1]),1]
```

```
probDIC <- probX$DIC

#extract simulates from simulated posterior distribution
prob50Resp =probX$sims.array[,1,(nObs+1):(nObs+nTx)]
prob75Resp =probX$sims.array[,1,(nObs+nTx+1):(nObs+2*nTx)]
prob90Resp =probX$sims.array[,1,(nObs+2*nTx+1):(nObs+3*nTx)]

#label simulates
dimnames(prob50Resp)[[2]] <- txNames
dimnames(prob75Resp)[[2]] <- txNames
dimnames(prob90Resp)[[2]] <- txNames

#duplicate etanercept sims for continuous etan option
etan25 <- (1:length(txNames))[txNames=="Etanercept 25mg"]

#add duplicates
prob50Resp <- cbind(prob50Resp,prob50Resp[,etan25])
prob75Resp <- cbind(prob75Resp,prob75Resp[,etan25])
prob90Resp <- cbind(prob90Resp,prob90Resp[,etan25])

#add names and label for continuous etan
txNames <- c(txNames,"Etanercept 25mg Continuous")
txLabels <- cbind("",txNames)

#relabel
dimnames(prob50Resp)[[2]] <- txNames
dimnames(prob75Resp)[[2]] <- txNames
dimnames(prob90Resp)[[2]] <- txNames
}

#generate utility vector

#generate DLQI distribution for different PASI levels
D00DLQI <- rnorm(nSims,D00Mean,D00SD/sqrt(D00N))
D50DLQI <- rnorm(nSims,D50Mean,D50SD/sqrt(D50N))
D75DLQI <- rnorm(nSims,D75Mean,D75SD/sqrt(D75N))
D90DLQI <- rnorm(nSims,D90Mean,D90SD/sqrt(D90N))

#generate EQ5D DLQI co-efficient distribution
EQ5DBeta <- rnorm(nSims,EQ5DBetaMean,EQ5DBetaSE)

#generate utility distributions for different PASI levels
D00Utility <- EQ5DBeta*D00DLQI
D50Utility <- EQ5DBeta*D50DLQI
D75Utility <- EQ5DBeta*D75DLQI
D90Utility <- EQ5DBeta*D90DLQI

#estimate mean and se utility for different PASI levels
D00UtilityMean <- mean(D00Utility)
D00UtilitySE <- sd(D00Utility)
D50UtilityMean <- mean(D50Utility)
D50UtilitySE <- sd(D50Utility)
D75UtilityMean <- mean(D75Utility)
D75UtilitySE <- sd(D75Utility)
D90UtilityMean <- mean(D90Utility)
D90UtilitySE <- sd(D90Utility)

#label cost variables
names(drugInitCost) <- drugTX
names(drugMinCost) <- drugTX
names(drugMaxCost) <- drugTX

#convert durations to years
periodResp <- periodRespWk/(365.25/7)
periodRespEffect <- periodRespEffectWk/(365.25/7)
```

```
	periodRespCost <- periodRespCostWk/(365.25/7)
	periodTrial <- periodTrialWk/(365.25/7)

	#label duration variables
	names(periodTrial) <- periodTX
	names(periodTrial) <- periodTX
	names(periodResp) <- periodTX
	names(periodRespEffect) <- periodTX
	names(periodRespCost) <- periodTX


#extract placebo response probs
plcb50Resp<-prob50Resp[,"Supportive Care"]
plcb75Resp<-prob75Resp[,"Supportive Care"]
plcb90Resp<-prob90Resp[,"Supportive Care"]
uPlacebo <-  D00Utility*(1-plcb50Resp)+D50Utility*(plcb50Resp-plcb75Resp)+D75Utility*(plcb75Resp-
plcb90Resp)+D90Utility*plcb90Resp


#derive placebo cost
if (pasiCut==50)
	{
	placeboCost <- nonRespHospCost*(1-prob50Resp[,"Supportive Care"])
	}

if (pasiCut==75)
	{
	placeboCost <- nonRespHospCost*(1-prob75Resp[,"Supportive Care"])
	}


#define decision model
psorModel <-
function(uPlacebo,placeboCost,prob50Resp,prob75Resp,prob90Resp,D00Utility,D50Utility,D75Utility,D90Utility,periodTrial,peri
odRespEffect,periodRespCost,periodResp,
		drugInitCost,drugMinCost,drugMaxCost,nonRespHospCost,nSims)
		{

		uAll <-  D00Utility*(1-prob50Resp)+D50Utility*(prob50Resp-prob75Resp)+D75Utility*(prob75Resp-
prob90Resp)+D90Utility*prob90Resp

		if (pasiCut==50)
			{
			pResp <- prob50Resp
			uResp<-  (D50Utility*(prob50Resp-prob75Resp)+D75Utility*(prob75Resp-
prob90Resp)+D90Utility*prob90Resp)/pResp
			}

		if (pasiCut==75)
			{
			pResp <- prob75Resp
			uResp<-  (D75Utility*(prob75Resp-prob90Resp)+D90Utility*prob90Resp)/pResp
			}

		drugCost <- gamma(nSims,drugMinCost,drugMaxCost)

		totalCost = drugInitCost + pResp*periodRespCost*drugCost+(1-pResp)*nonRespHospCost*periodTrial -
(periodTrial+pResp*periodRespCost)*placeboCost
		cost <- totalCost/(periodTrial+pResp*periodRespCost)

		totalEffect = periodTrial*(uAll-uPlacebo)+pResp*periodRespEffect*(uResp-uPlacebo)
		effect <- totalEffect/(periodTrial+pResp*periodRespEffect)

		return(list(cost=cost,qaly=effect))
		}
```

```
#run decision model for each treatment option

        cost <- numeric()
        qaly <- numeric()

for (drug in comparators)
        {
        x <- psorModel   (
                uPlacebo=uPlacebo,
                placeboCost=placeboCost,
                prob50Resp=prob50Resp[,drug],
                prob75Resp=prob75Resp[,drug],
                prob90Resp=prob90Resp[,drug],
                D00Utility=D00Utility,
                D50Utility=D50Utility,
                D75Utility=D75Utility,
                D90Utility=D90Utility,
                periodTrial=periodTrial[drug],
                periodRespEffect=periodRespEffect[drug],
                periodRespCost=periodRespCost[drug],
                periodResp=periodResp[drug],
                drugInitCost=drugInitCost[drug],
                drugMinCost=drugMinCost[drug],
                drugMaxCost=drugMaxCost[drug],
                nonRespHospCost=nonRespHospCost,
                nSims=nSims
                )

        cost <- cbind(cost,x$cost)
        qaly <- cbind(qaly,x$qaly)
        }

row.names(cost) <- character()
dimnames(cost)[[2]] <- comparators
dimnames(qaly)[[2]] <- comparators

qalyMean <- apply(qaly,2,mean)
costMean <- apply(cost,2,mean)
costTiles <- apply(cost,2,quantile,c(0.025,0.975))
qalyTiles <- apply(qaly,2,quantile,c(0.025,0.975))
options <- cbind(qalyMean,qalyCI=t(qalyTiles),costMean,costCI=t(costTiles))


index<-order(options[,"costMean"])
options<-options[index,]

drugs <- attributes(options)$dimnames[[1]]
retain <-options

icerChar <-""
domFlag <- TRUE

#tells function when to stop looking for dominated options
while (domFlag == TRUE)
        {

        l <- length(retain[,"qalyMean"])

        qalyDiff <- retain[,"qalyMean"][2:l] > retain[,"qalyMean"][1:(l-1)]
        nonDom <- TRUE

        if(l>2)
                {
                nonDom <- qalyDiff >0
                icerChar[!nonDom[drugs]] <- "Dominated"
```

```
            retain<-retain[c(TRUE,nonDom),]
            }

        if (sum(nonDom==FALSE)==0) domFlag<-FALSE
        }



#exclude dominated options
exDomFlag <-TRUE
while (exDomFlag ==TRUE)
        {
        #sort the data frame

        l  <- length(retain[,"costMean"])
        icer <- (retain[,"costMean"][2:l]-retain[,"costMean"][1:(l-1)])/(retain[,"qalyMean"][2:l]-retain[,"qalyMean"][1:(l-1)])

        #include first, last and options where ICER is less than next costlier option
        i <- length(icer)
        nonExDom <- TRUE

        if (i>1)
            {
            nonExDom <- icer[1:(i-1)]<icer[2:i]
            icerChar[!nonExDom[drugs]] <- "Extended Domination"
            retain<-retain[c(TRUE,nonExDom,TRUE),]
            }

        if (sum(nonExDom==FALSE)==0) exDomFlag<-FALSE
        }

names(icerChar) <- drugs

icerChar[names(icer)] <- as.numeric(trunc(icer))

supplcer <-trunc(options[,4]/options[,1])

options[,1:3] <- round(options[,1:3],3)
options[,4:6] <- trunc(options[,4:6])

icerResults <- cbind(options,icerChar,supplcer)

icerTitles <- rbind(c("QALYs","","","Costs","","","","",c("Mean","2.5% CI","97.5% CI","Mean","2.5% CI","97.5% CI","ICER","ICER
against Supportive Care"))
icerLabels <- cbind("",drugs)

#cost-effectiveness acceptability


        optSeq <- character()

        for (ce in ceRange)
            {

            netBenMean <- qalyMean*ce - costMean
            s <- comparators[order(netBenMean,decreasing=TRUE)]

            #Remove options which offer less net-benefit than supportive care
            s[netBenMean[order(netBenMean,decreasing=TRUE)]<0]=""

            optSeq <- rbind(optSeq,s)

            }
```

```
#cost-effectiveness acceptability

        probOptLabels <- rbind(character(),c("QALY WTP",comparators))
        probFeasLabels <- rbind(character(),c("QALY WTP",comparators))

        probOpt <- numeric()
        probFeas <- numeric()

        for (ce in ceRange)
                {

                netBen <- qaly*ce - cost
                optimum <- netBen
                optimum[] <- 0

                optimum[cbind(1:length(netBen[,1]),max.col(netBen))] <- 1
                feasible <- netBen >= netBen[,"Supportive Care"]

                probOpt <- rbind(probOpt,c(ce,apply(optimum,2,mean)))
                probFeas <-rbind(probFeas,c(ce,apply(feasible,2,mean)))

                }
```

Appendix 9

Findings from the economic evaluations

Data extraction table

Primary source	Feldman SR, Garton R, Averett W, Balkrishnan R and Vallee J. Strategy to manage the treatment of severe psoriasis: considerations of efficacy, safety and cost. *Expert Opin Pharmacother* 2003;**4**:1525–33.
Author	Feldman
Date	2003
Type of economic evaluation	Cost-effectiveness analysis
Currency used	US$
Year to which costs apply	2002
Perspective used	Third-party payer Authors state that indirect costs have been estimated, but these are not reported and it is unclear whether they are included in the cost-effectiveness analysis
Time frame	12 months
Comparators	UVB PUVA, 40 mg/30 treatments Methotrexate, 15 mg Acitretin, 25 mg/day Ciclosporin, 3 mg/kg/day (= 240 mg/day) Ciclosporin, 5 mg/kg/day (= 400 mg/day) Alefacept 15 mg i.m. (18 injections annually) Alefacept 7.5 mg i.v. (18 injections annually) Infliximab 5 mg/kg/day (6 infusions annually) Infliximab 10 mg/kg/day (6 infusions annually) Etanercept, 25 mg/kg twice weekly Etanercept, 50 mg/kg twice weekly
Source(s) of effectiveness data	Literature review: existing systematic reviews and supplementary review of recently published papers (for biologicals) Expert opinion
Source(s) of resource use data	Published clinical guidelines (dosage, dosing frequency, duration of treatment, laboratory tests) Manufacturers' guidelines (dosage, dosing frequency, duration of treatment) Expert opinion (physician office visits, duration of treatment for infliximab and etanercept)
Source(s) of unit cost data	Medicare fee schedules, national, median reimbursement value (provider costs, laboratory tests, intravenous infusion, UVB) Medicare fee schedules, local, median reimbursement value (liver biopsy) Drug Topics Red Book (drug acquisition costs)
Modelling approach used	Simple decision tree
Summary of effectiveness results	Treatment success rate, measured as percentage of patients achieving a 75% improvement in PASI score from baseline (PASI75)

	%
UVB	70
PUVA	80
Methotrexate (15 mg)	30
Acitretin	30
Ciclosporin	70
Alefacept	40
Infliximab	80
Etanercept	47

continued

Summary of cost results (annual)		US$
	UVB	3,600
	PUVA	4,600
	Methotrexate (15 mg)	1,600
	Acitretin (25 mg/day)	5,200
	Ciclosporin (3 mg/kg/day)	6,500
	Ciclosporin (5 mg/kg/day)	10,000
	Alefacept (i.v.)	16,000 (to 20,000)
	Infliximab (5 mg/kg)	18,000
	Etanercept (25 mg/kg, twice weekly)	16,900
	Etanercept (50 mg/kg, twice weekly)	33,000
Summary of cost-effectiveness results	Annual cost per treatment success	US$
	UVB	5,100
	PUVA	5,700
	Methotrexate (15 mg)	5,400
	Acitretin (25 mg/day)	17,300
	Ciclosporin (3 mg/kg/day)	6,500
	Ciclosporin (5 mg/kg/day)	14,200
	Alefacept (i.v.)	40,600
	Infliximab (5 mg/kg)	22,500
	Etanercept (25 mg/kg, twice weekly)	35,900
	Etanercept (50 mg/kg, twice weekly)	33,000
Sensitivity analysis	Variables investigated by deterministic sensitivity analysis include dose (ciclosporin, methotrexate, infliximab, and etanercept), delivery method (alefacept) and efficacy (all treatments) Under all analyses, phototherapy (UVB or PUVA) was the most cost-effective treatment, with methotrexate the most cost-effective **systemic** option	
Main conclusions	UVB phototherapy is the least costly and probably the safest way to manage psoriasis, but it may be inconvenient for patients. PUVA, methotrexate, alefacept, infliximab and etanercept all appear to be appropriate second-line choices for psoriasis, each with advantages and disadvantages, and considerable patient and physician judgement is required in deciding which of these agents to prescribe in which order. Ciclosporin is an appropriate therapy for short-term treatment of disease flare before transitioning to a safer long-term treatment	

Quality assessment table

All items are graded as either ✓ yes (item adequately addressed), × no (item not adequately addressed), **?** unclear or not enough information, NA not applicable or NS not stated.

Study question		Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	×	The authors report that indirect costs have been measured, but these do not appear to have been included in the cost analysis
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✓	The authors have excluded combination therapy 'for simplicity'
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	The comparators represent clinical practice in the USA
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	

continued

Study question		Comments
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	?	The absence of head-to-head trial data was acknowledged to be a shortcoming of the analysis
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	?	Baseline estimates of effectiveness were chosen by consensus, but details of this process are not reported. Effectiveness estimates were unadjusted against placebo
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	?	In the absence of trial or observational data, expert opinion formed the basis for several estimates of resource use
15. Appropriate unit costs estimated (with methodology)	?	Median fee schedule values were used
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	NA	Productivity costs are not reported
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	NA	
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	×	The model appears to be a simple decision tree, although this is not explicitly stated
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	?	The choice of model is not discussed Details of most of the important input parameters are reported, but some are not
24. All model outputs described adequately.	?	Cost per treatment success is reported for most treatments, although not all (especially where more than one dose for a particular therapy was explored)
Discounting		
25. Discount rate used for both costs and benefits	NA	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	NA	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and CIs are given for stochastic data	×	
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, cost-effectiveness acceptability curves)	×	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	×	

continued

Study question		Comments
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	×	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	NA	
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	×	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	×	
35. The choice of variables for sensitivity analysis is justified	**?**	
36. The ranges over which the variables are varied are stated	×	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	×	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	**?**	The comparators chosen, the type and frequency of laboratory tests and the unit costs reflect US clinical practice. For these reasons, findings may not be generalisable to the NHS

Appendix 10

Data extraction and quality assessment tables for economic evaluations submitted by manufacturers

Cost-effectiveness model submitted by Wyeth: data extraction

Primary source	Company submission.
Author	Wyeth Pharmaceuticals UK
Date	16 July 2004
Type of economic evaluation	Cost-effectiveness analysis; health effects in terms of QALYs; NHS cost perspective
Currency used	£ sterling
Year to which costs apply	Drug costs: BNF – year not specified Costs of adverse events: NHS Reference Costs – year not specified
Perspective used	NHS
Time frame	Results presented at 12 weeks (trial analysis) and 96 weeks (extrapolated analysis)
Comparators	For the 12-week trial analysis, the model compares the following options: (i) etanercept 25 mg twice weekly; (ii) etanercept 50 mg twice weekly; (iii) no systemic treatment. For the 96-week extrapolated model, there are two sets of comparisons. First: (i) continuous etanercept lower dose; (ii) continuous etanercept higher dose; (iii) no systemic therapy. Second: (i) intermittent etanercept lower dose; (ii) no systemic therapy
Source(s) of effectiveness data	All effectiveness evidence is taken from the three etanercept registration studies performed by Wyeth and Amgen: Studies 20021632; 20021639; 20021642. These studies provide information on baseline PASI and QoL (in terms of DLQI); change in DLQI and PASI over time (up to 24 weeks), adverse drug events related to the therapy. Subgroup analysis is undertaken by baseline DLQI and PASI In order to express effectiveness in terms of QALYs, DLQI (primary analysis) and PASI (secondary analysis) are 'mapped' to EQ-5D utility. This is based on an observational study of patients with psoriasis in Cardiff For the evaluation of the continuous and intermittent strategies, treatment starting and stopping rules (using PASI changes measured in the trials) are based on clinical opinion
Source(s) of resource use data	Dosage drugs: the trial evidence Monitoring and administration assumptions: clinical opinion Adverse events of drug: the trial evidence
Source of mortality data	No mortality data are included in the analysis
Sources of utility data	The 'mapping' of QoL (DLQI) and PASI to utility was based on a survey undertaken in Cardiff. This included all patients identified from hospital records as having been treated at a single acute NHS hospital for psoriasis over a 2-year period. Patients were asked to complete the DLQI and the EQ-5D. PASI data were taken from clinical notes (i.e. past data). A regression model was developed to predict (EQ-5D-based) utility from DLQI. The analysis found a statistically significant association between these measures and estimated each one-point increase in the DLQI to be associated with a fall of 0.0248 in patient utility Patients' DLQI scores at each visit were converted into utility scores using the algorithm: EQ-5D utility score = 0.956 – [0.0248 × (DLQI total score)]
Source(s) of unit cost data	Drug costs: BNF Costs for purposes of costing adverse events: NHS Reference Costs
Modelling approach used	The short-term (12-week) analysis is based on patient-level data pooled across the registration trials, so no formal modelling is involved The longer term extrapolation (for continuous and intermittent etanercept) is based on a model over a time horizon of 96 weeks. For **continuous therapy**, the model followed a

continued

	simplified Markov process. It was based on 8 treatment periods of 12 weeks (total time horizon of 96 weeks). Patients start the model receiving treatment with one of the three strategies (see above). At the end of the initial (12-week) treatment period the model reflects the probability of three events: (i) an improvement of at least 75% in PASI over baseline (PASI 75); (ii) an improvement of 50–75% in PASI over baseline; (iii) treatment failure (PASI response <50). Patients experiencing an improvement of PASI 50 or better are assumed to continue treatment; those who do not are assumed to cease treatment. By the end of a second period (24 weeks post-randomisation), those patients who continue therapy and achieve a PASI 75 response to therapy are assumed to stay on treatment. By the end of the second period, some of the patients who withdraw from therapy are assumed to achieve spontaneous response. In subsequent periods, patients are assumed to remain in their existing health state, except those who are removed from treatment but progressively achieve PASI 75 response at the rate observed in the no treatment group of the clinical trials (i.e. spontaneous remission)
	A similar extrapolation model is used to evaluate **intermittent** etanercept therapy. After 12 weeks, response is assessed and etanercept withdrawn from all patients
	Patients who do not achieve a PASI 50 response or better receive no further therapy. Patients who achieve a response of PASI 50 or better are eligible for retreatment. The patients receive a further course of 12 weeks' treatment once response has been lost
Summary of effectiveness results	The short-term (12-week) analysis indicates incremental QALYs of 0.018 (etanercept 25 mg compared with no systemic therapy), 0.020 (etanercept 50 mg compared with no systemic therapy) and 0.002 (etanercept 50 mg compared with etanercept 25 mg). For the 96-week model for continuous therapy, these estimates are, respectively, 0.152, 0.180 and 0.028, for all patients, and 0.312, 0.276 and –0.036, for patients with baseline PASI >20 and baseline DLQI >15
	For the 96-week model of intermittent 25 mg (twice per week) etanercept, incremental QALYs were 0.127 (compared with no systemic therapy) in all patients and 0.194 in patients with baseline PASI >10 and baseline DLQI >15
Summary of cost results	The costs of adverse events were found to be low and similar between the etanercept and placebo arms of the 3 registration trials
	For the 12-week analysis based on trial data, the costs were estimated as £2043 (drug), £76 (initial visit), £218 (follow-up visits), £15 (adverse events) and £2352 (total) with etanercept 25 mg. These costs were £4160, £76, £218, £9 and £4464, respectively, with etanercept 50 mg. They were £0, £0, £55, £18 and £72 with placebo (no systemic therapy). These costs were then used in the extrapolation models
Summary of cost-effectiveness results	The short-term (12-week) analysis indicates incremental costs per QALY gained of £124,732 (etanercept 25mg compared with no systemic therapy), £219,996 (etanercept 50 mg compared with no systemic therapy) and £1,255,840 (etanercept 50 mg compared with etanercept 25 mg). For the 96-week model for continuous therapy these estimates are, respectively, £53,056, £64,559 and £127,464 for all patients, and £25,926, £37,320 and 25 mg etanercept dominating for patients with baseline PASI >20 and baseline DLQI >15
	For the 96-week model of intermittent 25 mg (twice per week) etanercept, incremental costs per QALY gained were £37,199 (compared with no systemic therapy) in all patients, and £24,229 in patients with baseline PASI >10 and baseline DLQI >15
Sensitivity analysis	A range of scenario analyses were undertaken to assess how the cost per QALY gained varied with baseline PASI and DLQI. These showed that the ICERs were lower in patients with worse baseline QoL and clinical severity. No other sensitivity analyses were reported
Main conclusions	The estimated costs per QALY gained of etanercept were high if the time horizon is set equal to the follow-up in the registration trials (12 weeks)
	The use of an extrapolation model to estimate cost-effectiveness over 96 weeks suggests lower ICERs for continuous and intermittent therapy, particularly in patients with relatively poor baseline PASI and DLQI

Cost-effectiveness model submitted by Wyeth: quality assessment

All items will be graded as either ✓ (item adequately addressed), × no (item not adequately addressed), **?** unclear or not enough information, NA not applicable or NS not stated.

Study question		Comments
1. Costs and effects examined	**?**	Costs of hospitalisation for severe patients were not included
2. Alternatives compared	**?**	No comparison with other biological therapy (i.e. efalizumab) or other licensed systemic therapies (e.g. methotrexate). Comparison of etanercept at different doses with option of no systemic therapy, under different configurations regarding when the biological is used continuously or intermittently
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	×	No comparison with other biological therapy (i.e. efalizumab) or other licensed systemic therapies (e.g. methotrexate). Also no direct comparison of continuous and intermittent use of etanercept
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	This is based partly on what was done in the registration trials and partly on clinical advice regarding the continuous and intermittent strategies.
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	Cost-effectiveness/utility analysis; effects in terms of QALYs
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	Patient-level data from 3 registration trials which have been pooled for analysis
11. Potential biases identified (especially if data not from RCTs)	N/A	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	×	In pooling the data across the 3 trials, there is no apparent consideration of heterogeneity
Costs		
13. All the important and relevant resource use included	**?**	No consideration of hospitalisation costs
14. All the important and relevant resource use measured accurately (with methodology)	**?**	Little detail about costing of adverse events. No price year
15. Appropriate unit costs estimated (with methodology)	**?**	Little detail
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	×	Country stated (UK); year not stated

continued

Study question		Comments
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	QALYs
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	✓	Mapping from DLQI and based on EQ-5D
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	Based on EQ-5D index
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	Simple Markov model
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	Apparently no discounting used. Longest time horizon is 96 weeks, so this absence is not crucial
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	NA	
Allowance for uncertainty		
Stochastic analysis of patient-level data	×	
27. Details of statistical tests and CIs are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, cost-effectiveness acceptability curves)	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Probabilistic analysis of decision models	×	
30. Are all appropriate input parameters included with uncertainty?	NA	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	NA	
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Deterministic analysis	×	No clear analysis of uncertainty. Variability in cost-effectiveness according to baseline disease severity and QoL is assessed using scenario analysis
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	NA	
35. The choice of variables for sensitivity analysis is justified	NA	
36. The ranges over which the variables are varied are stated	NA	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	?	Only cost per QALY estimates presented for many of the subgroup analyses (by baseline severity and QoL)
39. Applicable to the NHS setting	✓	

Cost-effectiveness model submitted by Serono: data extraction

Primary source	Company submission
Author	Serono Ltd
Date	16 July 2004
Type of economic evaluation	Cost-effectiveness analysis; health effects in terms of QALYs; NHS cost perspective
Currency used	£ sterling
Year to which costs apply	Drug costs: 2003 Hospital resource use: 2001 to 2003
Perspective used	NHS
Time frame	Base-case of 10 years (alternatives for costs of 5 years and 1 year)
Comparators	Model compares alternative strategies, in moderate to severe psoriasis, of starting therapy with efalizumab or with (more potent) topical creams: calcipotriol or betamethasone
Source(s) of effectiveness data	Response rates (using a PASI 50 threshold) at 12 weeks for efalizumab are taken from 5 placebo-controlled registration trials: ACD2058g, ACD2059g, ACD2390g, ACD2600g and IMP24011. PASI 50 response data for topical therapy were taken from the placebo arms of those trials
	Adverse event data (which were attributed costs and, if serious, led to treatment discontinuation, were also taken from the active (efalizumab) and placebo (topicals) arms of the registration trials
	Discontinuation rates for reasons other than non-response or adverse events were taken from the registration trials (for efalizumab), a review of calcipotriol and betamethasone trials (for topicals)
Source(s) of resource use data	Efalizumab dosages, administration and monitoring: SPC and assumptions. Topical therapies: assumption of 27.7% use of calcipotriol and 40.7% betamethasone plus assumptions about clinician visits. No costs for emollient therapy, but some clinician visits assumed
	Resource use associated with adverse events were apparently taken from the registration trials
Source of mortality data	No mortality data are included in the analysis
Sources of utility data	Study by Zug *et al.*[26] based on a survey of 87 patients with psoriasis who responded to various utility instruments (the time trade-off was used in the model). Patients who failed to respond at 12 weeks (in terms of PASI 50) were assumed to have a utility of 0.59 based on the 'severe psoriasis' state valued by Zug *et al*. Those who responded were assumed to have a utility of 0.945, which was derived as the mean of the estimated utility for 'mild psoriasis' (0.89) and good health (1)
Source(s) of unit cost data	Drug costs: BNF 2003 Hospital resource use: PSSRU 2002–3, NHS Reference Costs 2003, Leeds Teaching Hospital NHS Trust provider-provider tariff 2001–2
Modelling approach used	The model takes the form of a decision tree. Patients start therapy with either efalizumab or topicals. The decision tree models the probability of continuation beyond 12 weeks of therapy based on treatment response (PASI 50) and adverse events. Patients responding at 12 weeks maintain the QALY gain of a responder until the end of the model (for 10 years) unless there is discontinuation of therapy after 12 weeks for reasons other than lack of efficacy or adverse events. Patients who discontinue with efalizumab are assumed to move to topicals, and those who discontinue with topicals are assumed to move to emollients for symptom relief (i.e. cannot achieve a PASI 50 response). After discontinuation, patients are assumed to accumulate QALYs based on the utility of severe psoriasis once the efficacy has worn off (based on relapse rates from the trials)
Summary of effectiveness results	Over a 10-year time horizon, the number of successfully-treated years (i.e. defined base on PASI 50 response) are 3.92 with efalizumab and 1.01 with topicals. The number of QALYs are 1.39 with efalizumab and 0.36 with topicals
Summary of cost results	The cost of efalizumab is £27,032, £18,488 and £5611 over 10, 5 and 1 years, respectively. The equivalent costs for topicals are £453, £303 and £123, respectively
Summary of cost-effectiveness results	The incremental cost per successfully treated year with efalizumab is £9082. The incremental cost per additional QALY with efalizumab is £25,582

continued

Sensitivity analysis	Probabilistic sensitivity analyses and expected costs and effects were taken from this, but no presentation of parameter uncertainty was undertaken (e.g. with cost-effectiveness planes or cost-effectiveness acceptability curves). A range of sensitivity analyses were undertaken. The most important of these (in terms of variation in the ICER) was a two-way sensitivity analysis of the utility values given to responders and non-responders. Over the range of variation in these inputs, the incremental cost per additional QALY ranged from £15,237 (utilities of 1.00 for a responder and 0.40 for a non-responder) to £92,001 (utilities of 0.80 for a responder and 0.70 for a non-responder)
Main conclusions	The results from the economic model show that the treatment cost with efalizumab for 1 year of treatment success (50% reduction in PASI score) is between £9082 and £9144 per patient. The cost/QALY results from the deterministic and probabilistic analyses were £25,759 and £25,582, respectively. Sensitivity analyses showed that the main driver of cost-effectiveness is the utility difference between a responder and a non-responder

Cost-effectiveness model submitted by Serono: quality assessment

All items will be graded as either ✓ (item adequately addressed), × no (item not adequately addressed), **?** unclear or not enough information, NA not applicable or NS not stated.

Study question		Comments
1. Costs and effects examined	✓	
2. Alternatives compared	**?**	No comparison with other biological therapy (i.e. etanercept) or other licensed systemic therapies (e.g. methotrexate)
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	×	No comparison with other biological therapy (i.e. etanercept) or other licensed systemic therapies (e.g. methotrexate)
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	This is based partly on what was done in the registration trials, and partly on assumptions about how therapies would be used in practice
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	Cost-effectiveness/utility analysis; effects in terms of successfully-treated years (based on PASI 50) and QALYs
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	From 5 registration trials and a review of RCTs for topical therapies (calcipotriol and betamethasone)
11. Potential biases identified (especially if data not from RCTs)	NA	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	
Costs		
13. All the important and relevant resource use included	✓	

continued

Study question		Comments
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	QALYs
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	✓	Clearly described but potential weakness of study (see main text)
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	✓	Derived directly from patients using the EQ-5D
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	Decision tree
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	**?**	The assumption of continued utility gains for responding patients (with the exception of a small number of discontinuers for reasons other than lack of efficacy and adverse events) is strong and not well justified
24. All model outputs described adequately	**?**	Costs are not disaggregated and there is a lack of clarity about the time horizons being used
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data	×	
27. Details of statistical tests and CIs are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, cost-effectiveness acceptability curves)	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Probabilistic analysis of decision models	✓	But methods and results not presented
30. Are all appropriate input parameters included with uncertainty?	NS	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	NS	
32. Are the probability distributions adequately detailed and appropriate?	NS	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NS	
Deterministic analysis	✓	Range of one-way (and one two-way) sensitivity analyses
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	

continued

Study question		Comments
35. The choice of variables for sensitivity analysis is justified	×	
36. The ranges over which the variables are varied are stated	**?**	Yes, but not justified
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	×	
39. Applicable to the NHS setting	✓	

Appendix 11

Treatment with Fumaderm

Fumaderm is normally introduced slowly during the first 6 weeks of treatment. There are two strengths of tablet, Fumaderm Initial being about one-quarter the strength of Fumaderm. Treatment is started with Fumaderm Initial and the dose is gradually increased. It is important to follow the instructions carefully to keep the risk of side-effects to a minimum.

Week	Tablet	Dose		
		Breakfast	Lunch	Dinner
1	Fumaderm Initial	–	–	1
2	Fumaderm Initial	1	–	1
3	Fumaderm Initial	1	1	1
4	Fumaderm	–	–	1
5	Fumaderm	1	–	1
6	Fumaderm	1	1	1

The normal final dose required is one Fumaderm tablet three times daily. Occasionally higher doses may be required.

Week	Tablet	Dose		
		Breakfast	Lunch	Dinner
7	Fumaderm	1	1	2
8	Fumaderm	2	1	2
9	Fumaderm	2	2	2

Two tablets of Fumaderm three times daily is the maximum dose.

The most common side-effects from Fumaderm are flushing of the face and a feeling of warmth. These symptoms are usually harmless and tend to get better during treatment. The tablets can sometimes cause indigestion, stomach cramps or diarrhoea. These can be unpleasant but tend to improve during continued treatment. If they cause problems, the daily dose should be reduced by one tablet. To avoid getting these side-effects it is best to take Fumaderm at meal times with plenty of liquid. If indigestion or diarrhoea occur, then milk products and yoghurt can be helpful.

Contraindications

Severe peptic ulceration; liver disease; renal impairment; pregnancy and lactation; abnormal white cell or platelet counts; other systemic medication for psoriasis.

Monitoring

Full blood count and differential, biochemical profile: before commencement, then fortnightly to 3 months, then monthly.

Discontinue Fumaderm immediately:

- if white blood cell count falls below 3000×10^9/l
- if creatinine rises above normal range.

*Reproduced with permission of Dr Robert Chalmers, Dermatology Centre, University of Manchester.

Appendix 12

Methods details of the cost-effectiveness modelling for treatments of chronic disease

Model structure

Plaque psoriasis is a chronic non-progressive disease with a number of treatment options; if an individual patient does not respond to or tolerate a particular treatment option, an alternative one may be tried. If an effective treatment is not found, then a patient will receive supportive care. This process is illustrated in *Figure 6*.

To identify the most cost-effective treatment, one needs to estimate the expected costs and benefits for all relevant comparators. It can be seen from *Figure 6* that to estimate the expected costs and benefits associated with a specific treatment option, one needs to estimate three items:

1. For patients who respond to the specific treatment, the costs and benefits over the treatment lifetime.
2. For patients who do not respond to the specific treatment, the cost and benefits over the period that the treatment was trialled.
3. For patients who do not respond to the specific treatment, costs and benefits of the future treatments. This will require estimates of items 1 and 2 for each of the subsequent treatment options.

Therefore, one needs to consider the cost-effectiveness of different treatment **strategies**, each consisting of a sequence of treatment options to be trialled for a patient, rather than the cost-effectiveness of individual treatments. This is illustrated in *Figure 7*.

The primary decision problem is to identify, for an individual patient, the optimum treatment strategy. In addition, one may wish to consider the definition of treatment success that leads to a patient being maintained on a particular treatment.

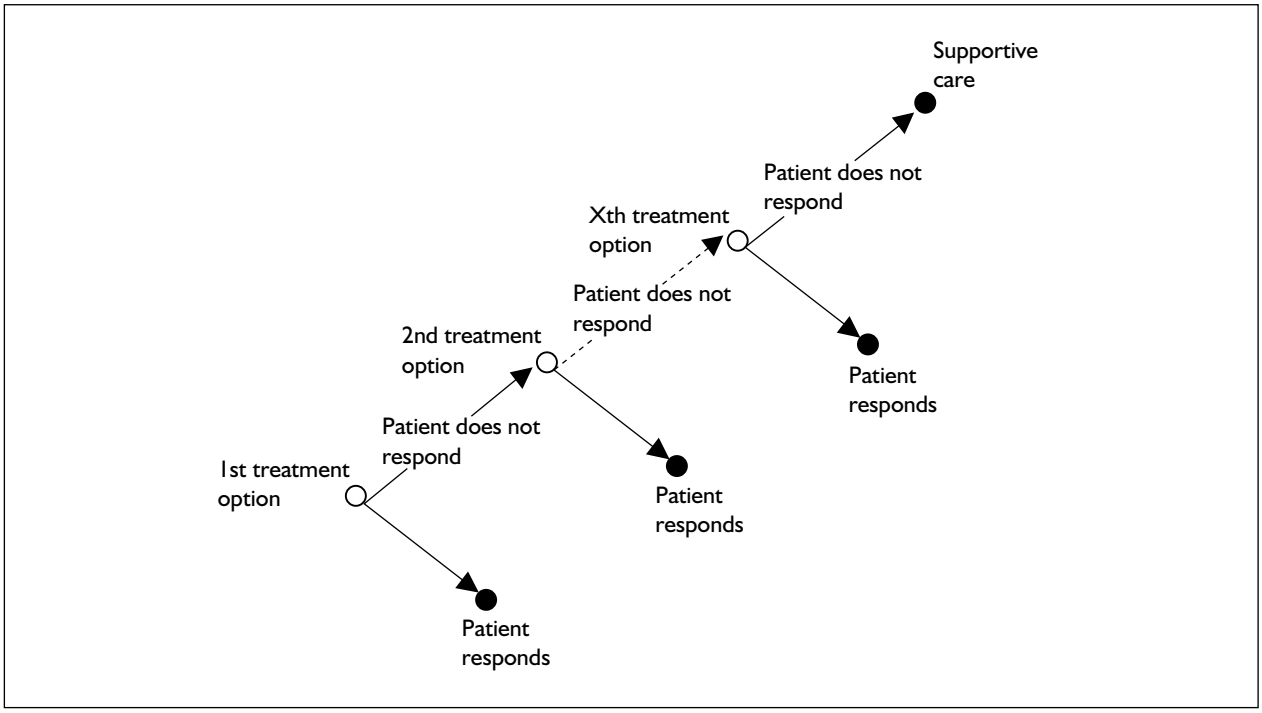

FIGURE 6 *Treatment of a chronic disease*

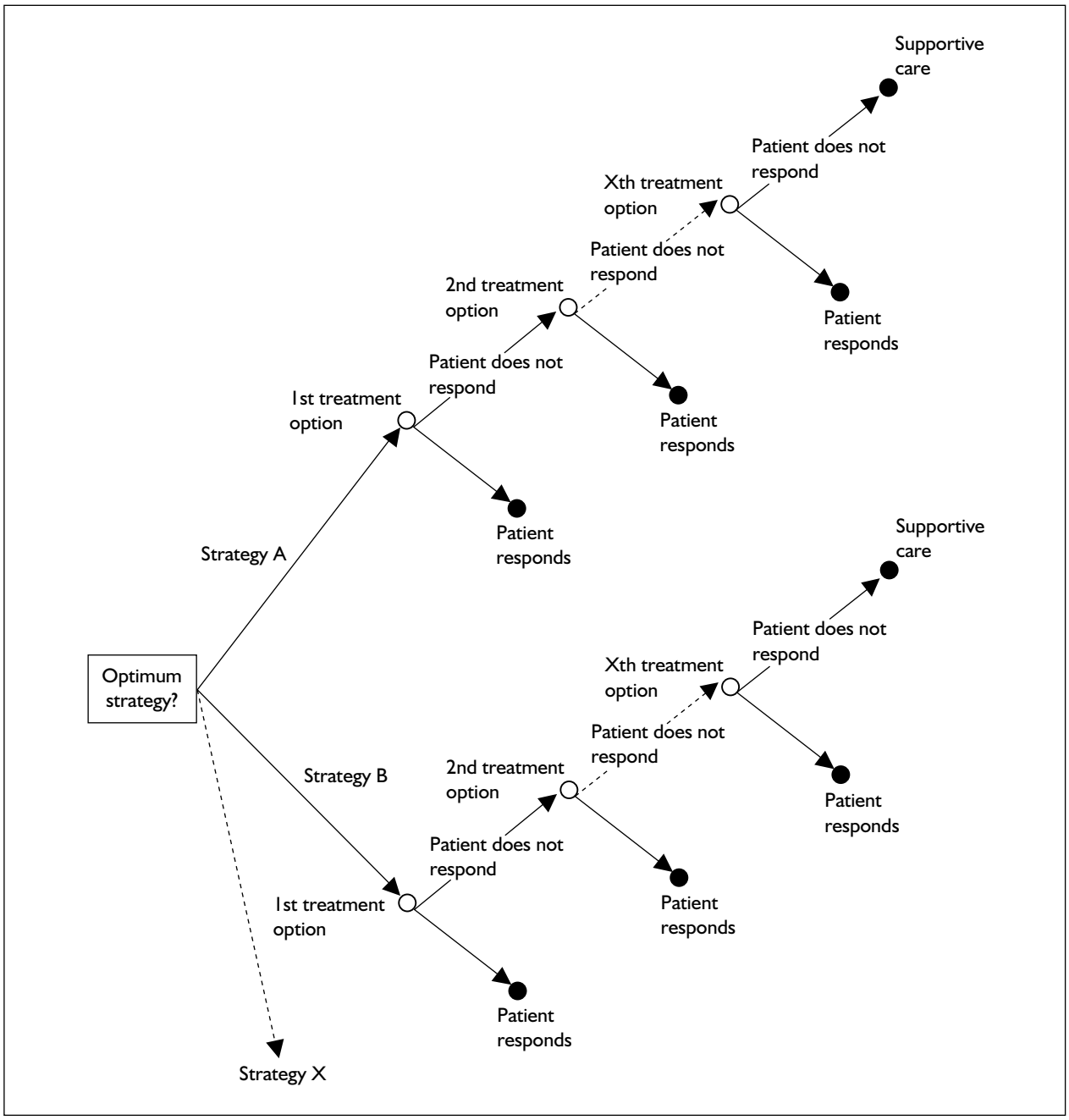

FIGURE 7 *Treatment sequences for chronic diseases*

Specific challenges

There are a number of specific challenges associated with the cost-effectiveness analysis for treatments of chronic diseases.

The number of potential treatment strategies

Each potential treatment strategy should be regarded as a separate comparator. With four treatment options, there are [(perm 4 from 4) + (perm 3 from 4) + (perm 2 from 4) + (perm 1 from 4)] or 24 + 24 + 12 + 4 = 64 potential treatment strategies. If we include the option to use treatment options in combination, there are even more possible sequences. *Table 72* shows that, as the number of treatment options increases, the number of potential strategies increases geometrically. As the number of treatment options increases, the cost-effectiveness analysis may not be tractable and the meaningful presentation of results including all potential strategies is difficult.

One option is to narrow the range of strategies based on existing opinion. However, existing expert opinions are likely to vary and the analysis

TABLE 72 *Number of treatment strategies*

Number of treatment options	Number of distinct treatment sequences
1	1
2	4
3	15
4	64
5	325
6	1,956
7	13,699

may simply reinforce, rather than potentially modify, existing opinion. An alternative option is to limit the number of treatment options included in the treatment strategy, but this may lead to an analysis which does not really address the decision problem and may be unable to modify existing opinion.

The absence of data regarding treatment response conditional on prior treatment

It is likely that the probability that a patient will respond to a treatment will vary according to his/her treatment history. For example, if a patient has failed to respond to a particular treatment option, he/she may be less likely to respond to further treatments from the same pharmacological class.

The need to select the optimum treatments for individual patients

If the analysis identifies a single treatment strategy as being the most cost-effective, this particular strategy may not be suitable for all (or any) individuals as:

- A particular treatment option in the strategy may be contraindicated for an individual patient.
- A particular treatment option in the strategy may have already been tried by an individual and found not to be tolerated or effective.
- The acceptability of known side-effects associated with a treatment option may vary between individuals. For instance, within the treatment of epilepsy the teratogenic risk associated with the anti-epileptic drug valproate may be acceptable to a female epileptic patient of reproductive age whereas the risk of hirsutism-associated phenytoin may be acceptable to a young male.
- A treatment option in the sequence may not be available, for example, due to the lack of the specialist facilities.
- The strategy may not correspond to accepted clinical nostrums, such as the requirement to try treatment options from a different therapeutic class following treatment failure. There will often be a lack of empirical evidence supporting these and they may vary between locations.

If the single strategy one has identified as being most cost-effective is not suitable for a group of individuals, the analysis will leave the decision-maker without useful information. This suggests that, in addition to the requirement to consider a wide variety of treatment strategies, one may also need to consider different sets of treatment options for different groups of individuals.

Extrapolation from short-term clinical trial data

The cost-effectiveness analysis will usually need to consider a longer treatment horizon than that observed in the available comparative clinical trials. If one expects the benefits or disbenefits of treatment to extend beyond the treatment period, it may be necessary to consider this in the model. For example, for progressive diseases such as rheumatoid arthritis or Parkinson's disease, one needs to consider the extent to which a treatment may provide symptomatic relief, a benefit restricted to the treatment period, and may retard the disease process and provide benefit beyond the treatment period.

The rheumatoid arthritis model developed by Brennan and colleagues[182] was a simple decision-tree model which incorporated the treatment effect as increasing utility only during the period of treatment; this corresponds to the treatment solely providing symptomatic relief and increasing expected utility only during the period of treatment. In contrast, the base-case model developed by Kobelt and colleagues[183] incorporated the relative treatment effect as a change in the Markov model transition matrix during the period of treatment; this corresponds to the treatment acting solely by retarding the disease process and not providing any symptomatic relief and will lead to the increase in expected utility from the treatment being maintained long after the treatment has finished. These differing approaches in modelling the treatment effect may lead to different estimates of cost-effectiveness. It is important that one is clear about the implications of different model structures and that the choice of model structure reflects decision-makers' beliefs regarding the natural history of the disease and treatment rather than analytical convenience.

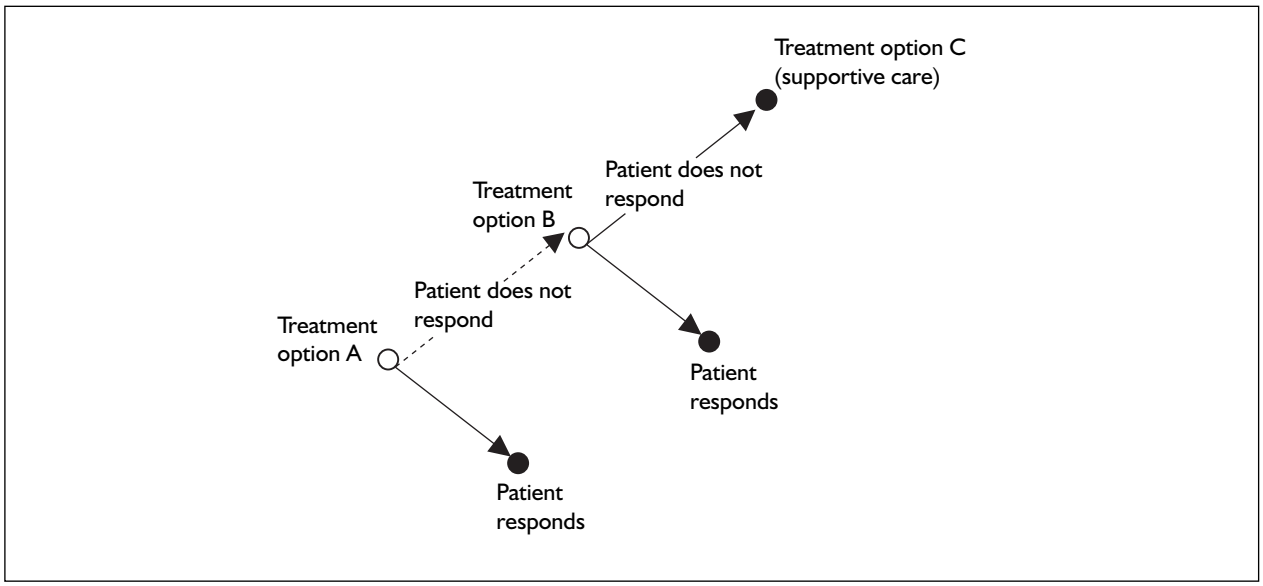

FIGURE 8 *Example of treatment sequence*

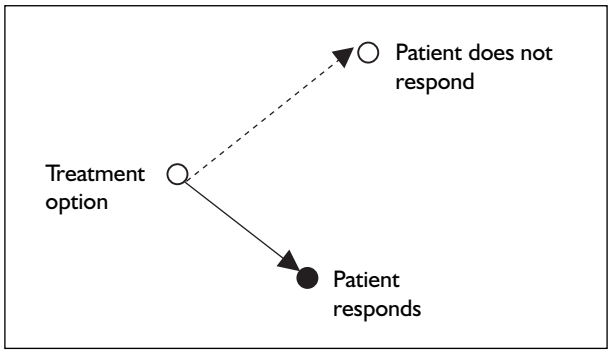

FIGURE 9 *Model for estimating treatment period net benefit*

Model structure

In the light of the considerations outlined above, the following analytical structure is proposed for the York Model for psoriasis.

Let us consider a single treatment strategy illustrated in *Figure 8* consisting of three treatment options, A, B and C, with treatment option C being supportive care.

Let NB_A be the expected net-benefit per unit time for a patient during the period that they are treated with treatment A, the **treatment period net-benefit**. This is the weighted average of the expected net-benefit over the treatment lifetime for those patients who respond to treatment and the expected net-benefit over the treatment trial period for those who do not respond *Figure 9*.

Similarly, NB_B is the expected treatment period net-benefit per unit time for the patients treated with treatment B and NB_C is the expected treatment period net-benefit for the patients treated with treatment C. If P_A is the probability of responding to treatment A and P_B is the probability of responding to treatment B, then the expected overall net-benefit per unit time of the strategy will be

$$NB_A + (1 - P_A)NB_B + (1 - P_A)(1 - P_B)NB_C$$

As was established earlier, the decision problem is to identify the optimum strategy that will result in the greatest expected net-benefit per unit time. The earlier in the strategy a treatment option is tried, the greater is the proportion of patients who will receive and respond to that option. Therefore, to maximise the expected total net-benefit per unit time for the treatment strategy, the options should be tried in order of decreasing expected treatment period net-benefit per unit time. If one can estimate the treatment period net-benefit for each individual treatment, the optimum strategy, based on the treatment options suitable for an individual patient, can be determined. One can also identify those treatment options that offer a lower expected net-benefit than supportive care and should not be used. This analysis is only suitable for treatments where one does not believe that there is an effect on disease progression and does not wish to condition efficacy on previous treatment as the treatment period net-benefit estimates for the various treatment options are regarded as independent.

Using this analytic approach, the results can be present as a table showing the optimum ordering of treatment options as a function of the monetary value of treatment benefit:

	Threshold WTP for a unit of effect (λ)		
	0	**10**	**100**
Optimal sequence[a]	AAA BBB CCC DDD	BBB AAA CCC DDD	CCC BBB AAA DDD

WTP, willingness to pay.
[a] Those options below supportive care should not be used.

In addition, one can present probabilistic results; for example:

Treatment	Probability treatment should be first line (λ = 100)	Probability treatment is cost-effective compared with supportive care (λ = 100)
AAA	0.3	0.8
BBB	0.5	0.7
CCC	0.1	0.1
DDD	0.1	0.05

To estimate the net-benefit for a treatment, one needs to consider the following parameters:

1. Probability that a patient responds.
2. For those patients who respond:
   (a) Expected treatment lifetime.
   (b) Treatment acquisition cost per unit time.
   (c) Utility for a responding patient; where possible, this should be treatment specific and accounting for the disutility associated with tolerable side-effects.
3. For those patients who do not respond:
   (a) Expected trial period.
   (b) Treatment acquisition cost per unit time.

Utility for a non-responding patient, where possible, should be treatment specific and account for the disutility associated with tolerable side-effects.

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Feedback

The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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ISSN 1366-5278