NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Adalimumab (Humira®) for the Treatment of Moderate to Severe Plaque Psoriasis

SPECIFICATION FOR MANUFACTURER/SPONSOR SUBMISSION OF EVIDENCE

Abbott Laboratories Ltd

27th September 2007

Contents

Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand name: Humira
Approved name: adalimumab
Therapeutic class: monoclonal antibody, anti-TNF-α agent, immunosuppressant

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

No. On 2nd April 2007, Abbott Laboratories simultaneously submitted a supplemental Biologics License Application (sBLA) with the U.S. Food and Drug Administration (FDA) and a Type II Variation to the European Medicines Agency (EMEA) seeking approval to market adalimumab as a treatment for moderate to severe chronic plaque psoriasis. It is anticipated that EU marketing authorisation will be granted Q4 2007.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

Rheumatoid arthritis

Adalimumab is licensed in the UK for the treatment of moderate to severe, active RA in adult patients when the response to traditional disease-modifying anti-rheumatic drugs including methotrexate has been inadequate. In this population, Adalimumab has been shown to reduce the rate of progression of joint damage as measured by x-ray, and to improve physical function and inhibit progression of structural damage when given in combination with methotrexate.

Adalimumab is also licensed for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate.

Ankylosing spondylitis

Adalimumab is licensed in the UK for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Psoriatic arthritis

Adalimumab is licensed in the UK for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Crohn's disease

Adalimumab is licensed in Europe for the treatment of severely active Crohn's disease in patients who have not responded despite a full and adequate treatment with an immunosuppressant and/or corticosteroid.

For induction treatment, adalimumab should be given in combination with corticosteroids. Adalimumab can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate.

Psoriasis

The anticipated indication is as follows:

Adalimumab is indicated for:

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

This proposed indication is subject to regulatory approval by the EMEA. In addition, adalimumab is currently undergoing a clinical development programme investigating its use as a treatment for paediatric Crohn's disease, juvenile arthritis and ulcerative colitis.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

A Marketing Authorisation Application was submitted to the EMEA on 2nd April 2007 for the use of adalimumab as a treatment for psoriasis. It is anticipated that the technology will receive marketing authorisation Q4 2007. Adalimumab is not currently licensed for use in the UK for the treatment of psoriasis, and as such it is unknown whether it is currently being used for this indication. However, adalimumab is being used in the UK for the treatment for psoriatic arthritis (PsA), for which there is evidence of an overlap between psoriasis and PsA. Gordon et al estimate that 6-34% of patients with psoriasis may develop psoriatic arthritis[1] and Mease and Goffe report that psoriasis precedes the onset of arthritis symptoms in approximately 70% of PsA cases[2].

[redacted]

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

No. Adalimumab does not have regulatory approval for use as a treatment of psoriasis outside of the UK. However, Abbott Laboratories submitted a supplemental Biologics License Application (sBLA) with the U.S. Food and Drug Administration (FDA) on 2nd April 2007 seeking approval for use of adalimumab as a treatment of moderate to severe plaque psoriasis.

Adalimumab is licensed in the USA and Europe for the treatment of the following indications: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Abbott will submit a dossier to the SMC fourth quarter 2007 for the use of adalimumab in psoriasis. Adalimumab is currently undergoing NICE assessment for rheumatoid arthritis and ankylosing spondylitis under the MTA process alongside etanercept and infliximab in both cases. NICE is evaluating adalimumab for the treatment of Crohn's disease under the MTA process alongside infliximab, certolizumab pegol and natalizumab; and NICE is also reviewing a submission under the STA process for use of adalimumab in the treatment of moderate to severely active psoriatic arthritis, final guidance for which is expected 22nd August 2007.

Adalimumab is currently being evaluated by the SMC as a treatment for severely active Crohn's disease in Scotland.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Adalimumab is available in the following two presentations:

- a 40mg solution for injection in a single-use pre-filled syringe (type I glass) for patient use: packs of 2 pre-filled syringes (0.8 ml sterile solution), each with 1 alcohol pad, in a blister are provided.
- a single-use automatic injection device with needleguard that delivers 40mg solution for injection by pushbutton (Humira Pen). Packs of: 2 pre-filled syringes with needleguard (0.8 ml sterile solution) in a blister, each with 1 alcohol pad are provided.

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The recommended dose of adalimumab for patients with plaque psoriasis is an initial 80mg adalimumab loading dose at Baseline followed by 40mg adalimumab at Week 1, and then subsequent doses of 40mg adalimumab every other week via subcutaneous injection. Adalimumab should be used as a maintenance therapy in patients with psoriasis. Available data suggest that clinical response is usually achieved within 16 weeks of treatment; continued therapy should therefore be carefully reconsidered in a patient not responding within this time period.

The proposed course of treatment is subject to regulatory approval by the EMEA.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The list price of both presentations of adalimumab (autoinjection pen and the pre-filled syringe) is £357.50 per 40mg injection (British National Formulary, March 2007; 53rd edition). The annual cost of adalimumab treatment in the first year is £9652.50 (80mg loading dose at baseline). The annual cost of adalimumab 40mg eow for subsequent years is £9295.

1.10 What is the setting for the use of the technology?

NICE guidance evaluating etanercept and efalizumab for psoriasis suggests that eligible patients for these treatments should have severe disease defined by a total Psoriasis Area Severity Index (PASI) of at least 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10. In addition, the

psoriasis should have failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments. This is in accordance with the BAD guidelines for the use of biological interventions for psoriasis[3], which include the anti-TNF agents etanercept and infliximab, and the cell adhesion molecule inhibitor, efalizumab. The BAD guidelines stipulate that eligible patients for these therapies should have severe disease defined by a PASI score of at least 10 or more and a DLQI score of more than 10. In addition, patients should fulfil at least one of the following criteria:

(i) have developed or are at higher than average risk of developing clinically important drug-related toxicity and where alternative standard therapy cannot be used.

(ii) are or have become intolerant to or cannot receive standard systemic therapy.

(iii) are or have become unresponsive to standard therapy.

(iv) have disease that is only controlled by repeated inpatient management.

(v) have significant, coexistent, unrelated comorbidity, which precludes use of systemic agents such as ciclosporin or methotrexate.

(vi) have severe, unstable, life-threatening disease (erythrodermic or pustular psoriasis).

(vii) have psoriatic arthritis fulfilling the British Society for Rheumatology (BSR) eligibility criteria for treatment with anti-TNF agents, in association with skin disease.

It is anticipated that adalimumab will be the first choice biological agent used in the NHS in England and Wales for patients who have moderate to severe chronic plaque psoriasis and who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

Adalimumab will be prescribed by dermatologists to patients with plaque psoriasis. Adalimumab is provided in a pre-filled syringe or pre-filled pen for subcutaneous self-administration at home, avoiding the need for reconstitution by patients and any further burden to dermatology services as a consequence of the need for intravenous infusion and monitoring for severe infusion reactions. The home delivery of adalimumab is provided by Abbott as a free of charge service.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Patients must be monitored closely during and after treatment with all anti-tumour necrosis factor (TNF) agents. The requirements for monitoring adalimumab are the same as for etanercept and infliximab, as defined by the BAD Guidelines[3]. All patients must undergo clinical assessment for tuberculosis, congestive heart failure, infections and demyelination. Infections and malignancy are a significant clinical concern although the actual associated risks appear to be low, based on the evidence accrued in the adalimumab clinical trial database. Previous or concomitant immunosuppressant treatment and PUVA therapy may compound such risks. Additional, serious potential toxicities include demyelinating disease and heart failure. Anti-TNF agents should not be given to people with a history of demyelinating disease or optic neuritis and treatment should be withdrawn if neurological symptoms develop[3]. It is anticipated that adalimumab will be licensed for use as a monotherapy in patients with psoriasis, in line with the licensed indications for etanercept and infliximab.

2 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with moderate to severe chronic plaque psoriasis	The submission will address the clinical and cost-effectiveness of treatment with adalimumab in accordance with the licensed indication.
Intervention	Adalimumab	Adalimumab
Comparator(s)	Standard therapies: • acitretin • ciclosporin • hydroxycarbamide • methotrexate • photo(chemo)therapy (PUVA) Biologic therapies: • etanercept • efalizumab • infliximab	All standard and biologic therapies were considered for inclusion in the evidence synthesis, which is used to inform the cost effectiveness modelling. A mixed treatment comparison (MTC) evidence synthesis following from the methods developed by the York Assessment Group was run to determine the comparative efficacy of the various treatments[4]. In order to perform the analysis, all trials must be connected through a 'chain' of evidence, where every treatment can be connected to placebo either directly, or through another treatment that is connected to placebo. The PASI 50, 75 and 90 response rates from the trials were used in a meta-analysis where the endpoints were jointly modelled using an ordered probit model. As per the York Assessment Group model previously developed for TA103, it was not possible to include acitretin, hydroxycarbamide and PUVA in the evidence synthesis and economic modelling, as the appropriate data are not available.
Outcomes	Outcomes to be considered include: • measures of severity of psoriasis • remission rate • adverse effects of treatment • health-related quality of life.	A range of outcomes to assess the impact of treatment with adalimumab on psoriasis will be considered, including the following: PASI 50/75/90/100 response Physician's Global Assessment of disease activity Patient's Global Assessment of disease activity Health-related quality of life will be assessed using the DLQI, SF-36 and EQ-5D. Pain associated with psoriatic plaques and PsA (where applicable) and pruritus related to psoriasis will be assessed using

		Visual Analogue Scales The safety of adalimumab will be assessed via analysis of adverse events Quality Adjusted Life Years (QALYs) are the primary outcome measure used in the economic model (cost-utility analysis). The QALY gain is determined by the level of PASI response.
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation should reflect the chronic nature of the condition. Costs will be considered from an NHS and Personal Social Services perspective.	The cost effectiveness of treatment is assessed in terms of incremental cost per quality-adjusted life year. The model considers the use of standard and biologic therapies over time as per the York Assessment Group model developed for TA103 for etanercept and efalizumab for the treatment of psoriasis. Costs are considered from an NHS perspective in the base case economic model analysis. Absenteeism from work will be included in the economic model in a sensitivity analysis.
Special considerations and other issues	Guidance will only be issued in accordance with the marketing authorisation. The appraisal will define severity of psoriasis according to PASI and DLQI. If the evidence allows, the appraisal will attempt to identify subgroups for whom this treatment would be particularly appropriate, such as people with concomitant psoriatic arthritis. It is anticipated that individuals may also be treated with topical therapies; where the	The economic modelling will consider the cost effectiveness of adalimumab in line with the proposed licensed indication. The economic modelling defines response using the PASI outcome measure, as this is the most widely reported measure of response. The effectiveness of adalimumab will also be considered using the DLQI outcome measure where available. The submission will discuss the treatment of patients with concomitant psoriatic arthritis (PsA) for whom treatment with adalimumab would be particularly appropriate. Detailed evidence on the clinical effectiveness and cost effectiveness of adalimumab for PsA will not be included as this is considered in full in the NICE STA for adalimumab for the treatment of PsA. Where the evidence permits, confounding by treatment with topical therapies will be considered

	evidence permits any resulting confounding factors will be taken into consideration.	

Section B

3 Executive summary

Psoriasis (Ps) affects approximately 2% of the general population[5]. Patients with severe disease constitute approximately 20–30% of all patients with psoriasis, they often require systemic treatment and represent a major economic burden to the NHS. The anti-TNF-α drug, adalimumab (HUMIRA®), represents an effective treatment option for patients with severe psoriasis in England and Wales. On 2nd April 2007, Abbott Laboratories simultaneously submitted a supplemental Biologics License Application (sBLA) with the U.S. Food and Drug Administration (FDA) and a Type II Variation to the European Medicines Agency (EMEA) seeking approval to market adalimumab for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA. EMEA approval is expected fourth quarter 2007. Adalimumab, a fully human monoclonal antibody, is available in the following two presentations: a 40mg solution for injection in a single-use pre-filled syringe and a single-use automatic injection prefilled pen, which allows patients to select a delivery system based on their own experiences and preferences, which may lead to increased adherence during long-term therapy. The recommended dose of adalimumab for patients with plaque psoriasis is an initial 80mg adalimumab loading dose at Baseline followed by 40mg adalimumab at Week 1, and then subsequent doses of 40mg adalimumab every other week via subcutaneous injection. Adalimumab should be used as a maintenance therapy in patients with psoriasis. The list price of both presentations of adalimumab (autoinjection pen and the pre-filled syringe) is £357.50 per 40mg injection.

The adalimumab psoriasis clinical trial programme provides robust evidence demonstrating the short- and long-term efficacy of adalimumab in a large patient population. The trials have shown that adalimumab (40mg eow) successfully improves the signs and symptoms of Ps, yielding statistically significant improvements in:

- The signs and symptoms of Ps in patients with chronic plaque psoriasis - measured by the PASI 50, 75, 90 and 100 response rates and the Physician Global Assessment of Disease (PGA).

- The quality of life of patients with Ps – as measured by the DLQI, EQ-5D and SF-36.

- The signs and symptoms of Ps in patients with chronic plaque psoriasis in a direct head-to-head comparison vs. methotrexate (MTX) – as measured by the PASI 75 response in the pivotal phase III trial, M04-716 (CHAMPION). This head-to-head study demonstrated the superior efficacy of adalimumab in the treatment of moderate to severe psoriasis in comparison to MTX and placebo (PASI 75 at Week 16: 80% for adalimumab vs. 36% for MTX and 19% for placebo).

Furthermore, data from 120 weeks of continuous 40mg adalimumab eow demonstrates that clinical response is maintained in the long-term. The evaluated study population in the clinical trial programme had characteristics comparable to patients with severe psoriasis in England and Wales.

Three therapeutic modalities are used singly or in combination in the treatment of Ps: topical agents, phototherapy, non-biologic systemic agents (methotrexate, ciclosporin) and biologic systemic therapy. There are currently three biological agents available for the treatment of patients with moderate to severe plaque psoriasis in the UK: etanercept, efalizumab and infliximab. The BAD guidelines suggest that the choice of agent by the dermatologist will depend on the clinical pattern of psoriasis, pre-existing co-morbidity, patient preference, prescriber preference and local facilities. In the UK, NICE recommends the use of etanercept

for up to 24 weeks in adults with severe disease defined by a total PASI score of 10 or more and a DLQI of more than 10 who have failed to respond to conventional systemic therapies. Efalizumab is only recommended for use in patients who have failed to respond to etanercept, or are intolerant of, or have contraindications to, treatment with etanercept.

A cost-effectiveness analysis was conducted using an adaptation of the York assessment group's economic modelling approach. This analysis was updated to incorporate additional evidence, particularly for the clinical efficacy of adalimumab. For the base case analysis incorporating only costs to the NHS, adalimumab was found to be the most cost-effective biologic strategy with additional costs of £4,993 (95%CI, 3,806-6,157) resulting in an ICER of £30,500 per QALY. The infliximab strategy costs the most (£7,736 [95%CI, 6,515-8,945]) resulting in an ICER of £42,000 per QALY compared to supportive care. All other biologic treatments have ICERs between £37,000 and £40,000 per QALY. The main strength of the evaluation is that it draws upon the analytical framework of the York model and considers the cost effectiveness of the main systemic therapies likely to be considered for the treatment of severe psoriasis. A number of areas have been identified for the York model where further research was merited. In particular, the model submitted by Abbott uses EQ-5D utilities collected directly in the adalimumab trials, which it is argued are the best estimates of utility gain by levels of psoriasis improvement. One of the main potential limitations of the analysis is that treatment effect is only considered according to PASI response. It is argued that improvements in the PASI score are not an ideal proxy for treatment response. This may be particularly the case for patients with concomitant psoriatic arthritis where improvements in arthritis symptoms would be expected with anti-TNF agents such as adalimumab, but not necessarily with other psoriasis treatments. Similarly, the PASI score may not correlate with patient functioning as closely as other outcome measures such as the DLQI. However, the PASI score has the benefit that it has been reported for the majority of systemic therapies. Furthermore, establishing a closer relationship between utility gains and disease severity may only serve to improve the ICERs of those treatments considered the most effective in the evidence synthesis (adalimumab and infliximab). Therefore, this limitation is unlikely to affect the relative ordering of the cost effectiveness of therapies in this therapeutic area.

Adalimumab should be recommended for use in England and Wales because of its proven efficacy in the treatment of psoriasis and co-morbidities associated with Ps (i.e. psoriatic arthritis and Crohn's disease); the eow dosing regimen that may improve patient compliance; the two presentations which allow patients to select a delivery system based on their own experiences and preferences; the greater convenience to the patient as adalimumab can be administered at home or elsewhere; and the potential reduction in immunogenicity because adalimumab is a fully human monoclonal antibody. Furthermore, adalimumab is the only biologic for which there is clinical evidence of superiority to methotrexate in an RCT, and as such should be the first choice biologic agent for patients who have had an inadequate response to systemic therapy. Adalimumab is recommended by NICE for the treatment of psoriatic arthritis when used in accordance with the BSR guidelines. It should be noted that around 30% of patients in the adalimumab psoriasis trials had concomitant psoriatic arthritis. Results from the economic modelling conducted for this appraisal indicate that adalimumab is likely to be the most cost effective biologic therapy for the treatment of severe psoriasis.

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Psoriasis (Ps) is an inflammatory papulosquamous skin disease associated with significant morbidity. It was originally thought to be a disorder primarily of epidermal keratinocytes, but is now recognised as one of the most common immune-mediated disorders. Accurate figures for the prevalence of Ps are difficult to obtain because of an absence of validated diagnostic criteria, however estimates vary from 0·5% to 4·6%, with rates varying between countries and ethnicity. Psoriasis tends to be more frequent in Northern Europe and Scandinavia with the prevalence of Ps estimated to be between 1.5% and 3% of the general population. NICE guidance on the use of etanercept and efalizumab for the treatment of adults with psoriasis indicates that approximately 2% of the UK population have psoriasis[5]. The disease generally occurs in adults with an equal distribution between the sexes.

Despite being the subject of intense research over the years, the precise aetiology of psoriasis still remains unknown. It is universally recognised that genetic factors play a very important role, as supported by frequent family clustering, high concordance rates in monozygotic twins and the identification of at least nine chromosomal loci for which statistically significant evidence for linkage to Ps has been observed[6]. However, there is also increasing evidence pointing towards the influence of environmental factors, which trigger or exacerbate Ps. These include infections, particularly those caused by streptococci, stressful life events, alcohol consumption, cigarette smoking, diet *i.e.* patients trending towards obesity, and medications *e.g.* lithium, beta-adrenergic antagonists, anti-malarials and non-steroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis (psoriasis vulgaris) accounts for 80-90% of all cases of psoriasis[7,8], with guttate psoriasis occurring in about 10% of patients, and erythrodermic and pustular psoriasis each occurring in fewer than 3% of patients. The papulosquamous plaques of psoriasis vulgaris are well delineated from surrounding normal skin and are red or salmon pink in colour, covered by white or silvery scales. Psoriatic plaques occur most often symmetrically on the elbows, knees, lower back, and buttocks[9]. In addition the scalp, nails, intertriginous areas, and genitalia are often involved. The extent of involvement can escalate to full body coverage in more severe cases. Extensive body coverage with very thick, or more inflamed lesions is more likely to itch, be tender, or bleed[9]. A UK study of people with severe psoriasis found that 60% had taken time off work in the previous year as a direct result of their condition[5]. In addition, people with severe disease may require a number of hospitalisations each year, whereby the average length of a hospital stay is around 20 days[5]. Furthermore, there is increasing awareness that Ps is associated with systemic disorders, including Crohn's disease, and more worrying is the emerging relationship between psoriasis and cardiovascular disease[10]. There are also robust data indicating an overlap between Ps and psoriatic arthritis (PsA). Gordon et al estimate that 6-34% of patients with psoriasis may develop psoriatic arthritis[1] and Mease and Goffe report that 30% of patients with Ps have PsA and that psoriasis precedes the onset of arthritis symptoms in approximately 70% of PsA cases[2].

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. Patients with severe disease constitute approximately 20–30% of all patients with psoriasis, often require systemic treatment, and represent a major burden to the National Health Service. Assessment of psoriasis severity is not an exact science and the definition of 'severe' will inevitably differ, both amongst and between dermatologists and patients[11]. The British Association of Dermatology (BAD) guidelines suggest that a Psoriasis Area and Severity Index (PASI) score of $\geq$ 10 (range 0–72) has been shown to correlate with a number of indicators commonly associated with severe disease such as need for hospital admission or use of systemic

therapy[3]. Understandably this is a subjective assessment and furthermore, the effect of psoriasis on the patient's quality of life has to be taken into account. Quality of life studies in psoriasis reveal a negative impact on patients comparable with that seen in cancer, arthritis and heart disease[12,13]. 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 as well as clinical extent in the definition of severe psoriasis[11].

Due to the diverse presentations of psoriasis, approaches to treatment must be individualised on the basis of the nature and extent of disease, anatomical locations, quality-of-life implications, coexistent psoriatic arthritis, triggering factors (such as infections, medications, and stress), and the patient's commitment to therapy. Three therapeutic modalities are used singly or in combination in the treatment of Ps:

1. **Topical agents –**

    - Emollients, corticosteroids, vitamin D3 analogues, tazarotene, coal tar and dithranol

2. **Phototherapy and photochemotherapy –**

    - Broadband UVB, narrowband UVB, PUVA (topical or systemic)

3. **Systemic medications –**

    - Traditional:
        - Methotrexate
        - Ciclosporin
        - Retinoids

    - Biologicals:
        - Adalimumab
        - Efalizumab
        - Etanercept
        - Infliximab

Generally, topical agents are used in the treatment of mild disease (<5% body surface area [BSA]); phototherapy is generally used in moderate disease (5-10% BSA); and photochemotherapy and systemic medications are used in patients with severe psoriasis (>10% BSA). However, as Menter and Griffiths state in their review of the current and future management of psoriasis, "of overriding importance is the need to review the effect of psoriasis on the patient's quality of life (*e.g.* on social and personal interactions) and modify the treatment plan accordingly"[14]. As such, mild psoriasis on the palms or soles frequently needs more intensive therapy than does psoriasis elsewhere. Psychosocial assessments and response to previous treatments should also be considered when selecting therapies.

Although topical treatments remain the mainstay for mild disease and are effective for individual plaques, these agents are often cosmetically unacceptable due to texture, staining and smell. Topical treatments are also incredibly time consuming and may require up to 20hrs/week in application, and as such compliance with these agents is a huge problem. Furthermore, topical treatments would not be expected to have any effect on the co-morbidities associated with Ps. Phototherapy is an effective treatment in patients with moderate Ps but requires the use of specialist equipment and is associated with the time burden of visiting the treatment centre. Although there is a lot of experience with UVB treatment and it is important in Ps management, it is also associated with the side effects of burning and potential carcinogenicity, in fact the NB-UVB guidelines suggest a ceiling of 450 treatments, due to the risk of carcinogenicity[15]. Photochemotherapy, in particular PUVA (a

combination of a photosensitising medication [psoralen] and long-wavelength ultraviolet A [UVA] light) is used for psoriasis resistant to topical preparations and UVB. However, it has acute adverse effects (i.e. skin burning, nausea and pain) and chronic consequences (i.e. skin ageing, pigmentation and carcinogenicity). In addition, there is often a physician-imposed limit on the duration of treatment.

Traditional systemic therapies, particularly methotrexate and ciclosporin, have been shown to be efficacious in treating patients with moderate to severe disease[16,17]. However, these drugs are associated with the potential for major long-term toxicity *e.g.* in the case of methotrexate: myelosuppression, hepatotoxicity, pneumonitis, stomatitis and foetal death; and for ciclosporin: nephrotoxicity, hypertension, immunosuppression with increased risk of infection and malignancy[14]. In addition, there is a risk of clinically significant drug-drug interactions that can occur with methotrexate. Furthermore and importantly, a proportion of patients have treatment resistant disease *i.e.* are intolerant of, or unresponsive to these traditional systemic therapies[18].

In the last decade, increased understanding of the immune pathways critical to the pathogenesis of psoriasis have led to the development of biological agents specifically targeted to these steps. The anti-tumour necrosis factor alpha (TNF-α) agents etanercept and infliximab, which inhibit the pro-inflammatory cytokine TNF-α thought to play a key role in potentiating inflammatory responses associated with psoriasis and PsA, are available in the UK for the treatment of moderate to severe plaque psoriasis in adult patients who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA. The LFA-1 cell adhesion molecule inhibitor, efalizumab, is also available in the UK for the same patient population. Randomised controlled trials have shown all these biological agents to be effective in the treatment of moderate to severe Ps.

Etanercept (*Enbrel®*) is a recombinant human TNF receptor fusion protein that binds competitively to TNF-α inhibiting binding of TNF-α to its receptors. It is administered subcutaneously (sc) at doses of either 50mg once weekly (*i.e.* 52 injections per year) or 25mg twice weekly (*i.e.* 104 injections per year).

Infliximab (*Remicade®*) is a chimeric (part human, part mouse) monoclonal antibody that competitively inhibits the binding of TNF-α to its receptor. It is administered in hospital by intravenous (iv) infusion over 2 hours at weeks 0, 2 and 6 and 8-weekly thereafter at a dose of 5mg/kg.

Efalizumab (*Raptiva®*) is a recombinant humanised monoclonal antibody that binds specifically to the CD11a subunit of LFA-1 (lymphocyte function-associated antigen-1), a leukocyte cell surface protein. 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 and therapy may be continued only in patients who responded to treatment (PGA good or better).

4.2 What was the rationale for the development of the new technology?

In December 2002 and September 2003, adalimumab was approved for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis (RA) in the USA and in the EU, respectively. Subsequently in August 2005, adalimumab received EMEA Marketing Authorisation for the treatment of active and progressive psoriatic arthritis (PsA) based on data from the PsA clinical trial programme, which demonstrated the significant efficacy of adalimumab in the treatment of both the arthritis and the psoriasis component of PsA. As there is increasing evidence documenting the overlap between PsA and Ps (Gordon et al estimate that 6-34% of patients with psoriasis may develop psoriatic arthritis[1]), and since adalimumab has been shown to be safe and effective as a treatment of autoimmune diseases such as RA, PsA, AS and Crohn's disease, and there is increasing evidence that TNF activity

has a major role in the pathogenesis of Ps, a clinical programme was developed to study the safety and efficacy of adalimumab in patients with Ps. Studies have demonstrated that:

- Adalimumab is effective in reducing the signs and symptoms of Ps in patients with moderate to severe chronic plaque psoriasis.
- Adalimumab is effective in reducing the signs and symptoms of Ps with a rapid onset of action.
- Adalimumab is significantly superior to methotrexate in reducing the signs and symptoms of Ps.
- Adalimumab produces substantial improvement in the quality of life of patients with Ps.
- Adalimumab is well tolerated, which is consistent with data from adalimumab-treated subjects in other indications and data from studies of other anti-TNF agents.

4.3 What is the principal mechanism of action of the technology?

Elevated levels of TNF-α play an important role in pathologic inflammation, including psoriasis, where TNF-α contributes to proliferation and decreased maturation of keratinocytes and associated vascular changes. Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences, which binds specifically to the pro-inflammatory cytokine TNF-α and neutralises the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF-α, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1 [endothelial leukocyte adhesion molecule-1], VCAM-1 [vascular cell adhesion molecule-1], and ICAM-1 [intracellular adhesion molecule-1] with an IC_{50} of 1-2 X 10^{-10} M).

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Adalimumab should be recommended as a treatment option for use in patients that have failed to respond to systemic therapies, or are intolerant to these treatments and have a PASI ≥10 and DLQI >10 in line with the current NICE recommendation for the use of etanercept and efalizumab. In the two pivotal phase III adalimumab clinical trials, M04-716 (CHAMPION) and M03-656 (REVEAL), the mean baseline PASI and DLQI scores of subjects fulfilled the criteria of severe disease suggested by NICE and the trial subjects were comparable to patients with active severe Ps in England and Wales. In these subjects, adalimumab (40mg eow) successfully improved the signs and symptoms of Ps, yielding statistically significant improvements in:

- The signs and symptoms of Ps in patients with chronic plaque psoriasis - measured by the PASI 50, 75 and 90 response rates and the Physician Global Assessment of Disease (PGA).

- The signs and symptoms of Ps in patients with chronic plaque psoriasis in a direct head-to-head comparison vs. methotrexate – as measured by the PASI 75 response.

- The quality of life of patients with Ps – measured by the DLQI, EQ-5D and SF-36.

There are currently three biological agents licensed for the treatment of patients with moderate to severe plaque psoriasis in the UK as of 27th September 2007: etanercept, efalizumab and infliximab. The BAD guidelines suggest that the choice of agent by the dermatologist will depend on the clinical pattern of psoriasis, pre-existing co-morbidity, patient preference, prescriber preference and local facilities. In the UK, NICE recommends the use of etanercept for up to 24 weeks in adults with severe disease defined by a total PASI score of 10 or more and a DLQI of more than 10 who have failed to respond to conventional systemic therapies. Efalizumab is only recommended for use in patients who have failed to respond to etanercept, or are intolerant of, or have contraindications to, treatment with etanercept[5].

Adalimumab is an effective treatment for the co-morbidities of Ps, with proven efficacy in the treatment of PsA[19] and Crohn's disease[20,21,22,23]. This is in comparison to efalizumab, which is not licensed for the treatment of PsA or Crohn's disease.

Adalimumab is a fully human monoclonal antibody. As such, immunogenicity may be reduced when compared to other monoclonal antibodies that contain non-human sequences, *e.g.* infliximab. The development of antibodies to infliximab may lead to infusion reactions, loss of efficacy, and delayed hypersensitivity reactions. The antibody construction of adalimumab has a long half-life, which facilitates every other week (eow) dosing compared to etanercept, which requires either a once-weekly or twice-weekly injection regimen. The reduced treatment burden of adalimumab may improve patient compliance, which is often a problem in patients with Ps who have extensive BSA coverage.

Adalimumab is supplied as a single-use automatic injection device with needleguard that delivers 40 adalimumab by pushbutton or as a pre-filled syringe that does not require reconstitution by the patient. Adalimumab is supplied to the patient via the Healthcare At Home service, which provides trained nurses to teach the patients and caregivers how to administer the injection properly. The service is provided free of charge by Abbott and as such there are no additional administration costs to the NHS. In addition, the two presentations of adalimumab (pre-filled syringe or prefilled pen) allow patients to select a delivery system based on their own experiences and preferences, which may lead to increased adherence during long-term therapy. Therefore, one of the clear advantages of adalimumab is its greater convenience to the patient in comparison to infliximab, which must be infused intravenously in a hospital setting and monitored for severe infusion reactions over several hours. Furthermore, the NHS National Patient Safety Agency (NPSA) has recently issued guidance promoting the safer use of injectable medicines in hospitals. The NPSA advocates preparing the injection/infusion preparation in an aseptic environment[24]. As such, infliximab, which is currently prepared on the ward, will have to be prepared in an aseptic suite in pharmacy by the pharmacist or pharmacy technician, which may have implications in the treatment of Ps where it may not be feasible to adequately prepare infliximab at dermatology centres.

To summarise, the proposed licence for adalimumab is for the treatment of adult patients with moderate to severe plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA. Adalimumab should be recommended as a treatment option for use in patients that have failed to respond to systemic therapies, or are intolerant to these treatments and have a PASI ≥10 and DLQI >10 for the following reasons: because of its proven efficacy in the treatment of psoriasis and the co-morbidities associated with Ps; the eow dosing regimen that may improve patient compliance; the two presentations which allow patients to select a delivery system based on their own experiences and preferences; the greater convenience to the patient as adalimumab can be administered at home or elsewhere; and the potential reduction in immunogenicity because adalimumab is a fully human monoclonal antibody. Furthermore, adalimumab is the only biologic for which there is clinical evidence of superiority to methotrexate, and as such should be the first choice biologic agent for patients who have had an inadequate response to systemic therapy.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Although there exist a number of potential therapies to treat chronic plaque psoriasis, some uncertainties still exist regarding best practice.

Type of psoriasis: There are several forms of psoriasis, and a patient may move from one type to another. The extent of involvement can range from small areas to almost total coverage. Psoriasis can change from stable plaques to an unstable form, typified by eruptive inflammatory lesions that can be easily irritated by topical treatment. RCTs of biological agents in psoriasis and the licensed indications only cover chronic plaque psoriasis, which is

the commonest form. There is some limited literature of data in other variants of psoriasis, however these areas need to be explored further.

Limitations with current assessment of psoriasis: All the current disease severity assessment tools are imperfect, and most require some training to complete[3]. The PASI measure is the main tool and validated for use to assess disease severity and treatment response in a clinical trial setting. However, it does have its limitations in that it is often too cumbersome to use in clinical practice. A PASI score of ≥10 has been shown to correlate well with severe disease. PASI scores > 30 are rare, such that almost half the range is of little value. In addition, in patients with PASI score of 10 at baseline, the final score is rarely 0 due to residual erythema. However, a comparison of efficacy data between new and old clinical trials will benefit from keeping PASI as one of the measures[25]. The impact of psoriasis on a patient is more likely to be related to the area affected and the attitudes of the patient. The degree of psychological and social disability that accompanies psoriasis can be underestimated[26]. There is a movement to argue that quality of life (QoL) would be a better method of determining the severity of Ps. In the clinical setting, treatment judgements may be largely guided by QoL issues. A number of quality of life measures exist e.g. DLQI and the more recent SPI. It does not appear that one will cover all the issues that quality of life encompasses. Additional testing is needed to better define which elements of quality of life are sensitive and predictive of clinically meaningful changes[27]. There is currently no ''gold standard'' measure in dermatology. This will require refinement of existing instruments and a consensus-building process similar to OMERACT, with the goal being the standardisation of assessment tools. The initial work of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and the International Psoriasis Council is encouraging in this regard, and standardisation is likely to be accomplished in the years ahead with the close cooperation of dermatologists and rheumatologists[28].

Limitations of current therapies: Current therapies have their limitations. Adherence to topical therapy regimens is poor, and even when patients are told that drug use is monitored, treatment is adhered to just over half the time[29]. Systemic therapies are associated with the potential for major long-term toxicity and a proportion of patients have treatment-resistant disease[3]. There are few comparative studies which have examined the relative efficacy and safety of the different interventions. Those that do have failed to address clinically important questions such as duration of remission when treatment is stopped or whether efficacy is maintained with continuous or intermittent use. Strategies to reduce toxicity from long-term treatment include rotational or sequential use of systemic therapy, drug holidays, and combination therapy[29]. Short- and long-term courses of many such therapies do not provide sufficient periods of remission, and very few patients are ever completely disease free, making clearance an unrealistic expectation. In addition, although many patients are able to achieve disease control with currently available non-biologic systemic therapies or strategies, some are ineligible because of side effects or comorbidities. However, as a consequence, many patients are unable to maintain uninterrupted control of their psoriasis, leading to dissatisfaction with treatment. As psoriasis is chronic and essentially incurable, well tolerated, long-term therapies that can achieve control of psoriasis are required[30].

New approaches: Doctors, including dermatologists, often fail to appreciate the extent of the psychological disability and even when it is correctly identified, less than a third of patients receive appropriate psychological interventions. Such factors may affect treatment outcome, but they are potentially amenable to intervention[27, 29].

Comorbidity of CV disease and malignancy: Patients with severe disease seem to have at least a twofold or threefold increase in mortality from cardiovascular disease. Several studies have also shown an increased risk for a variety of malignancies. The relative influence of known confounders such as concomitant therapy with immunosuppressants and phototherapy, obesity, smoking, and alcohol is not yet clear[29].

Disease modification: The concept of disease modification in psoriasis is new and not as well investigated as for rheumatoid arthritis. There is speculation that early use of disease-modifying antirheumatic drugs may have a microscopic skin modulation role. However, this is

likely to be difficult to prove because there is generally a poor understanding of natural disease progression in psoriasis[30].

Criteria to define disease severity: There is some debate in the literature regarding the criteria to define severity. The EMEA position is that currently there is still no consensus or widely accepted definition of what represents mild, moderate or severe plaque psoriasis[25]. The BAD advises the following to define severe disease: PASI score of 10 or more (or a BSA of 10% or greater where PASI is not applicable) and a DLQI > 10. Disease should have been severe for 6 months, resistant to treatment and the patient should be a candidate for systemic therapy[3].

4.6 Provide details of any relevant guidelines or protocols.

Adalimumab is not currently licensed for psoriasis in the UK (as of 27th September 2007), as such there are no guidelines making recommendations for its use. However, the British Association of Dermatologists (BAD) has issued guidelines on the use of biologics for Ps, for which the same recommendations are likely to apply for adalimumab. The BAD guidelines stipulate that eligible patients for treatment with etanercept, efalizumab and infliximab should have severe disease defined by a PASI of at least 10 or more and a DLQI of more than 10. In addition, patients should fulfil at least one of the following criteria[3]:

- have developed or are at higher than average risk of developing clinically important drug-related toxicity and where alternative standard therapy cannot be used.
- are or have become intolerant to or cannot receive standard systemic therapy.
- are or have become unresponsive to standard therapy.
- have disease that is only controlled by repeated inpatient management.
- have significant, coexistent, unrelated comorbidity, which precludes use of systemic agents such as ciclosporin or methotrexate.
- have severe, unstable, life-threatening disease (erythrodermic or pustular psoriasis).
- have psoriatic arthritis fulfilling the British Society for Rheumatology (BSR) eligibility criteria for treatment with anti-TNF agents, in association with skin disease.

Treatment should be initiated and monitored by consultant dermatologists experienced in managing difficult psoriasis. This should include knowledge and experience of standard therapies and management of those who fail to respond. They must be familiar with, and/or have access to health care professionals trained in the use of the tools recommended for determining treatment eligibility and disease response. Supervising consultants will be responsible for ensuring that all patients receiving therapy are registered with the BAD Biological Therapy Register throughout the treatment period[3].

The National Institute for Health and Clinical Excellence has provided guidance on the use of etanercept and efalizumab for adults with psoriasis[5]. Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met.

- The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more **and** a Dermatology Life Quality Index (DLQI) of more than 10.
- The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments.

Efalizumab, within its licensed indications, is recommended for the treatment of adults with plaque psoriasis only if their psoriasis has failed to respond to etanercept or they are shown to be intolerant of, or have contraindications to, treatment with etanercept[5].

It is recommended that the use of etanercept and efalizumab for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. If a person has both psoriasis and psoriatic arthritis their treatment should be managed by collaboration between a rheumatologist and a dermatologist[5].

The SMC issued guidance on the use of infliximab for psoriasis on 9 March 2007. The SMC states that, "infliximab (Remicade®) is accepted for restricted use within NHS Scotland for the treatment of severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapy including ciclosporin, methotrexate or psoralen ultraviolet A (PUVA)"[31].

In addition, the SMC issued advice on 10th December 2004 that efalizumab (Raptiva®) is not recommended for use within NHS Scotland for the treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or have a contra-indication to, or are intolerant to other systemic therapies, including ciclosporin, methotrexate and PUVA (photochemotherapy)[32].

Abbott is unaware of any other guidelines or protocols in the UK, other than the aforementioned that would be relevant to the current submission.

5 Clinical evidence

5.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Rigorous electronic and manual literature searches were conducted to identify published and unpublished trials of adalimumab for the treatment of psoriasis. Initially to ensure all the data were captured, all trials were included in the search strategy. Once all the trials had been identified, randomised controlled trials of adalimumab for the treatment of psoriasis were retrieved manually. It was not deemed necessary to search older databases as the clinical phase of adalimumab began in 1997.

A number of databases and conference abstracts were searched, including company databases. The relevant search terms were entered into the database being searched and the terms were then combined to form search strings. The titles and abstracts (if available) of all papers revealed at this stage were then reviewed and eliminated manually if they were not relevant to the search. Appendix 2, Section 9.2, details the search strategies and subsequent results from the database and publication sites searched.

Inclusion criteria: all randomised controlled trials (RCTs) comparing adalimumab to an alternative treatment (including placebo) when used for the treatment of psoriasis. Trials of patients with psoriatic arthritis were also identified and considered important, but have not been included in Section 5.2.1 because the list of RCTs is specifically for trials evaluating adalimumab for Ps. Open-labelled controlled trials, prospective studies, crossover studies, and comparative studies were also included. These trials were included in the search string to capture all the studies pertaining to adalimumab for Ps, the RCTs were then extracted manually after a thorough inspection of the citations.

Exclusion criteria: Reviews and studies that did not fit the inclusion criteria or studies based on juvenile data (0-17 years old) were excluded.

The most recent literature search was undertaken on the 8th August 2007.

5.2 Study selection

5.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group.

For purposes of this question, “the intervention” is considered to be adalimumab for the treatment of psoriasis. Comparative studies of adalimumab in other indications (*e.g.* rheumatoid arthritis, ankylosing spondylitis, and Crohn’s disease) are not considered relevant. A complete list of the relevant RCTs is presented in Figure 5.2.1 and further details of these are provided in Table 5.2.1.

Figure 5.2.1: Adalimumab Psoriasis Clinical Trial Programme

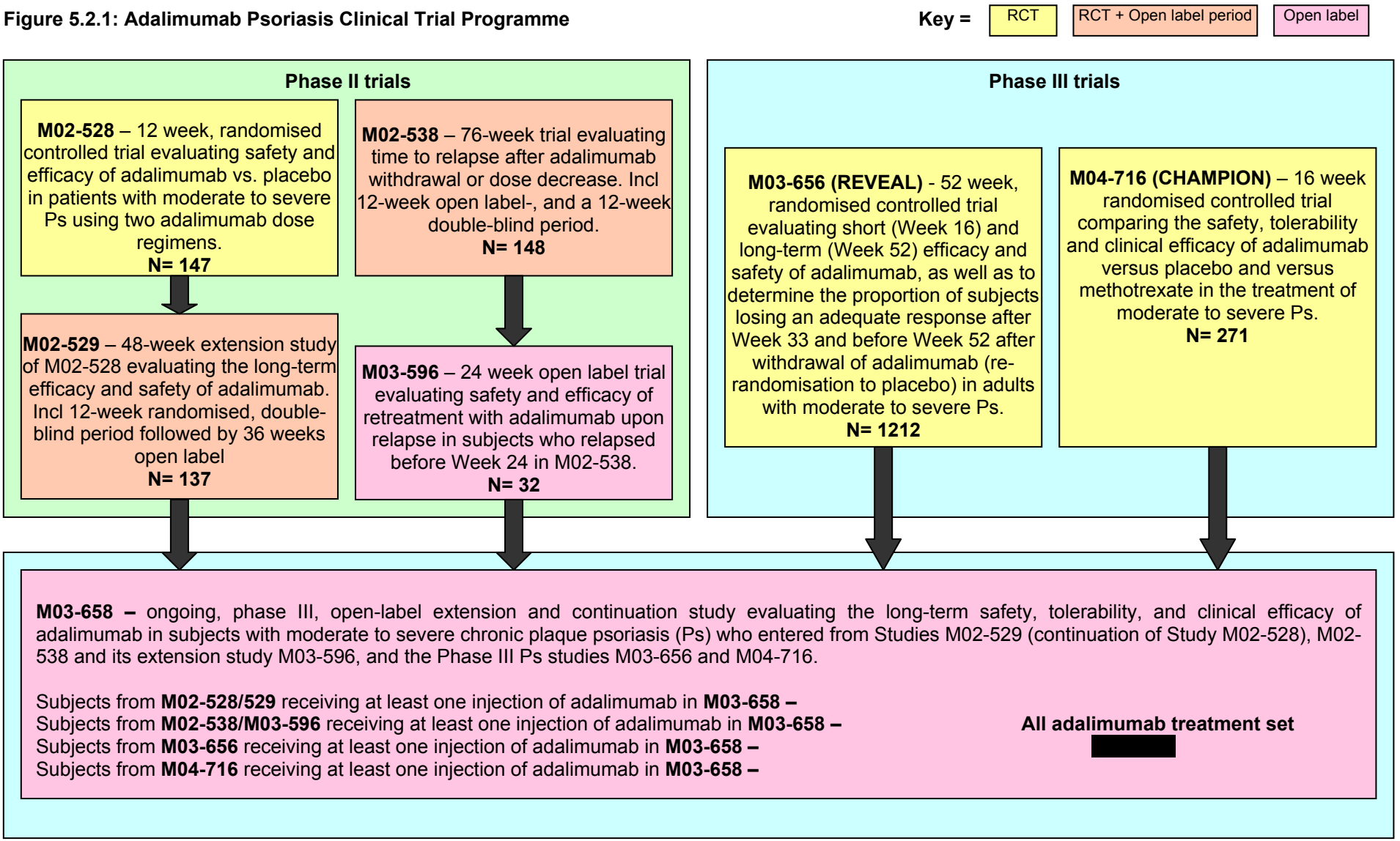


Table 5.2.1: Summary of Adalimumab Psoriasis Clinical Trial Programme

Study ID Number of Centres/ Locations Duration Total Enrolment	Design, Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	Number of Subjects by Treatment Arm Entered/ Completed	Subject Sex Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Randomised controlled Studies							
M02-528 [33,34,35, 36, 37, 38, 39] 18/ USA Canada 12 weeks **N= 147**[a]	Phase II Multicentre, randomised, double-blind, placebo-controlled, dose ranging	Adalimumab 40 mg every other week (eow) sc + placebo eow sc Adalimumab 40 mg weekly sc Placebo weekly sc	Efficacy, Safety, and Pharmacokinetics	Adalimumab eow: 45/43 Adalimumab weekly: 50/47 Placebo: 52/50	Adalimumab eow: 32 Male/13 Female 46 (20-71) Adalimumab weekly: 33 Male/17 Female 42 (24-86) Placebo: 34 Male/18 Female 43 (20-70)	Moderate to severe chronic plaque psoriasis (BSA ≥ 5%) Inadequate response to topical therapy	Proportion of subjects achieving a ≥ PASI 75 response at Week 12.
M02-538 [40, 41] 16/ USA Canada 76 weeks **N = 148**	Phase II Multicentre, randomised, 12-week open-label period 12-week double-blind period 52 week follow-up period Time to relapse after treatment withdrawal or dose decrease	12-week open-label period: 80mg adalimumab at Week 0 and 1 Adalimumab 40mg weekly sc 12-week double-blind period: Treatment withdrawal (placebo) Dose decrease (adalimumab 40mg eow sc) 52 week follow-up period: No treatment	Time to relapse after adalimumab treatment withdrawal or dose decrease.	12-week open-label period: 148/136 12-week double-blind period: 136/96 52 week follow-up period: 96 analysed for efficacy 148 analysed for safety	All subjects: 93 Male/55 female 44 (18-69)	Moderate to severe chronic plaque psoriasis (BSA ≥ 5%)	Time to relapse after Week 12 through to Week 24 for subjects who had achieved a Week 12 ≥ PASI 50 response relative to Baseline.
M03-656 REVEAL [42, 43, 44, 45] 81/ USA Canada	Phase III Multicentre, randomised	Period A: Adalimumab 40 mg eow sc Placebo eow sc	Efficacy, Safety, and Pharmacokinetics	Period A: Adalimumab (ADA): 814/783 Placebo: 398/355	Period A: Adalimumab: 546 Male/268 Female 44 (18-79) Placebo:	Moderate to severe chronic plaque psoriasis (BSA ≥ 10%, PASI ≥ 12, PGA of at least moderate	1. Proportion of subjects achieving a ≥ PASI 75 response at Week 16

52 weeks **N = 1212**	Period A: 16-week, double-blind, placebo-controlled period Period B: 17-week, open-label period Period C: 19-week, double-blind, placebo-controlled period	Period B: Adalimumab 40 mg eow sc Period C: Adalimumab 40 mg eow sc Placebo eow sc		Period B: ADA/ADA: 580/550 Placebo/adalimumab: 26/23 Period C: ADA/ADA/ADA: 250/227 ADA/ADA/Placebo: 240/184 Placebo/ADA/ADA: 22/18	257 Male/141 Female 46 (18-82) Period B: ADA/ADA: 408 Male/172 Female 44 (18-77) Placebo/ADA: 12 Male/14 Female 47.5 (21-70) Period C: ADA/ADA/ADA: 176 Male/74 Female 44 (18-77) ADA/ADA/Placebo: 179 Male/61 Female 43 (18-77) Placebo/ADA/ADA: 10 Male/12 Female 47.5 (26-70)	disease)	2. Proportion of subjects losing an adequate response after re-randomisation to placebo at Week 33 and on or before Week 52.
M04-716 [46, 47, 48, 49, 50] **CHAMPION** 28/Europe Canada 16 weeks **N = 271**	Phase III Multicentre, randomised, double-blind, double-dummy, placebo- and active-controlled	Adalimumab 40 mg eow sc + placebo weekly po Methotrexate 7.5mg[b] weekly po + placebo eow sc Placebo eow sc and weekly po	Efficacy and Safety	Adalimumab: 108/104 Methotrexate: 110/104 Placebo: 53/48	Adalimumab: 70 Male/38 Female 42 (19–81) Methotrexate: 73 Male/37 Female 41 (19-74) Placebo: 35 Male/18 Female 41 (20-70)	Moderate to severe chronic plaque psoriasis (BSA ≥ 10%, PASI ≥ 10, PGA of at least moderate disease)	Proportion of subjects achieving a ≥ PASI 75 response at Week 16.
Extension Studies							
M02-529 [33, 38, 39, 51, 52, 53, 54] 18/ USA Canada 48 weeks **N = 137**	Phase II Multicentre, randomised 12-week double-blind period 36-week open-label period	Adalimumab 40 mg eow sc Adalimumab 40 mg weekly sc Adalimumab 40 mg eow sc Subjects with < PASI 50 any time on or after Week 12 eligible to increase dose to	Efficacy and Safety	12-Week Double-Blind Period Adalimumab eow: 43/42 Adalimumab weekly: 47/44 Placebo/ Adalimumab: 47/46 36-Week Open-label Period Adalimumab eow: 42/35	Adalimumab eow: 30 Male/13 Female 46 (20-71) Adalimumab weekly: 33 Male/14 Female 42 (24-86) Placebo/Adalimumab	Moderate to severe chronic plaque psoriasis Completion of lead-in Study M02-528	Proportion of subjects achieving a ≥ PASI 75 response at Week 12

		adalimumab weekly		Adalimumab weekly: 44/33 Placebo/ Adalimumab 40 mg eow sc: 46/38	40 mg eow SC: 33 Male/14Female 44 (20-70)		
M03-596 14/USA Canada 24 weeks **N = 32**	Phase II Multicentre, randomised 12-week open-label period 12-week double-blind period	12-week open-label period: 80mg adalimumab at Week 0 and 1 40mg adalimumab ew sc 12-week double-blind period: Subjects with ≥ PASI 50 response (relative to Week 0 of M02-538) continued, double-blind treatment arms from Study M02-538: 40 mg adalimumab eow or placebo eow.	Safety and efficacy of retreatment with adalimumab upon relapse from M02-538	12-week open-label period: 32/24 12-week double-blind period: 24/15	All subjects: 20 Male/12 Female 50.5 (19-66)	Any of the 136 subjects who were randomised into Study M02-538 and had < PASI 50 response (relapse) after Week 12 and on or before Week 24 of Study M02-538 Moderate to severe plaque psoriasis	Proportion of subjects with clinical response, defined as ≥ PASI 50 response relative to the Week 0 PASI in the lead-in study, Study M02-538, following 12 weeks (Week 12) of re-treatment with open-label adalimumab.
M03-658 [55, 56] 104/USA Europe Canada 2 years [redacted]	Phase III Multicentre, open-label	Adalimumab 40 mg eow sc[d, e]	Efficacy and Safety	[redacted]/not applicable ([redacted] subjects are ongoing as of [redacted])	[redacted] Male/[redacted] Female 44 (18-81)	Moderate to severe chronic plaque psoriasis. Subjects who participated in Study M02-529 (continuation of M02-528), M02-538, M03-596 (extension study of study M02-538), M03-656, or M04-716 and remained eligible.	1. Number and proportion of subjects achieving a ≥ PASI 50/75/90 response every 12 weeks. 2. Number and proportion of subjects achieving a PGA of "Clear or Minimal" every 12 weeks.

a. A total of 148 subjects were randomised in Study M02-528; however, one subject randomised to the adalimumab 40 mg eow arm withdrew consent prior to the performance of Baseline procedures. This subject did not receive study medication.
b. Dose escalation of MTX from 7.5 mg up to 25 mg was allowed.
c. The sample size of this study was determined by the number of subjects who were eligible based on the inclusion/exclusion criteria of this study and who participated in Studies M02-529, M02-538, M03-596 and the Phase 3 psoriasis studies (M03-656 and M04-716) with adalimumab.
d. Dose escalation of adalimumab from 40 mg eow to 40 mg weekly was allowed.
e. In all studies except Study M03-658 and those otherwise stated, an initial dose of 80 mg adalimumab was administered to adalimumab-treated subjects followed by 40mg at Week 1 and eow subsequently.

5.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

The inclusion and exclusion criteria to identify the list of relevant RCTs did not differ from the criteria applied to the search strategy used to identify the complete list of RCTs in Section 5.2.1. This is due to the fact that there is limited published data about adalimumab for the relevant patient group (psoriasis), as such the relevant RCTs were easily extracted manually from the systematic review. Appendix 2, Section 9.2 details the search strategies and subsequent hits from the database and publication sites searched.

Inclusion criteria:

All randomised controlled trials (RCTs) comparing adalimumab to an alternative treatment (including placebo) when used for the treatment of psoriasis. Open-labelled controlled trials, prospective studies, crossover studies, and comparative studies were also included. These trials were included in the search string to capture all the studies pertaining to adalimumab for Ps, the RCTs were then extracted manually after a thorough inspection of the citations.

Exclusion criteria:

Reviews and studies that did not fit the inclusion criteria or studies based on juvenile data (0-17 years old) were excluded.

5.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

The details of the relevant RCTs can be found in Figure 5.2.1 and Table 5.2.1. A flow diagram of the number of studies included and excluded as per the QUORUM statement is presented in Section 5.2.6.

5.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

Details of the relevant non-randomised controlled trials can be found in Table 5.2.1 under the heading: Extension Studies. The methodology and results for these studies are presented in Sections 5.3 and 5.4 alongside the controlled trials for the reasons outlined below.

- **M02-529** – 48 week continuation trial of M02-528 evaluating the long-term clinical safety and efficacy of adalimumab in subjects with chronic plaque psoriasis who had completed the 12-week lead in study. M02-529 included a 12-week randomised blinded phase followed by a 36-week open label period. The 12-week double-blind period was a continuation of the randomisation in M02-528. This trial is relevant to the decision problem as it demonstrates the long-term efficacy and safety of adalimumab for the treatment of psoriasis.

- **M03-596** – 24-week trial evaluating the safety and efficacy of retreatment with adalimumab upon relapse. Any subjects who were randomised in M02-538 and had < PASI 50 response (relapse) after Week 12 and on or before Week 24 of Study M02-

538 were entitled to enter this study. M03-596 included a 12-week open-label period followed by a 12-week randomised, blinded period. This trial is partly relevant to the decision problem because it demonstrates that adalimumab is effective in subjects with moderate to severe chronic plaque psoriasis who are retreated with open-label adalimumab after loss of clinical response (< PASI 50 response) following adalimumab dose decrease or withdrawal. However, retreatment was with 40mg adalimumab weekly dosing, which is not the proposed dosing regimen.

- **M03-658** – 2 year, multicentre, open-label extension trial evaluating the long-term safety, efficacy and tolerability of adalimumab in patients with moderate to severe plaque psoriasis who have entered from studies, M02-528, M02-529, M02-538, M03-596, M03-656 and M04-716. This trial is relevant to the decision problem because it provides data on the long-term use of adalimumab in a large patient population (N=[redacted]).

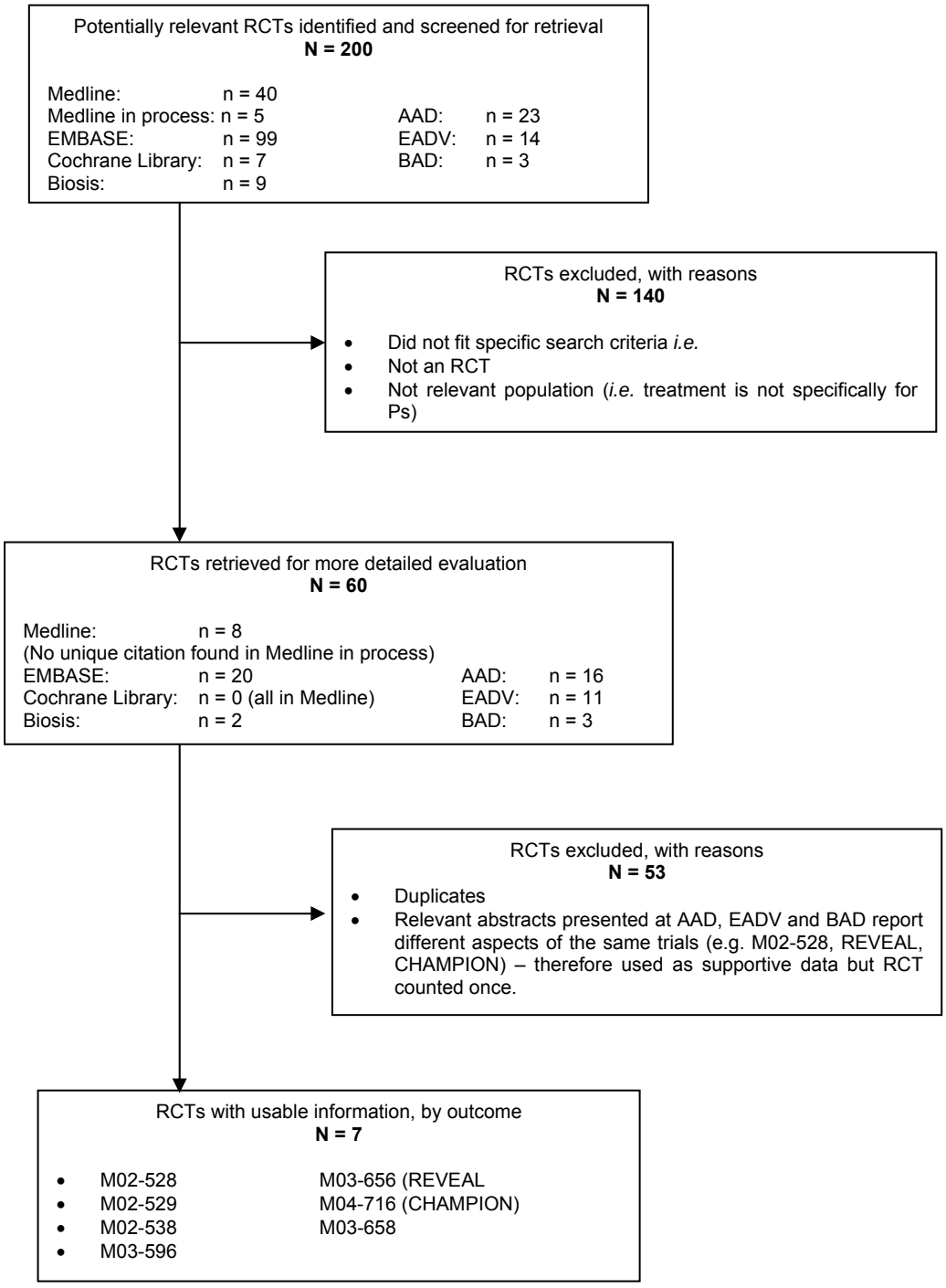
5.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

- **M03-658 –** This 2-year, multicentre, open-label extension trial is currently ongoing at sites in Europe, Canada and the USA. As of 29 June 2006, a total of [redacted] patients were enrolled on this study, preliminary data for which are available[55].

[redacted]

5.2.6 A flow diagram of numbers of studies included and excluded at each stage as per the QUORUM statement.



5.3 Summary of methodology of relevant RCTs

Summary information on the methodology of the relevant RCTs identified in the systematic review is presented in tabular form below. These are as follows: the phase II trials M02-528 and M02-538; the two pivotal phase III trials M03-656 (REVEAL) and M04-716 (CHAMPION); and the continuation trials M02-529, M03-596 and M03-658. A CONSORT flow diagram of patient numbers for each trial is also included, with the exception of M03-658, which is currently ongoing.

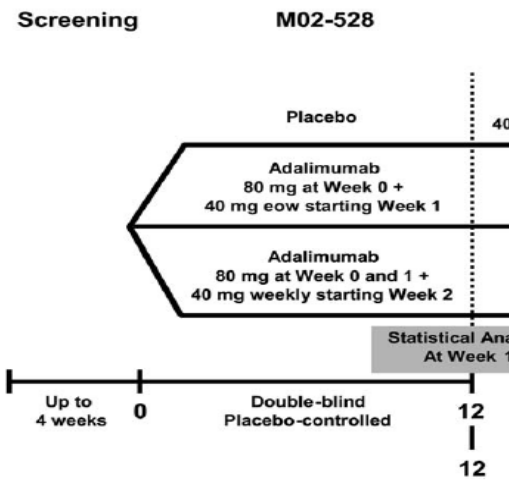
The five trials M02-528, M02-529, M03-656 (REVEAL), M04-716 (CHAMPION) and M03-658 form the evidence base for the efficacy of adalimumab in the treatment of moderate to severe plaque psoriasis. Studies M02-538 and M03-596 were also conducted as part of the psoriasis development programme, but the treatment regimen was different from that used in the five studies aforementioned, and data from these trials were not included in the evidence base demonstrating the efficacy of adalimumab for the EMEA submission. In the regulatory filing, no claim for efficacy was intended based on these two studies. These two studies have been included in this section because they are RCTs and provide data on time to relapse in patients who had dose reduction or treatment withdrawal and also provided data concerning re-treatment with adalimumab in patients who had relapsed following dose reduction or treatment withdrawal.

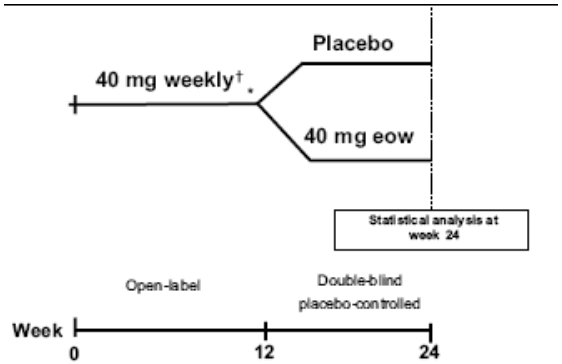
Details of methodology include:

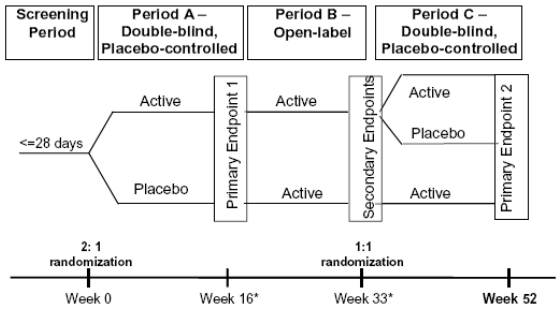
- Methods (study duration, blinding, randomisation, interventions, description of study)
- Participants (inclusion & exclusion criteria, baseline characteristics)
- Patient numbers (numbers eligible to enter study, CONSORT flow chart)
- Outcome (primary and secondary outcomes investigated, explanation of outcomes and relevance to decision problem)
- Statistical analysis and definition of study groups (hypotheses, statistical analysis, sample size calculation)
- Critical appraisal of the trials (allocation concealment, comparability of study groups, confounding factors etc.)

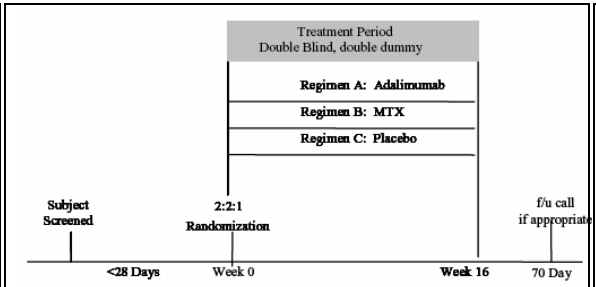
Descriptions of study method and results are derived where possible from the publications (*i.e.* manuscripts, abstracts or conference posters). In some cases where there is little or no published information available (e.g. M03-596), or further detail is required, then the necessary information has been derived from the clinical study reports. Where information is sourced from the clinical study report this is specifically indicated and referenced.

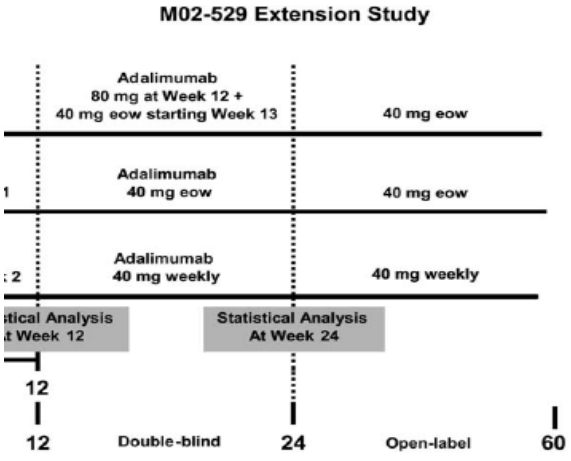
5.3.1 Methods

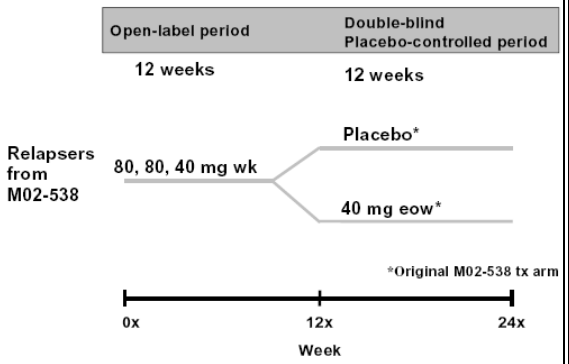
Study	Intervention/Duration	Study type/Design	Randomisation Method	Blinding Method
M02-528[33, 57]	**Intervention:** Subjects were randomly assigned to one of three treatment groups (two active treatment groups or placebo). 1. Adalimumab (ADA) 40mg eow: ADA 80mg (2x injections of 40mg) administered at Week 0; ADA 40mg administered eow starting at Week 1 – Week 11. Placebo administered on alternate weeks. 2 injections given at Week 1 – ADA 40mg + placebo. 2. Adalimumab 40mg weekly: ADA 80mg (2x injections of 40mg) administered at Week 0 and Week 1; ADA 40mg weekly from Week 2- Week 11. 3. Placebo administered weekly beginning at Week 0 through Week 11 (two injections at Week 0 and Week 1). **Duration:** 4-week screening period, followed by a blinded 12-week treatment period, and a 30-day Follow-up visit for subjects who did not complete 12 weeks of treatment or who did not enter extension study M02-529. A final phone call was made to the Subject 40 days after the Follow-up visit (70 days after last dose) to determine the status of any adverse events (AEs) or the occurrence of any SAEs.	 **Design:** Phase II, randomised, placebo-controlled, multicentre, multinational, dose-ranging study conducted at 19 sites in the USA and Canada to evaluate the safety efficacy and pharmacokinetics of adalimumab in adult patients with moderate to severe chronic plaque psoriasis.	Patients were centrally randomised 1:1:1 to receive one of three treatment options. Randomisation was blocked by study site and weight strata, which was defined as < 70 kg, 70-100 kg, and > 100 kg. The randomisation schedule was prepared by the Statistics Department of Abbott and ClinPhone (an Interactive Voice Response System [IVRS]) was used to randomise subjects.	Abbott, the Investigator, site staff, and the subject remained blinded to the subject's treatment throughout the course of the study. In order to maintain the blind throughout the study, prefilled syringes and study drug kits were identically labelled and all subjects received the same number of injections at the same timepoints. ClinPhone provided access to blinded subject treatment information in the case of a medical emergency. For no reason was the blind broken during the study. Only after the blinded portion of the M02−529 extension study database was cleaned and locked were Study M02-528 treatment group assignments unblinded.
Study	**Intervention/Duration**	**Study type/Design**	**Randomisation Method**	**Blinding Method**

M02-538[40, 40, 58]	**Intervention:** During the open-label period of the study (Week 0 through Week 11), all subjects were to receive a loading dose of adalimumab 80 mg at Weeks 0 and 1. For the next ten study weeks (Week 2 to 11), subjects received adalimumab 40 mg weekly. At the Week 12 visit, subjects who were ≥ PASI 50 responders were to be randomised to either 40 mg adalimumab eow or placebo eow (double-blind period of the study which lasted through to Week 24). Study drug was to be administered subcutaneously using sterile technique. No study drug was administered in the follow-up period. **Duration:** This was a 76-week study, which included a 12-week open-label treatment period, a 12-week double-blind treatment period, and a 30−, 90-, 180-, 270-, and 360-day follow-up visit until relapse or Week 76, whichever came first, for those subjects who did not relapse previously during the study. For those subjects who terminated from the study early for reasons other than relapse, follow-up visits were to be conducted at 30 and 90 days after the subject's final dose of study medication.	 **Design:** Phase II, multi-centre, exploratory efficacy and safety study to evaluate the time to relapse after adalimumab 40 mg weekly withdrawal (placebo treatment) or dose decrease (adalimumab 40 mg eow treatment) in subjects with moderate to severe chronic plaque psoriasis following the receipt of 12 weeks of adalimumab 40 mg weekly therapy (open-label treatment) conducted at 16 study sites in the US and Canada. Subjects who relapsed on or before Week 24 were eligible for enrolment in Study M03-596, in which they received retreatment with adalimumab. Subjects who relapsed after Week 24 and on or before Week 76 were eligible for immediate enrolment in Study M03-658.	At Week 12, subjects with a PASI 50 or greater response were randomised to adalimumab 40 mg eow or placebo in a 1:1 ratio assigned by ClinPhone (IVRS). Subjects were centrally randomised at Week 12, blocked by site and stratified by Week 12 PASI response (PASI 50 to < 75 response, ≥ PASI 75 response) by ClinPhone.	Abbott, the Investigator, site study personnel, and the subject were blinded to each subject's treatment assignment beginning at Week 12. ClinPhone provided access to blinded subject treatment information in the case of a medical emergency in which the Investigator believed that knowledge of study drug treatment was required.
Study	**Intervention/Duration**	**Study type/Design**	**Randomisation Method**	**Blinding Method**

M03-656[43, 59] **REVEAL**	**Intervention:** Period A: a 16-week, double-blind, placebo-controlled treatment period in which subjects were randomised in a 2:1 ratio to receive: (1) 80 mg adalimumab (two 40 mg injections) sc at Baseline, followed by 40 mg adalimumab sc eow from Week 1 to Week 15. Subjects with at least a PASI 75 response at Week 16 were to receive two placebo injections at Week 16 in a blinded fashion; or, (2) two placebo injections sc at Baseline, followed by one placebo injection SC eow from Week 1 to Week 15. Placebo subjects with at least a PASI 75 response at Week 16 were to receive 80 mg adalimumab (two 40 mg injections) at Week 16 in a blinded fashion. Period B: a 17-week, open-label treatment period in which all subjects who achieved at least a PASI 75 response at Week 16 (the end of Period A), received open-label 40mg adalimumab eow sc for an evaluation of long term response. Period C: a 19-week, double-blind, placebo-controlled treatment period in which subjects who maintained at least a PASI 75 response at Week 33 (the end of Period B) and were originally randomised to adalimumab in Period A, were re-randomised in a 1:1 ratio to receive either 40 mg adalimumab eow sc or placebo to compare the proportion of subjects losing an adequate response after Week 33 and on or before Week 52 in the two treatment groups. Subjects originally randomised in Period A to receive placebo and were eligible for Period C, were to continue to receive adalimumab in a blinded fashion. **Duration:** 52 weeks. Complete participation in the trial consisted of: a maximum 28 screening period; Period A: a 16-week,	 Note: Subjects originally randomised to placebo in Period A and were eligible for Period C, were to receive adalimumab in a blinded fashion in Period C. * ≥ PASI 75 responders continued on in the study. **Design:** Pivotal, multicentre, phase III study at 81 sites in the USA and Canada in adult subjects with moderate to severe chronic plaque Ps, and consisted of a screening period and three treatment periods (A, B, and C). In Period A, the objective was to confirm the short-term clinical efficacy, safety, and tolerability of adalimumab compared with placebo, as demonstrated in the Phase 2 study, M02-528. In Period B, the long-term efficacy, safety, and tolerability of open-label adalimumab through 33 weeks of therapy was assessed. In Period C, adalimumab was compared with placebo with respect to the proportion of subjects losing an adequate response after Week 33 and on or before Week 52. Subjects ended the study when they reached Week 52 or prematurely discontinued. Pharmacokinetic (PK) and pharmacodynamic parameters were assessed throughout the study.	The randomisation schedules were generated at Abbott before the start of the study and were provided to the Interactive Voice Response/Interactive Web Response System (IVRS/IWRS.) The subjects were randomised by centre in a 2:1 ratio to receive either adalimumab or placebo at Baseline. A block size of 6 was used for randomisation in Period A. Subjects who were randomised to adalimumab at Baseline (Period A), reached a ≥ PASI 75 response at Week 16, and maintained a ≥ PASI 75 response at Week 33, were to be re-randomised by centre in a 1:1 ratio to receive either adalimumab or placebo at Week 33 (Period C). A block size of 4 was to be used for re-randomisation in Period C. To maintain the blind during Periods A and C, IVRS/IWRS was used to dispense the appropriate study medication to subjects.	The Abbott clinical team responsible for the conduct of the study, the Investigator, site study personnel, and the subject were to remain blinded to each subject's randomised treatment assignment throughout the course of the study. A copy of the randomisation schedule was released to those personnel responsible for serum AAA and adalimumab bioanalysis. Bioanalytical personnel were not to share the randomisation schedule with anyone associated with the study without written permission. The IVRS/IWRS provided access to blinded subject treatment information in the case of medical emergency during the double-blind periods. Period B was open-label, and all subjects received adalimumab treatment. The Week 16 dose was double-blind, so that subjects who received placebo treatment in Period A received two injections of 40 mg adalimumab sc at that visit, and subjects who received adalimumab treatment in Period A received two placebo injections in order to keep the blind. In the case of an emergency, Abbott was to be notified within 48 hours of the blind being broken. The date and reason that the blind was broken was to be conveyed to Abbott and recorded on the appropriate CRF. In the event the Abbott Clinical Project Team had to break the blind, the reason was to be documented in a note to the study file.

	double-blind treatment period; Period B: a 17-week, open-label treatment period; Period C: a 19-week, double-blind treatment period; and a 70-day post-last dose telephone call for subjects who discontinued/completed the study and did not enrol in Study M03-658.			
Study	**Intervention/Duration**	**Study type/Design**	**Randomisation Method**	**Blinding Method**
M04-716 [46, 60] **CHAMPION**	**Intervention:** Regimen A: Adalimumab: 80 mg adalimumab (two 40 mg injections) subcutaneously (SC) at Baseline (Week 0), followed by 40 mg adalimumab SC every other week (eow) from Week 1 to Week 15. Placebo capsule(s) Per Os (PO) once weekly from Baseline (Week 0) to Week 15. Regimen B: MTX: Two placebo injections SC at Baseline (Week 0), followed by one placebo injection SC eow from Week 1 to Week 15. MTX (7.5-25.0 mg) capsule(s) PO once weekly from Baseline (Week 0) to Week 15. The dose of MTX was to be 7.5 mg at Week 0 and Week 1, 10 mg at Week 2 and Week 3, and 15 mg from Week 4 until Week 15. It was to be adjusted to aspartate transaminase (AST), alanine transaminase (ALT), white blood cell count, platelet count, and serum creatinine from Week 2 until Week 15. The dose of MTX was to be increased to 20 mg at Week 8 and 25 mg at Week 12 if PASI 50 response (50% reduction in Baseline Ps Area and Severity Index [PASI] score) was not achieved and if there was no safety concern.	 **Design:** Pivotal, phase III, 16-week multicentre, double-blind, double-dummy study designed to evaluate the safety, tolerability, and clinical efficacy of adalimumab *vs.* placebo and *vs.* methotrexate (MTX) in the treatment of adult subjects with moderate to severe chronic plaque Ps at 28 sites in Europe and Canada. To maintain blinding, matching placebo SC injections and Per Os (PO) oral capsules were to be dispensed such that all subjects would receive oral capsule(s) weekly and SC injections eow. All subjects were to take approximately 5 mg once weekly supplement of oral folate throughout the treatment period in order to reduce side effects associated with MTX as suggested by previous studies. Folate was not administered on the day the oral study medication was taken, but was taken on any day beginning 48 hours after ingestion of oral study drug.	The randomisation schedules were generated at Abbott before the start of the study and were provided to the Interactive Voice Response system (IVRS). Subjects were randomised to one of three possible treatment regimens in a 2:2:1 (adalimumab, MTX, placebo) ratio at Week 0. All treatments were assigned by the IVRS in order to maintain blinding for Regimen A (adalimumab), Regimen B (methotrexate, and Regimen C (placebo). All subjects were assigned a unique identification number by the IVRS as they were screened for the study. The IVRS also assigned a randomisation number according to the randomisation scheme at Week 0; this number was	The Abbott clinical team responsible for the conduct of the study, the Investigator, site study personnel and the subject were blinded to each subject's randomised treatment group throughout the course of the study. The IVRS provided access to blinded subject treatment information in the case of a medical emergency during the study. If an Investigator believed that it was in a subject's best interest to know his/her study drug assignment or, in the case of an emergency, if the Investigator believed knowing this information would allow him/her to better treat the subject, the Investigator was to contact the IVRS to obtain the subject's drug assignment. Unless identification of the study drug was required for emergency therapeutic measures, every effort was to be made to contact the Abbott Medical Monitor prior to breaking the blind. In the case of an emergency, Abbott was to be notified within 48 hours of the blind being broken. The date and reason that the blind was broken was to be conveyed to Abbott and recorded

	Regimen C: placebo: Two placebo injections SC at Baseline (Week 0), followed by one placebo injection SC eow from Week 1 to Week 15. Placebo capsule(s) PO once weekly from Baseline (Week 0) to Week 15. All treatment groups were to receive the last dose of study drug at Week 15. No study drug was to be administered at the final (Week 16) visit. **Duration:** The maximum duration of enrolment for any subject in Study M04-716 was 30 weeks. The study consisted of: a maximum 28-day Screening period, a 16-week, double-blind, double-dummy treatment period, a 70-day post last dose telephone call for subjects who prematurely discontinued or completed the study and did not enrol into the extension study, Study M03-658.	All subjects who had successfully completed the study through Week 16 were eligible for treatment with open-label adalimumab in Study M03-658.	maintained by the IVRS and not provided to the site.	appropriately. In the event the Abbott Clinical Project Team had to break the blind, the reason was to be documented.
Study	**Intervention/Duration**	**Study type/Design**	**Randomisation Method**	**Blinding Method**
M02-529[33, 61]	**Intervention:** Subjects who received adalimumab in Study M02-528 continued to receive their previously assigned M02-528 dose of adalimumab (40 mg eow or 40 mg weekly) through to Week 12 of this study. Subjects who received placebo previously in Study M02-528 received a loading dose of adalimumab 80 mg on Week 0 of Study M02-529 (synonymous with Week 12 of M02-528) and then adalimumab 40 mg eow beginning on Week 1. Following completion of Week 12, subjects received unblinded open-label study medication until Week 48 – doses of adalimumab remained the same as for the blinded period. **Duration:** Subjects in the placebo/ adalimumab 40 mg eow treatment group received treatment with adalimumab for up		Randomisation occurred in the lead-in study, Study M02-528. Subjects retained the subject number assigned to them in the lead-in study. Following completion of the 12-week blinded period, ClinPhone (IVRS system) assigned unblinded, open-label study medication to subjects at their next study visit.	Drug administration was performed in a blinded fashion as assigned by ClinPhone. Study medication administration remained blinded until all subjects completed Week 12. At Week 12, subjects with ≥ PASI 50 response (*i.e.*, at least a 50% reduction from Baseline in PASI score) relative to the Study M02-528 Baseline PASI score continued their current therapy for up to an additional 36 weeks. At any time on or after Week 12 of this study, subjects with < PASI 50 response were eligible to receive open-label, weekly adalimumab therapy (rescue subjects). If, after at least eight weeks of weekly therapy, the subject did not achieve ≥ PASI 50 response relative to the Study M02-528 Baseline

	to 48 weeks in this study. Subjects in the adalimumab 40 mg eow and adalimumab 40 mg weekly treatment groups received adalimumab for up to 60 weeks when duration of treatment in the lead-in study, Study M02-528, and duration of treatment in this study are combined (12 weeks and 48 weeks, respectively).	**Design:** A continuation trial of adalimumab in subjects with moderate to severe chronic plaque psoriasis who successfully completed the double blind, placebo-controlled, 12-week lead-in study, Study M02-528 at 18 sites in the USA and Canada. Included a blinded 12-week treatment period (Week 0 to Week 12) and a 36-week open-label treatment period (after Week 12 to Week 48). A 30-day follow-up visit and a final phone call 70 days from last dose occurred upon completion or termination of subjects who were not eligible or who did not choose to enrol in the extension study, Study M03-658, a long-term safety, tolerability, and efficacy study.		PASI score, the subject was to be discontinued from Study M02-529. Prefilled syringes and study drug kits were identically labelled and all subjects received the same number of injections at the same timepoints. For no reason was the blind broken during the study.
Study	**Intervention/Duration**	**Study type/Design**	**Randomisation Method**	**Blinding Method**
M03-596[62]	**Intervention:** All subjects received retreatment with 80 mg adalimumab sc at Week 0 (study entry) and at Week 1 followed by adalimumab 40 mg weekly from Week 2 to Week 11 (open-label period). Subjects with ≥ PASI 50 response (relative to Study M02-538 Week 0) at Week 12 (start of the double-blind period) continued in a double-blind manner in their assigned treatment arm from Study M02-538: 40 mg adalimumab eow or placebo eow. Subjects who relapsed (< PASI 50 response after Week 12, but before Week 24) were to be discontinued from the study. Likewise, subjects who experienced rebound (PASI score ≥125% of the Week 0 PASI score in Study M02-538 or new generalised pustular or erythrodermic psoriasis) after Week 12 were discontinued from the study. **Duration:** 24 weeks. The study included a 12-week open-label treatment period, a 12-week double-blind treatment period, a 30-day post last dose follow-up visit, and a 70-day post last dose follow-up telephone call to determine adverse events (AEs).	 **Design:** A 24-week, phase II, multicentre, efficacy and safety study to evaluate clinical response following retreatment with adalimumab in subjects with moderate to severe chronic plaque psoriasis who discontinued from Study M02-538 due to relapse by Week 24 (< PASI 50 response after 12 weeks of open-label adalimumab treatment). The study consisted of two study periods, an open-label period (Week 0 to Week 11) and a double-blind period (Week 12 to Week 24). The design of this was chosen to evaluate the efficacy and safety of a second adalimumab treatment cycle in subjects who achieved clinical response after a first adalimumab treatment cycle (weekly), but relapsed following	Subjects retained the randomised subject number assigned to them in Study M02-538. To maintain the blind, ClinPhone (IVRS system) was used to determine any change in dosing that might have occurred.	Abbott, the Investigator, site study personnel, and the subject were blinded to each subject's treatment beginning at Week 12. Individual subject treatment assignment remained blinded to Abbott personnel until the time of database lock from data analysis. ClinPhone provided access to blinded subject treatment information in the case of a medical emergency.

		randomisation to either adalimumab 40 mg eow or placebo.		
Study	**Intervention/Duration**	**Study type/Design**	**Randomisation Method**	**Blinding Method**
M03-658[55, 63]	**Intervention:** All subjects received open-label adalimumab 40 mg eow subcutaneous (SC) beginning at study entry (Week 0) and for the duration of the study (at least two years). Efficacy and safety measurements were performed throughout the study. PASI response was determined every 12 weeks. If, at any time on or after Week 24, a subject did not maintain or achieve a reduction in PASI score of at least 50% (≥ PASI 50) relative to his/her Week 0 score in the initial Ps study, the Principal Investigator and the subject were to evaluate the risk/benefit of having the subject dose escalate to 40 mg weekly adalimumab dosing. If the subject did not wish to dose escalate, the risk/benefit of having the subject continue in the study was to be discussed. Subjects who dose escalated were to continue on 40 mg weekly dosing until a PASI 75 response was achieved. Once the PASI 75 response was achieved, the subject was to resume 40 mg eow dosing. Subjects who were dose escalated were to have an additional visit 6 weeks after the escalation. Any subject who developed erythrodermic or generalised pustular Ps was to be discontinued from the study. If the subject's PASI response fell back to less than 50% for a second time, a second round of dose escalation to 40 mg weekly was permitted, following the rules specified above. If the subject dose escalated for a second time, the subject had to remain on 40 mg weekly dosing for the remainder of the study regardless of the PASI response achieved. **Duration:** At least 2 years.	**Design:** open-label long-term study for subjects who had participated in adalimumab Ps Studies M02-529, M02-538, M03-596, M03-656, and M04-716 and who had either prematurely terminated from one of these studies due to relapse/loss of adequate response (M02-538, M03-596, or M03-656) or had completed the study (Study M02-529, M03-596, M03-656, or M04-716). Subjects were evaluated for entry into Study M03-658 at the final visit of the most recent Ps study in which they participated. **Objectives:** 1) To evaluate the long-term safety and efficacy of adalimumab 40 mg eow in subjects who entered from Studies M02-529, M02-538, M03-596, M03-656, and M04-716. 2) To describe the safety and efficacy of adalimumab in subjects who underwent dose escalation to adalimumab 40 mg weekly (whether dose escalation occurred in the lead-in Study M02-529 or in Study M03 − 658). 3) To describe the safety and efficacy of adalimumab in subjects randomised to placebo in Period C of Study M03-656 who underwent re-treatment when entering Study M03- 658.	N/A – open-label extension trial of preceding adalimumab Ps studies.	N/A – open-label extension trial of preceding adalimumab Ps studies.

5.3.2 Participants

Study	Inclusion criteria	Exclusion Criteria	Baseline Demographics and Disease Characteristics			
M02-528 [33, 34, 57]	Men and women ≥ 18 years of age; clinical diagnosis of moderate to severe chronic plaque psoriasis defined by ≥ 5% BSA involvement for at least 1 year; active psoriasis, despite topical therapies, defined by ≥ 5% BSA involvement at Screening and Baseline; female subjects who were either not of childbearing potential, defined as postmenopausal for at least one year or surgically sterile or were of childbearing potential and practicing birth control throughout the study n; subjects were judged to be in generally good health; subjects were evaluated for latent TB infections; any subjects who demonstrated evidence of prior TB infection were allowed to participate in the study provided conditions were met; subjects were able and willing to give written informed consent; subjects were able to self-inject study medication or had a designee or nurse capable of injection of the study medication; medicated shampoos and low potency topical steroids for use on palms, soles, face, and groin only; topical psoriasis therapies, phototherapy, and excessive sun exposure or tanning booth use were discontinued for 2 weeks prior to study entry and throughout the study; non-biologic systemic psoriasis therapies and biologic agents were discontinued 4 and 12 weeks prior to study entry, respectively; investigative chemical agents were discontinued at least 30 days or five half-lives prior to study entry.	Active skin diseases or skin infections (bacterial, fungal, or viral) that interfered with evaluation of psoriasis; prior exposure to any anti-TNF therapy; history of neurologic symptoms suggestive of central nervous system demyelinating disease; history of cancer or lymphoproliferative disease other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix; history of active TB or listeriosis, persistent chronic or active infections requiring hospitalisation or treatment, anti-retroviral therapy use; subjects who had abnormal laboratory results at Screening; subject had erythrodermic psoriasis, generalized pustular psoriasis, or medication induced or exacerbated psoriasis.	**Characteristic**	**Placebo N = 52**	**Adalimumab 40mg eow N = 45**	**Adalimumab 40mg weekly N = 50**
			Age, y	43 (20-70)	46 (20-71)	44 (24-86)
			Male, %	65	71	66
			Caucasian, %	92	89	90
			Body weight, kg	94 (50-147)	93 (63-159)	99 (42-149)
			Duration of Ps, y	19 (1.0-39.9)	21 (1.3-57.9)	18 (1.7-47.7)
			BSA affected, %	28 (7-75)	29 (6-58)	25 (5-83)
			PASI score	16.0 (5.5-40.4)	16.7 (5.4-39.0)	14.5 (2.3-42.4)
			History of PsA, %	31	33	24
			PGA, %			
			Severe psoriasis	8	9	8
			Moderate to severe psoriasis	29	56	42
			DLQI Score [a]	12.2 (10.0, 14.4)	13.3 (10.7, 15.8)	13.6 (11.3, 15.9)
			EQ-5D Score [a]	0.67 (0.59, 0.76)	0.69 (0.59, 0.79)	0.69 (0.60, 0.78)
			Ps treatments received within the past 12 months, n (%)			
			Topical therapy	41 (78.8)	32 (71.1)	40 (80.0)
			Systemic therapy	19 (36.5)	19 (42.2)	22 (44.0)

			BSA, body surface area; *eow*, every other week; *PASI*, Psoriasis Area and Severity Index, *PGA*, Physician's Global Assessment; *PsA*, psoriatic arthritis; *DLQI*, Dermatology Life Quality Index *EQ-5D*, EuroQOL-5D. Values represent mean and ranges unless otherwise specified. [a] Values expressed as mean (95% CI) Patients were well balanced across treatment groups with respect to demographic characteristics and baseline disease activity.

Study	Inclusion criteria	Exclusion Criteria	Baseline Demographics and Disease Characteristics			
M02-538[40, 40, 58]	Men and women ≥ 18 years of age; subjects had a clinical diagnosis of Ps for 1 year determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the Investigator; subjects had moderate to severe plaque Ps defined by ≥ 5% BSA involvement for at least 2 months before Screening and Baseline; subjects had a PASI score of ≥ 8 at Screening and the Baseline visit; subjects had active disease despite topical therapy; topical psoriasis therapies, phototherapy, and excessive sun exposure or tanning booth use were discontinued for 2 weeks prior to study entry and throughout the study; non-biologic systemic psoriasis therapies and biologic agents were discontinued 4 and 12 weeks prior to study entry, respectively; investigative chemical agents were discontinued at least 30 days or five half-lives prior to study entry.	Active skin diseases or skin infections that might interfere with evaluation of Ps; taking oral or injectable corticosteroids during the study; poorly controlled medical condition; history of neurologic symptoms suggestive of demyelinating disease; history of cancer or lymphoproliferative disease; history of listeriosis, untreated TB, persistent chronic infections, or recent active infections requiring hospitalisation or treatment with intravenous anti-infectives within 30 days or oral anti-infectives within 14 days prior to the Baseline visit; erythrodermic Ps, generalised or localized pustular Ps, medication induced or medication-exacerbated Ps.		**Randomised from 12-weeks open-label 40 mg adalimumab weekly**	
			Characteristic	**Placebo [a] N = 68**	**Adalimumab 40mg eow [b] N = 68**	**Not Randomised N = 12**
			Age, y	45.1 ± 10.6	43.0 ± 11.3	38.5 ± 11.8
			Male, %	66.2	55.9	83.3
			Caucasian, %	95.6	91.2	100
			Ps duration, y	20.2 ± 10.8	20.6 ± 11.9	13.3 ± 11.7
			PASI Score [c]	16.3 (14.5, 18.1)	16.4 (14.4, 18.4)	16.6 (15.1, 17.7)
			% BSA	25.0 ± 20.5	25.3 ± 20.5	22.8 ± 18.4
			Ps treatments received within the past 12 months, n (%)			
			Topical	57 (83.8)	58 (85.3)	10 (83.3)
			Phototherapy	12 (17.7)	12 (17.7)	1 (8.3)
			Systemic	18 (26.5)	20 (29.4)	4 (33.3)
			Biologic	19 (27.9)	17 (25)	3 (25)

			[a] 40mg adalimumab weekly Week 0 to Week 11, placebo Week 12 to Week 24 [b] 40mg adalimumab weekly Week 0 to Week 11, adalimumab 40mg eow Week 12 to Week 24 [c] PASI scores are expressed as mean (95% CI) Values are presented as mean ± SD unless otherwise stated. Baseline values are derived from Week 0 of this trial. Patients subsequently received 12 weeks open-label adalimumab weekly prior to randomisation. Patients were well balanced across treatment groups with respect to demographic characteristics and baseline disease activity.

Study	Inclusion criteria	Exclusion Criteria	Baseline Demographics and Disease Characteristics		
M03-656 REVEAL [43, 59]	Men and women ≥ 18 years of age; subjects had a clinical diagnosis of Ps for at least 6 months as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the Investigator; subjects had stable plaque Ps for at least 2 months; subjects had moderate to severe plaque Ps defined by ≥ 10% BSA involvement at the Baseline visit and a PASI score of ≥ 12 at the Baseline visit; subject had a PGA of at least moderate disease at the Baseline visit; subjects were evaluated for latent tuberculosis (TB) infection with a purified protein derivative (PPD) test and CXR; subjects who demonstrated evidence of latent TB infection were allowed to participate in the study provided conditions were met; subjects were able and willing to provide written informed consent; subjects were allowed to use: shampoos that contain no corticosteroid, bland emollients, low potency topical corticosteroids on the palms, soles, face, inframammary area, and groin only; topical psoriasis therapies, phototherapy, and excessive sun exposure or tanning booth use were discontinued for 2 weeks prior to study entry and throughout the study; non-biologic systemic psoriasis therapies and biologic agents were discontinued 4 and 12 weeks prior to study entry, respectively; investigative	Previous exposure to any systemic anti-TNF (*e.g.,* thalidomide) or biologic anti-TNF therapy (*e.g.,* infliximab or etanercept), including adalimumab; active skin diseases or skin infections that might interfere with evaluation of Ps; history of an allergic reaction to constituents of study drug; poorly controlled medical condition; history of neurologic symptoms suggestive of demyelinating disease; history of cancer or lymphoproliferative disease; history of listeriosis, untreated TB, persistent chronic infections, or recent active infections requiring hospitalisation or treatment with intravenous anti-infectives within 30 days or oral anti-infectives within 14 days prior to the Baseline visit; use of anti-retroviral therapy at any time during the study; erythrodermic Ps, generalised or localised pustular Ps, medication induced or medication-exacerbated Ps, or new onset guttate Ps.	**Characteristic**	**Placebo N = 398**	**Adalimumab N = 814**
			Age, y	45.4 ± 13.4	44.1 ± 13.2
			Male, %	64.6	67.1
			Caucasian, %	90.2	91.2
			Body weight, kg	94.1 ± 23.0	92.3 ± 23.0
			Duration of Ps, y	18.4 ± 11.94	18.1 ± 11.91
			BSA affected, %	25.6 ± 14.76	25.8 ± 15.51
			PASI score	18.8 ± 7.09	19.0 ± 7.08
			% with PsA	28.4	27.5
			PGA, n (%)		
			Severe or very severe psoriasis	178 (44.7)	397 (48.8)
			Moderate psoriasis	220 (55.3)	417 (51.2)
			DLQI Score	11.4 + 6.95	11.4 + 6.62
			Ps treatments received within the past 12 months, n (%)		
			Topical	290 (72.9)	618 (75.9)
			Phototherapy	59 (14.8)	138 (17.0)
			Systemic (non-biologic)	88 (22.1)	188 (23.1)

	chemical agents were discontinued at least 30 days or five half-lives prior to study entry.		Systemic (biologic)*	53 (13.3)	97 (11.9)
			Laser	0	1 (0.1)
			* Previous biologic therapy included treatment with efalizumab and alefacept. Values expressed as mean + SD unless otherwise stated. Baseline characteristic were similar across treatment groups and are consistent with expectations for patients with moderate to severe chronic plaque psoriasis.		

Study	Inclusion criteria	Exclusion Criteria	Baseline Demographics and Disease Characteristics			
M04-716 CHAMPION [46,]	Men and women ≥ 18 years of age; candidates for systemic therapy or phototherapy with active psoriasis despite treatment with topical agents; a clinical diagnosis of psoriasis for at least 1 year as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the Investigator; stable plaque psoriasis for at least 2 months before Screening and at Baseline visits; moderate to severe plaque psoriasis defined by ≥ 10% BSA involvement and PASI score of ≥ 10 at the Baseline visit; female subjects who were either not of childbearing potential, defined as postmenopausal for at least one year or surgically sterile or were of childbearing potential and practicing birth control; subjects evaluated for latent TB infection with a PPD test and CXR; subjects were willing to provide written informed consent; subjects were allowed to use: shampoos that contain no corticosteroid, bland emollients, low potency topical corticosteroids on the palms, soles, face, inframammary area, and groin only; topical psoriasis therapies, phototherapy, and excessive sun exposure or tanning booth use were discontinued for 2 weeks prior to study entry and throughout the study; non-biologic systemic psoriasis therapies and biologic	Previous exposure to any systemic anti-TNF therapy including adalimumab; previous exposure to methotrexate (MTX); active skin diseases or skin infections that might interfere with evaluation of psoriasis; history of an allergic reaction to constituents of study drugs (adalimumab, MTX, or matching placebo); poorly controlled medical condition; history of clinically significant haematological, renal, or liver disease; history of neurologic symptoms suggestive of central nervous system demyelinating disease; history of cancer or lymphoproliferative disease; history of listeriosis, histoplasmosis, untreated TB, persistent chronic infections, or recent active infections requiring hospitalisation or treatment with IV anti-infectives within 30 days or oral anti-infectives within 14 days prior to the Baseline visit; use of anti-retroviral therapy during the study; abnormal laboratory results; erythrodermic psoriasis, generalized or localised pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis.	**Characteristic**	**Placebo N = 53**	**Methotrexate N = 110**	**Adalimumab N = 108 [+]**
			Age, y	40.7 ± 11.43	41.6 ± 11.98	42.9 ± 12.57
			Male, %	66	66.4	64.8
			Caucasian, %	92.5	95.5	95.4
			Body weight, kg	82.6 ± 19.91	83.1 ± 17.50	81.7 ± 19.98
			Duration of Ps, months	225.3 ± 104.2	226.5 ± 122.1	214.8 ± 121.1
			BSA affected, %	28.4 ± 16.09	32.4 ± 20.60	33.6 ± 19.88
			PASI score	19.2 ± 6.89	19.4 ± 7.39	20.2 ± 7.53
			% with PsA	20.8	17.3	21.3
			PGA, n (%)			
			Severe or very severe psoriasis	33 (62.3)	51 (46.4)	55 (50.9) [a]
			Moderate psoriasis	20 (37.7)	58 (52.7)	51 (47.7) [a]
			DLQI Score	11.7 ± 7.02	9.8 ± 5.82	11.8 ± 6.54
			EQ-5D Score	0.7 ± 0.27	0.7 ± 0.21	0.7 ± 0.28
			Ps treatments received within the past 12 months, n (%)			

	agents were discontinued 4 and 12 weeks prior to study entry, respectively; investigative chemical agents were discontinued at least 30 days or five half-lives prior to study entry.		UVB	6 (11.3)	16 (14.5)	21 (19.4)
			Systemic retinoids	7 (13.2)	11 (10.0)	10 (9.3)
			Unspecified systemic therapies	5 (9.4)	5 (4.5)	9 (8.3)
			Ciclosporin	5 (9.4)	9 (8.2)	8 (7.4)
			Systemic PUVA	6 (11.3)	7 (6.4)	5 (4.6)
			Topical PUVA	3 (5.7)	3 (2.7)	2 (1.9)
			Biologic Therapy*	2 (3.8)	2 (1.8)	2 (1.9)
			Systemic corticosteroids	1 (1.9)	2 (1.8)	2 (1.9)
			Values presented as mean ± SD unless otherwise stated. [+] One patient was withdrawn before receiving any study medication [a] Percentages calculated on 107 subjects * Previous biologic therapy included treatment with efalizumab and alefacept. Baseline characteristic were similar across treatment groups and are consistent with expectations for patients with moderate to severe chronic plaque psoriasis.			

Study	Inclusion criteria	Exclusion Criteria	Baseline Demographics and Disease Characteristics			
M02-529[33, 61]	Subjects must have successfully completed study M02-528; subjects who early terminated from Study M02-528 could not enter M02-529; men and women ≥ 18 years of age; female subjects who were either not of childbearing potential, or were of childbearing potential and practicing birth control throughout the study;; subject was able and willing to give written informed consent to comply with the requirements of this study protocol; subject was able to self-inject study medication or had a designee or nurse capable of injection of the study medication; topical psoriasis therapies, phototherapy, and excessive sun exposure or tanning booth use were discontinued for 2 weeks prior to study entry and throughout the study; non-biologic systemic psoriasis	Active skin diseases that may have interfered with evaluation of psoriasis; prior exposure to any anti-TNF therapy other than adalimumab; used topical therapy other than the following: medicated, non-corticosteroid containing shampoos, low potency topical steroids to be used for palms, soles, face, and groin area only; poorly controlled medical condition; history of neurologic symptoms suggestive of central nervous system demyelinating disease; history of cancer; history of active tuberculosis (TB) or listeriosis, or persistent chronic or active infections requiring hospitalisation prior to entry; use of anti-retroviral therapy at any time prior to or during the study; erythrodermic psoriasis, generalised pustular psoriasis, or medication-induced or	**Characteristic**	**Placebo/ Adalimumab eow N = 47**	**Adalimumab 40mg eow N = 43**	**Adalimumab 40mg weekly N = 47**
			Age, y	44.4 ± 12.9	45.4 ± 11.8	43.5 ± 13.4
			Male, %	70.2	69.8	70.2
			Caucasian, %	91.5	88.4	89.4
			Body weight, kg	96.2 ± 21.9	92.4 ± 21.7	99.8 ± 23.2
			Duration of Ps, y	19.0 ± 9.6	21.0 ± 13.0	18.26 ± 10.8
			BSA affected, %	28.0 ± 18.0	28.8 ± 15.9	25.0 ± 18.8
			PASI score	16.0 ± 7.5	16.5 ± 6.9	14.6 ± 7.7

	therapies and biologic agents were discontinued 4 and 12 weeks prior to study entry, respectively; investigative chemical agents were discontinued at least 30 days or five half-lives prior to study entry.	exacerbated psoriasis.	History of PsA, % — 25.5 — 34.9 — 21.3 PGA, % Severe psoriasis — 6.4 — 9.3 — 8.5 Moderate to severe psoriasis — 29.8 — 55.8 — 42.6 DLQI Score — 11.6 ± 6.6 — 13.4 ± 7.3 — 13.0 ± 7.5 EQ-5D Score — 0.651 ± 0.267 — 0.660 ± 0.279 — 0.656 ± 0.307 [a] Ps treatments received within the past 12 months, n (%) Topical therapy — 36 (76.6) — 30 (69.8) — 37 (78.7) Systemic therapy — 17 (36.2) — 18 (41.9) — 21(44.7) Phototherapy — 13 (27.7) — 10 (23.7) — 10 (21.3) [a] N = 46 for the EQ-5D Adalimumab 40mg weekly group. Values are expressed as mean ± SD unless otherwise stated. Note: Baseline values for patients in M02-529 = Baseline values of the same patients in M02-528. Patients were well balanced across treatment groups with respect to demographic characteristics and baseline disease activity.

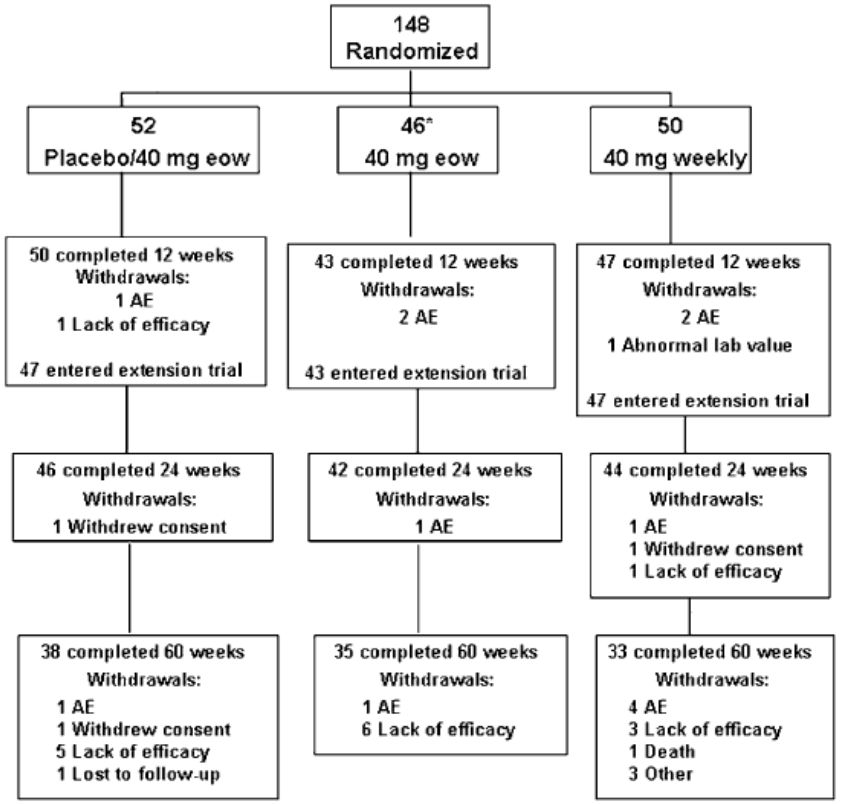
Study	Inclusion criteria	Exclusion Criteria	Baseline Demographics and Disease Characteristics
M03-596[62]	Subjects must have been randomised and relapsed on or before Week 24 of Study M02-538; men and women ≥ 18 years of age; female subjects who were either not of childbearing potential, or were of childbearing potential and practicing birth control;; subjects must have been able and willing to give written informed consent; subjects were allowed to use medicated shampoos and bland (without beta or alpha hydroxy acids) emollients.	The following subjects from Study M02-538 were not eligible for enrolment in study M03-596: (a) subjects who prematurely discontinued M02-538 for reasons other than relapse, (b) subjects who experienced rebound in M02-538, and (c) subjects who completed M02-538; active skin diseases that may have interfered with evaluation of psoriasis; used topical therapies for the treatment of psoriasis including corticosteroids, vitamin D analogues, and retinoids during the study; poorly controlled medical conditions; history of neurologic symptoms suggestive of central nervous	**Characteristic** — **Adalimumab weekly/ placebo [a] N = 21** — **Adalimumab weekly/ adalimumab eow [a] N = 11** — **Subjects who discontinued in the open-label period [b] N = 8** Age, y — 46.9 ± 11.0 — 49.4 ± 13.9 — 51.4 ± 13.2 Male, % — 76.2 — 36.4 — 62.5 Caucasian, % — 100 — 90.9 — 87.5 Weight, kg — 100.2 + 22.9 — 88.6 + 15.6 — 94.6 + 25.7 Ps duration — 19.0 ± 9.4 — 19.4 ± 15.0 — 16.3 ± 8.3 % BSA — 25.9 ± 25.1 — 26.1 ± 21.7 — 21.6 ± 14.6

		system demyelinating disease; history of cancer or lymphoproliferative disease; history of active tuberculosis (TB) or listeriosis, or persistent chronic or active infections requiring hospitalisation prior to study entry; use of anti-retroviral therapy at any time prior to or during the study; abnormal laboratory or other test results as determined by the Investigator; history of clinically significant drug or alcohol abuse in the last year; erythrodermic psoriasis or generalised pustular psoriasis.	PASI Score [c]	16.6 (12.8, 20.4)	14.9 (10.1,19.7)	14.4 (9.5-19.4)
			PGA, %			
			Severe psoriasis	23.8	9.1	12.5
			Moderate to severe psoriasis	28.6	36.4	25.0
			Values are expressed as mean + SD unless otherwise stated. [a] In Study M03-596, all subjects received 12-weeks of treatment with open-label adalimumab (loading doses of adalimumab 80 mg at Week 0 and at Week 1 followed by adalimumab 40 mg weekly from Week 2 to Week 11). Subjects who were PASI 50 responders at Week 12 were to have received adalimumab 40 mg eow or placebo from Week 12 to Week 24. Subjects were to have received open-label adalimumab followed by either placebo or adalimumab 40 mg eow for 12 weeks in the lead-in study, Study M02-538. [b] Subjects who discontinued in the open-label period are counted separately in the column titled "Subjects Who Discontinued in the Open-label Period," but are also counted in the column of the treatment group they discontinued from. [c] Values expressed as mean (95% CI). All demographic and Baseline characteristic data were from Study M02-538. No meaningful differences were observed in demographic data between the placebo and adalimumab 40 mg eow treatment groups; however, the following differences were observed nonetheless: subjects randomised to receive placebo were younger (46.9 years) than subjects randomised to receive adalimumab 40 mg eow (49.4 years). A greater proportion of subjects randomised to receive placebo were male than subjects randomised to receive adalimumab 40 mg eow (76.2% *vs.*36.4%, respectively). Subjects randomised to receive placebo weighed more (100.2 kg) than subjects randomised to receive adalimumab 40 mg eow (88.6 kg).			
Study	**Inclusion criteria**	**Exclusion Criteria**	**Baseline Demographics and Disease Characteristics**			
M03-658[55, 63]	Study M02−529 or Study M03−596 Ps subjects with ≥ PASI 50 (50% reduction in PASI score) at the final study visit; subjects who relapsed after Week 24 in M02 − 538; phase III (M03−656, M04−716) Ps subjects who met the study criteria for entering Study M03 − 658, specified in their preceding Phase	The following subjects in a preceding Ps study with adalimumab were not eligible for enrolment in Study M03-658: (a) Study M02-538 subjects who prematurely discontinued for reasons other than relapse, (b) Study M02-529 and M03-596 subjects who had < PASI 50 at the final study visit, (c) subjects who	**Characteristic**	**All Adalimumab Treatment Set* N =** [redacted]		
			Age, y	[redacted]		
			Male, %	[redacted]		
			Caucasian, %	[redacted]		
			Duration of Ps, y	[redacted]		

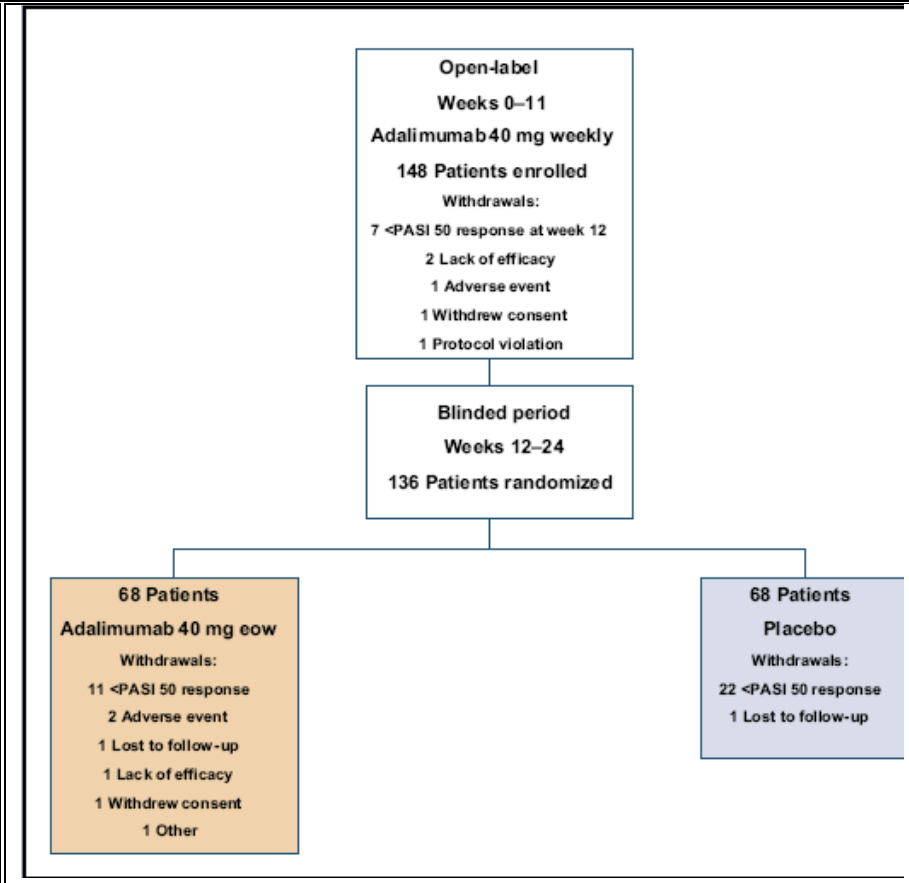
	III study protocol; subjects were judged to be in generally good health as determined by the Principal Investigator based upon the results of laboratory evaluations and physical examinations done throughout the preceding Ps study with adalimumab; subjects had to be able and willing to give written informed consentl; subjects had to be able to self-inject study medication or have a designee who could inject the study medication. Subjects were allowed to use medicated shampoos that did not contain corticosteroids, bland emollients and low potency topical corticosteroids on the palms, soles, face, inframammary area, and groin only.	completed the M02-538 360-day follow-up visit, and (d) subjects who did not meet the requirements for entering M03-658 specified in their Phase III protocol; for any reason, subject was considered by the Investigator to be an unsuitable candidate for continuing therapy in the M03-658 study; abnormal laboratory or other test results that would make it unsuitable for the subject to participate in this study; other active skin diseases that may interfere with evaluation of Ps; poorly controlled medical condition; history of neurologic symptoms suggestive of central nervous system demyelinating disease; history of cancer or lymphoproliferative disease; history of active tuberculosis or listeriosis, or ongoing chronic or active infections requiring hospitalisation, or chronic use of an anti-infective agent; use of anti-retroviral therapy at any time during the study; have immune deficiency or be immunocompromised; history of clinically significant drug or alcohol abuse in the last year; subject had erythrodermic Ps or generalised pustular Ps.	BSA affected, % PASI score PsA Status, % (self-reported) PGA, n (%) [a] Severe psoriasis Moderate psoriasis	[redacted] [redacted] [redacted] [redacted] [redacted]
			* All Adalimumab Treatment Set is defined as any subject who has received one dose of adalimumab in Study M03-658 and comprises patients who partook in the preceding Ps studies: M02-528/529, M02-538, M03-656 and M03-656. Values are expressed as mean ± SD unless otherwise stated. [a] Physician's Global Assessment (PGA) – data from the severe sub-group includes very severe patients as well (n=[redacted]). In addition, there are no PGA data for [redacted] subjects – percentages were calculated excluding non-missing values. Baseline values are derived from the last evaluation prior to the first study drug administration (placebo, MTX or adalimumab) in the initial studies.	

5.3.3 Patient numbers

M02-528 Patient numbers presented as a CONSORT Flow chart.	M02-538 Patient numbers presented as a CONSORT Flow chart.

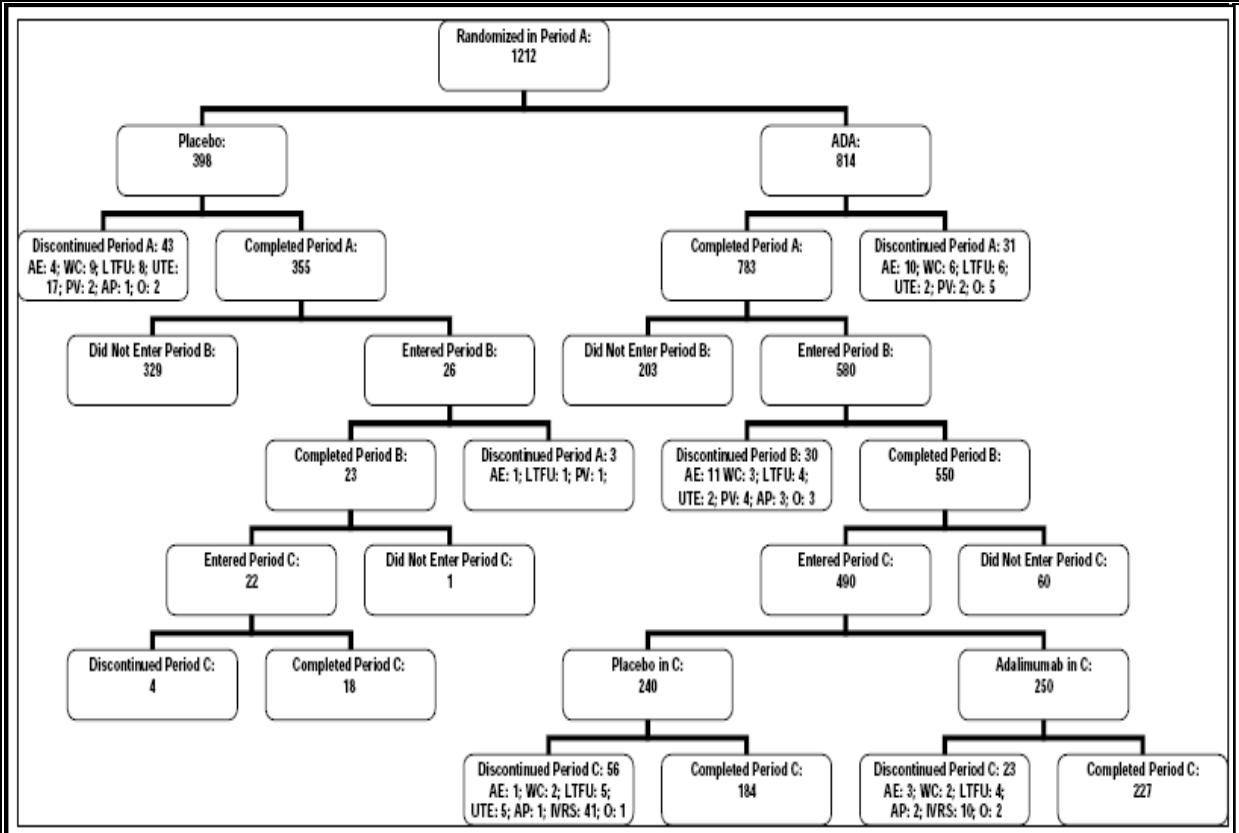


Patient disposition from Gordon et al, 2006.[33]
AE, Adverse event; eow, every other week.
*One patient was randomised, but withdrew informed consent and did not receive treatment.



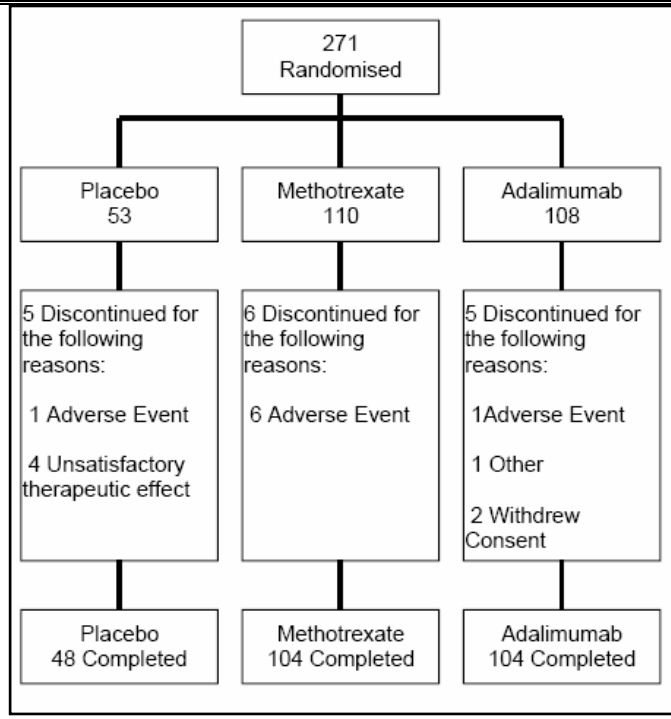
Patient disposition from Gordon et al, 2007[40].
AE, Adverse event; eow, every other week.

M03-656 (REVEAL) **Patient numbers presented as a CONSORT Flow chart.**	M04-716 (CHAMPION) **Patient numbers presented as a CONSORT Flow chart.**
Patient disposition derived from the Clinical Study Report.[59] ADA = Adalimumab	



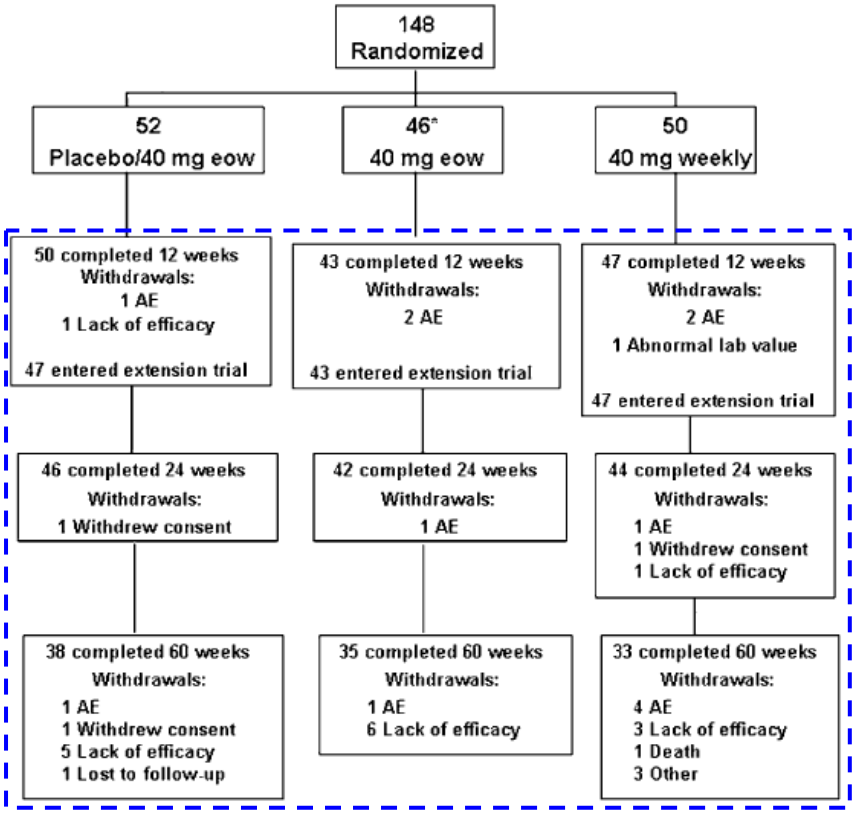
AP = administrative problem; IVRS = PASI < 75 (Period B) or loss of an adequate response (Period C)]; LTFU = lost to follow-up; O = Other; PV = protocol violation; UTE = unsatisfactory therapeutic effect; WC = withdrew consent

M02-529
Patient numbers presented as a CONSORT Flow chart.



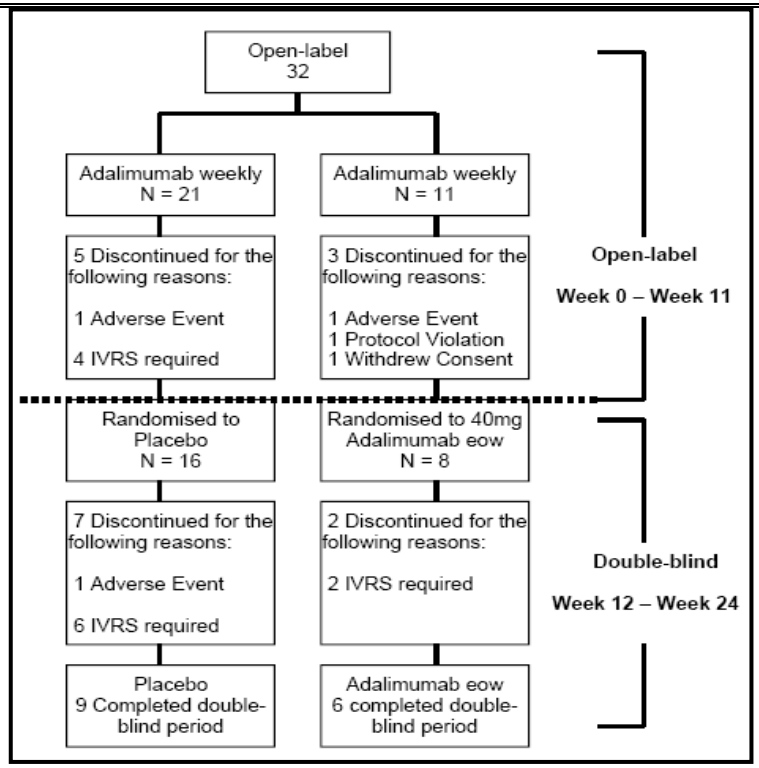
Over 90% of the subjects completed the study. The proportion of subjects who withdrew from the study was highest in the placebo treatment group (9.4%) and lowest in the adalimumab treatment group (3.7%). Most subjects prematurely discontinued from the study due to the occurrence of an AE or due to unsatisfactory therapeutic effect. Six (5.5%) MTX-treated subjects withdrew from the study with a primary reason of AE compared with one (1.9%) placebo-treated and one (0.9%) adalimumab-treated subject. Four placebo-treated subjects (7.5%) withdrew from the study with a primary reason of unsatisfactory therapeutic effect; no subjects in either the MTX or adalimumab treatment groups withdrew for this reason. Over 80% of patients entered M03-658.

M03-596
Patient numbers presented as a CONSORT Flow chart.



The blue dotted line separates study M02-529 from the 12-week lead in study, M02-528.

Patient disposition from Gordon et al, 2006.[33]
AE, Adverse event; eow, every other week.
*One patient was randomised, but withdrew informed consent and did not receive treatment.



eow: every other week;
IVRS: Interactive Voice Response System
Note: Subjects are presented by their randomised treatment assignment in Study M02-538.
In Study M03-596, all subjects received 12-weeks of treatment with open-label adalimumab (loading doses of adalimumab 80 mg at Week 0 and at Week 1 followed by adalimumab 40 mg weekly from Week 2 to Week 11). Subjects who were PASI 50 responders at Week 12 were to have received adalimumab 40 mg eow or placebo from Week 12 to Week 24. Subjects were to have received open-label adalimumab followed by either placebo or adalimumab 40 mg eow for 12 weeks in the lead-in study, M02-538.
[c.] PASI response less than 50% at Week 12.
[d.] PASI response less than 50% after Week 12, but on or before Week 24.

Patient numbers have not been presented for the open-label extension trial, M03-658, because the trial is currently ongoing. Details of the participants in this trial are presented in Figure 5.2.1 and Table 5.2.1.

5.3.4 Outcomes

Standard statistical, clinical, and laboratory procedures were used in the adalimumab psoriasis clinical trial programme. All efficacy measurements are standard for assessing disease severity in subjects with psoriasis and all clinical and laboratory procedures used are standard and generally accepted.

Study	Primary Outcome(s)	Secondary Outcome(s)
M02-528[33, 57]	The primary efficacy analysis was the proportion of patients achieving a clinical response defined by at least a 75% improvement in PASI score (PASI 75) relative to Baseline at Week 12.	Secondary outcomes measured in no particular rank order are as follows: • Proportion of subjects achieving clinical response defined as at least a PASI 75 response at Weeks 1, 2, 4 and 8. • Proportion of subjects achieving clinical response defined as at least a PASI 50 response (*i.e.*, at least a 50% reduction in PASI score relative to Baseline) at Weeks 1, 2, 4, 8 and 12. • Proportion of subjects achieving at least a PASI 50 response or at least a PASI 75 response at any time during the 12 weeks. • Time to PASI 50 and PASI 75 response. • Proportion of subjects achieving at least a PASI 90 response (*i.e.*, at least a 90% reduction in PASI score relative to Baseline) at Week 12. • Proportion of subjects achieving at least a PASI 90 response at Week 12. • Change from Baseline in QoL assessments (DLQI, SF-36 Health Status Survey, [redacted], and EQ-5D Health Questionnaire) at Week 12. • Proportion of subjects with a PGA of "*clear*" or "*almost clear*" at Weeks 4, 8, and 12.
M02-538[40, 58]	The primary efficacy endpoint was the time to relapse beginning at Week 12 through Week 24 in subjects who had achieved a ≥ PASI 50 response at Week 12. Relapse was defined as < PASI 50 response after randomisation at Week 12.	For all randomised subjects, secondary efficacy endpoints were as follows: • The proportion of subjects who relapsed. • The proportion of subjects with clinical response defined as ≥ PASI 75 response at Week 12, Week 24, and at the 90-, 180-, 270-, and 360-day post last dose follow-up visits. • The proportion of subjects with a PGA of "*clear*" or "*almost clear*" at Week 12, Week 24, at the 90-, 180-, 270-, and 360-day post last dose follow-up visits. • The proportion of subjects with clinical response defined as ≥ PASI 50 response at Week 24 and at the 90-, 180-, 270-, and 360-day post last dose follow-up visits. • The proportion of subjects achieving ≥ PASI 50 response and ≥ PASI 75 response at any time during the study • The change from maximum PASI response during the first 12 weeks of the study at the subject's final visit. • The time to relapse from Week 24 through the 360-day post last dose follow-up visit for non-relapsers at Week 24.

		For all subjects enrolled in the study, secondary efficacy variables were to include: • The time to PASI 50 and PASI 75 response • The proportion of subjects with clinical response defined as ≥ PASI 75 at Week 12 • The proportion of subjects with a PGA of "*clear*"/"*almost clear*" at Week 12.
M03-656 REVEAL	The REVEAL study had two independent primary endpoints: 1. The first primary endpoint was the percentage of patients in treatment Period A achieving ≥PASI 75 response at Week 16 relative to Baseline PASI scores. Patients randomised to adalimumab at Week 0 with ≥PASI 75 response at Weeks 16 and 33, were then re-randomised to either continue adalimumab or to switch to placebo treatment in treatment Period C. As such, 2. The second primary endpoint was the percentage of patients in treatment Period C losing an adequate response after Week 33 and on or before Week 52. Losing an adequate response was defined as <PASI 50 (relative to Week 0) and at least a 6-point increase in the PASI score relative to Week 33.	Secondary efficacy endpoints for all subjects randomised at Baseline (Period A) included the following: • Proportion of subjects achieving a PGA of clear or minimal at Weeks 4, 8, 12 and 16. • Proportion of subjects achieving ≥ PASI 50, 90 and 100 responses at Weeks 4, 8, 12 and 16. • Change from Baseline in DLQI at Weeks 4 and 16. • Proportion of subjects with DLQI = 0 at Week 16. • Time to PASI 50, 75, 90 and 100 responses on or before Week 16. • Change from Baseline in SF-36 domains at Week 16. Secondary efficacy variables for all subjects who continued into Period B (Week 17) included the following: • Proportion of subjects achieving ≥ PASI 75 and 90 responses at Week 33. • Proportion of subjects achieving a PGA of clear or minimal at Week 33. • Change from Baseline in DLQI at Week 33. • Proportion of subjects with DLQI = 0 at Week 33. • Change from Baseline in SF-36 PCS at Week 33. Secondary efficacy outcomes analysed for all subjects re-randomised at Week 33 (Period C) included the following: • Time to loss of PASI 50 and 75 responses after Week 33. • Time to loss of an adequate response after Week 33. • Proportion of subjects achieving ≥ PASI 50, 75, 90, and 100 responses at Week 52. • Proportion of subjects achieving a PGA of clear or minimal at Week 52. • Proportion of subjects with DLQI = 0 at Week 52. • Change from Week 33 in SF-36 PCS at Week 52.

M04-716 CHAMPION	The primary efficacy outcome was the proportion of subjects achieving clinical response, defined as at least a 75% reduction in PASI score (≥ PASI 75 response) at Week 16 relative to the Baseline (Week 0) PASI score.	Secondary outcomes measured included the following: • Proportion of subjects achieving a PGA of "clear" or "minimal" at Weeks 4, 8, 12, and 16. • Proportion of subjects achieving ≧ PASI 50, 90 and 100 at Week 16. • Proportion of subjects achieving ≧ PASI 50, 75 and 90 at Weeks 8 and 12. • Change from Baseline in DLQI at Weeks 12 and 16. • Proportion of subjects with DLQI=0 at Weeks 12 and 16. • Change from Baseline in EQ-5D Index Score at Weeks 12 and 16. • Proportion of subjects achieving ≧ PASI 50 and 75 at Week 4. • Proportion of subjects with improvement in PGA at Weeks 4, 8, 12 and 16. • Change from Baseline in Ps/PsA pain at Week 16. • Change from baseline in Ps-related pruritus at Week 16. • Proportion of patients reporting good or complete disease severity control at Week 16.
M02-529	The primary efficacy variable was the proportion of subjects achieving clinical response as defined by at least a PASI 75 response (*i.e.*, at least a 75% reduction in PASI score relative to the Baseline value of M02-528) at Week 12 of M02-529 (i.e. Week 24 of M02-528).	Secondary efficacy endpoints assessed in the trial were as follows: • The proportion of subjects achieving a clinical response defined by ≥ PASI 75 response at Weeks 24 and 48 compared to the Study M02-528 Baseline. • The proportion of subjects achieving a clinical response defined by ≥ PASI 50 response at Weeks 12, 24, and 48 compared to M02- 528 Baseline. • The proportion of subjects achieving a clinical response defined by ≥ PASI 90 (*i.e.*, at least a 90% reduction from Baseline in PASI score) response at Weeks 12, 24, and 48 compared to M02 -528 Baseline. • Change from M02-528 Baseline for DLQI, SF-36, [redacted], and EQ-5D at Weeks 12, 24, and 48. • Proportion of subjects with a PGA score of "*clear*" or "*almost clear*" at Weeks 12, 24, and 48.
M03-596	The primary efficacy variable was the proportion of subjects with clinical response, defined as ≥ PASI 50 response (*i.e.,* at least a 50% reduction in PASI score) at Week 12 compared to the Week 0 PASI score in the lead-in study, Study M02 − 538.	For those subjects with ≥ PASI 50 at Week 12, secondary efficacy outcomes were as follows: • Proportion of subjects with clinical response defined as at least a PASI 75 improvement at Week 12. • Time to relapse beginning after Week 12 through to Week 24. Relapse defined as when the improvement in PASI falls below 50% after Week 12. • Proportion of subjects who relapsed after Week 12. For all enrolled subjects, secondary efficacy variables were to include:

		• Time to PASI 50 and 75 responses. • Proportion of subjects with a PGA of clear/almost clear at Week 12. • Proportion of subjects achieving at least a PASI 50 or PASI 75 response at any time during the study.
M03-658	The efficacy variables in M03-658 are the PASI response and PGA.	The number/proportion of subjects who achieve ≥ PASI 50, ≥ PASI 75, ≥ PASI 90, and a PASI 100 response are to be summarised every 12 weeks. In addition, the time to PASI 50/75/90/100 responses, change from Baseline to PASI response, and percentage change in PASI response are to be summarised. The number/proportion of subjects who achieve 'clear' or 'minimal' on the 6-point PGA and the number/proportion of subjects who achieve 'clear' on the 6-point PGA are to be summarised every 12 weeks until study completion, in addition to the proportion of subjects with improvement in PGA by visit.

Validity and Description of Outcome Measures			
PASI Score The Psoriasis and Severity Index (PASI) score is a commonly used outcome measure that assesses the extent and severity of skin involvement. A PASI 75 response indicates a >75% improvement in the score. The PASI is a composite index indicating the severity of the three main characteristics of psoriatic plaques (erythema, scaling, and thickness) weighted by the amount of coverage of these plaques in the four main body areas (*i.e.*, head, trunk, upper extremities, and lower extremities). PASI scores can range from 0 to 72, with higher scores indicating greater severity. A PASI 50, PASI 90 and PASI 100 response are defined as greater than a 50%, 90% or 100% improvement in these variables, respectively. The PASI score is a recommended measure of outcome in clinical trials of Ps by the EMEA[25].	**PGA Score** The Physician's Global Assessment (PGA) of psoriasis severity is a commonly used, standardised global score, which is used as a static assessment of all psoriatic lesions on a 6- or 7-point scale: 1) Severe: very marked plaque elevation, scaling, and/or erythema; 2) Moderate to severe: marked plaque elevation, scaling, and/or erythema; 3) Moderate: moderate plaque elevation, scaling, and/or erythema; 4) Mild to moderate: intermediate between moderate and mild; 5) Mild: slight plaque elevation, scaling, and/or erythema; 6) Almost clear: intermediate between mild and clear; and 7) Clear: no signs of psoriasis (post-inflammatory hypopigmentation or hyperpigmentation could be present). It gives a general impression of severity or improvement of psoriasis on treatment and is a suggested measure of outcome by the EMEA[25]. In the adalimumab Ps trials M03-656 and M04-716, the PGA scale was different for to that used in M02-528/529 and M02-538 (6-point vs. 7-point scale).	**EQ-5D Questionnaire** The EQ-5D Health Questionnaire was used to assess how a subject described his/her health state on the day of the visit by asking questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It is a validated measure of general quality of life, but not specifically for psoriasis patients. Subjects were asked to tick off the box next to the statement(s) that best described his/her health on the day of the visit. The EQ-5D visual analogue scale (VAS) consisted of a 100 mm VAS scale designed to quantify the subject's health state was at the time of the visit. The low end of the scale (0 mm) represented the "*best health state you can imagine*" and the high end (100 mm) represented the "*worst health state you can imagine*."	**Dermatology Quality of Life Index (DLQI)** The Dermatology Quality of Life Index (DLQI) is a validated scale to assess health related quality of life in patients with psoriasis. The instrument contains ten items dealing with the subject's skin. The score on the DLQI has a possible range of 0 to 30, with 30 corresponding to the worst HRQL. The DLQI was developed to contain six subscale scores: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. The MCID has been described for DLQI for psoriasis patients as a change of 5.0 units [64]. The DLQI is a suggested scale to assess patient reported outcomes in Ps trials by the EMEA[25].
Short-Form SF-36 Questionnaire The impact of therapy on overall health-related quality of life of subjects in the studies was assessed using the generic Short-Form (SF-36) questionnaire, which has proven validity and reliability including two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores, and 8 domain scores, including physical function, bodily pain, role limitations–physical, general health, vitality, social function, role limitations–emotional, and	[redacted]	**Relapse** The EMEA suggests that relapse, defined as when the achieved maximal improvement from baseline is reduced by >50%, is a valid efficacy endpoint for Ps trials. A more subjective definition would be a relapse of psoriasis necessitating the re-initiation of treatment[25]. In trial M02-538, relapse is defined as < PASI 50 response after randomisation at Week 12.	

mental health. Domain scores range from 0–100, with higher scores reflecting better health status.			

5.3.5 Statistical analysis and definition of study groups

Study	Hypotheses	Statistical Analyses	Sample Size Calculation
M02-528[33, 57]	**Primary:** The primary analysis was the comparison between adalimumab treatment groups and the placebo treatment group of the proportion of subjects achieving at least a PASI 75 response at Week 12 using the Cochran-Mantel-Haenszel (CMH) test adjusted for weight category. Subjects without Week 12 evaluations were to be classified as "failures." An adjustment for multiple testing was to be done following the closed testing procedure. An initial overall comparison of the three treatment groups was to be tested. If this was significant (α=0.05), pairwise comparisons of each adalimumab dose group *vs.* placebo were to be performed. Summary statistics of the primary analysis included point estimates of clinical response rate for each treatment group, the difference in clinical response rate between each adalimumab dose group and placebo, and the corresponding 95% confidence intervals (CI). In analysing the primary variable, subjects without a PASI score at Week 12 were considered as not achieving a PASI 75 response. A supportive analysis of the primary variable was performed using the Last Observation Carried Forward (LOCF) approach to impute missing values. **Secondary:** No adjustments for alpha level were used for the secondary efficacy analyses. Continuous variables were analysed fitting an ANOVA model including factors for weight strata and treatment. The CMH test adjusted for weight category was used for discrete variables. Descriptive statistics were also provided. The time to PASI 50 and PASI 75 response were compared with the log rank test stratified for weight category.	All statistical tests were two-sided. The centre effect was not included in any analyses since there were not enough subjects per treatment arm within each centre for a meaningful analysis. Unless otherwise stated, all statistical tests were to be conducted at an alpha = 0.05 level (2-sided). Continuous variables were summarised by the number of observations, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables were summarised by counts and percentages. Demographic and Baseline characteristics were summarised and compared. Continuous variables were compared using a ranked analysis of variance (ANOVA). The ANOVA model included weight strata and treatment as factors. Discrete variables were compared using the Cochran-Mantel-Haenszel (CMH) test adjusted for weight category. The primary efficacy analyses were conducted on the Full Analysis Set according to the intent-to-treat (ITT) principle. The Full Analysis Set is defined as all randomised subjects who received at least one dose of study medication. The Full Analysis Set was analysed as randomised and adjusted for the weight categories according to the treatment and weight category assigned by ClinPhone at randomisation. Safety analyses were also conducted for all subjects who received at least one dose of study medication.	The sample size was calculated using nQuery advisor 4.0. The rationale for the study sample size was based on the hypothesis tests for the primary efficacy endpoint. Assuming a 22% clinical response in the placebo arm and a 55% of clinical response in the active arms, 50 subjects per treatment arm provided 90% power in the test of comparing two treatment groups with a 2-sided alpha of 0.05.

M02-538[40], [58]	**Primary:** The primary efficacy analysis was the time to relapse after Week 12 up to Week 24 relative to the randomisation visit. The equality of the pattern of relapse between treatment groups was assessed fitting a Cox proportional hazards model with factors for Week 12 PASI response and treatment. If sufficiently low numbers of relapses occurred between scheduled visits, life-table analyses were performed instead. **Secondary:** The comparison between treatment groups of discrete secondary variables was done using the CMH test adjusted for Week 12 PASI response. Summary statistics included point estimates of the clinical response rate for each treatment group, the difference in proportion between the adalimumab dose group and placebo, and the corresponding 95% confidence intervals. Continuous secondary variables were analysed fitting an ANCOVA model including factors for treatment and Week 12 PASI response group. The equality of the pattern of relapse from Week 24 to Week 76 for non-relapsers at Week 24 between treatment groups was assessed fitting a Cox proportional hazards model with factors for Week 12 PASI response and treatment. If sufficiently low numbers of relapses occurred between scheduled visits, life-table analyses were performed instead. The time to relapse from Week 12 up to Week 76 was summarised for the group of subjects randomised to receive placebo. Additional logistic regression and ANCOVA analyses included Baseline covariates such as sex, ethnicity, age, and PASI score, if some of these covariates were found to be important confounders.	All statistical tests were two-sided. The centre effect was not included in any analyses since there were not enough subjects per treatment arm within each centre for a meaningful analysis. Unless otherwise stated, all statistical tests were to be conducted at an alpha = 0.05 level (2-sided). Continuous variables were summarised by the number of observations, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables were summarised by counts and percentages. Demographic and Baseline characteristics were to be summarised and compared. Continuous variables were to be compared using a ranked analysis of covariance (ANCOVA). The ANCOVA model was to include PASI response strata and treatment as factors. Discrete variables were to be compared using the Cochran-Mantel-Haenszel (CMH) test adjusted for PASI category. The primary efficacy analyses were conducted on a modified Intent-to-Treat (ITT) population, which is defined as all randomised subjects who received at least one dose of study medication. The data collected across all subjects, collected in the subgroup of subjects not randomised, and collected in the open-label portion of the study were summarised. The safety analyses consisted of all subjects who received at least one dose of the study medication.	The sample size was calculated using nQuery Advisor 4.0. The rationale for the study sample size is based on the hypothesis tests for the primary efficacy variable. Twenty percent of the active arm and 50% of the placebo arm were expected to relapse up to Week 24, resulting in a hazard ratio of 0.322. Assuming a constant hazard ratio of 0.322, 58 subjects per treatment arm provides 90% power in the test of comparing the two treatment groups for time to relapse with an overall 2-sided alpha of 0.05. The adjustment for the interim analysis followed the Haybittle/ Peto approach. Results were assessed at an alpha level of 0.001 and 0.05 in the interim and final analyses, respectively. Based on the assumption that 20% of the subjects who receive open-label treatment for 12 weeks may not be eligible for randomisation at Week 12, at least 145 subjects were needed to begin the open-label treatment at Week 0.
M03-656[43, 59] **REVEAL**	**Primary:** There were two independent primary efficacy analyses in this study: 1) Proportion of subjects with a ≥ PASI 75 response at Week 16 relative to the Baseline PASI score in the adalimumab treatment group *vs.* the placebo treatment group (Period A); 2) Proportion of subjects losing an adequate response after Week 33 and on or before Week 52 (Period C). The proportion of subjects with a ≥ PASI 75 response at Week 16 was analysed using the Cochran-Mantel-Haenszel (CMH) test adjusting for centre. Subjects who did not have a Week 16 PASI score were imputed as non-responders in the primary analysis. The proportion of subjects losing an adequate response after Week 33 and on or before Week 52 was analysed using the CMH test adjusting for centre. In the primary analysis, a missing Week 52 PASI assessment was imputed as	All statistical tests were to be two-tailed and performed at the 0.5 level of statistical significance. Descriptive statistics were to be provided. These included the number of observations (N), mean, standard deviation (SD), minimum, 1st quartile (25th percentile), median, 3rd quartile (75th percentile), and maximum for continuous variables; and counts (N) and percentages for discrete variables. Demographics and Baseline characteristics of the study subjects were summarised for each subject population. Descriptive statistics were to be presented. These variables were analysed to assess the comparability of the two treatment groups provided by randomisation in Period A and Period C; continuous variables were analysed using one-	The power was calculated using nQuery Advisory 4.0. This study was designed to enrol approximately 1200 subjects in order to provide adequate information to characterise the safety profile of long-term treatment of adalimumab. Assuming that PASI 75 response rates at Week 16 were 62% and 4% in the adalimumab and placebo treatment groups, respectively, this sample size would provide more than 99% power to detect the difference between adalimumab and placebo in Period A. Based on data obtained in subjects receiving adalimumab 40 mg sc eow in Studies M02-528 and M02-

	loss of an adequate response if it was a result of premature discontinuation due to lack of efficacy or study drug toxicity. A missing value was not to be imputed for any other reason. **Secondary:** The secondary analysis for Periods A and C were analysed in the corresponding ITT population according to rank order. Fisher's Exact test, one-way ANOVA, and Log-rank test were used to assess potential treatment differences for discrete variables, continuous variables, and time to event variables, respectively. The Breslow-Day test was used to examine homogeneity across centers in the ≥ PASI 75 response rate at Week 16. Counts and percentages of subjects with a ≥ PASI 75 response at Week 16 were to be presented for each centre as well. Summary statistics were provided for the secondary variables in Period B. Key efficacy results were also to be analysed by demographics, Baseline characteristics, and the following subgroups: subjects who used the arm as a site of injection; and subjects with a) a medical history of PsA, b) a hand x-ray diagnosis of PsA, and c) the combination of medical history and hand x-ray diagnosis of PsA. Analyses based on non-responder imputation, observed cases, and last observations carried forward (LOCF) were provided as appropriate.	way analysis of variance (ANOVA); and discrete variables were analysed using Fisher's Exact test. The Intent-to-Treat (ITT) Analysis set was used for the efficacy analyses in this study. The ITT Analysis Set in Period A is defined as all subjects randomised at Baseline; the ITT Analysis Set in Period B is defined as all subjects who entered Period B; and the ITT Analysis Set in Period C is defined as all subjects re-randomised at Week 33. Subjects included in the ITT Analysis Set were analysed as randomised. That is, all subjects were to be included in the treatment group to which they are randomised, regardless of which treatment the subjects actually received. Efficacy information during period C for subjects who were originally randomised to the placebo treatment group in Period A and retained ≥ PASI 75 response at Weeks 16 and 33 was summarised separately. The safety analyses consisted of all subjects who received at least one dose of the study medication.	529, the following assumptions were made: 62% of the subjects in the adalimumab treatment group in Period A would reach a ≥ PASI 75 response at Week 16 and continue into Period B; 90% of the subjects in Period B would maintain a ≥ PASI 75 response at Week 33, and 90% of those subjects would be re-randomised into Period C. Therefore, it was expected that approximately 400 subjects would be re-randomised into Period C. Assuming that 21.8% and 34.5% of subjects re-randomised to adalimumab and placebo, respectively, in Period C would experience loss of an adequate response or discontinue from the study due to lack of efficacy or drug toxicity after Week 33 and on or before Week 52, this sample size would provide approximately 75% power to detect the difference between adalimumab and placebo treatment in Period C.
M04-716 CHAMPION	**Primary:** The primary efficacy analyses compared the proportions of subjects with at least a 75% reduction in PASI score (≥ PASI 75) at Week 16 relative to the Baseline (Week 0) PASI score, in the adalimumab 40 mg eow treatment group with the proportions in the placebo and MTX treatment groups. The tests were performed in the following sequence: 1. The superiority of adalimumab *vs.* placebo was established by Cochran- Mantel-Haenszel (CMH) stratified by country at alpha level of 0.05. 2. The comparison of adalimumab and MTX was to be performed if the superiority of adalimumab *vs.* placebo was established. The 95% confidence interval for the difference in the clinical response rate between the adalimumab treatment group and the MTX treatment group was then calculated based on the CMH statistic stratified by country. Non-inferiority of adalimumab *vs.* MTX was established if the lower limit of the confidence interval for the difference (adalimumab – MTX) was between –0.2 and 0.0 and the upper limit was positive. If the lower limit of the confidence interval	All statistical tests were two-tailed and performed at the 0.5 level of statistical significance. All p-values were rounded to three decimal places. Descriptive statistics were provided. These included the number of observations (N), mean, standard deviation (SD), minimum, 1st quartile (25th percentile), median, 3rd quartile (75^{th} percentile), and maximum for continuous variables; and counts (N) and percentages for discrete variables. The analyses were performed using SAS software. The Intent-to-Treat (ITT) subject population was used for the efficacy analyses. The ITT Analysis Set was defined as all subjects who were randomised at Week 0. The all-treated subject population, consisting of adalimumab subjects who received at least one injection, MTX subjects who received at least one dose of oral capsule, and placebo subjects who received at least one injection or oral capsule, was used for the safety analyses.	The sample size was calculated using nQuery Advisory 4.0. Approximately 250 subjects were randomised in a 2:2:1 ratio to receive adalimumab, MTX, or placebo. Assuming that the clinical response rates were 62% in adalimumab treatment group, 60% in the MTX treatment group, and 4% in the placebo treatment group, this sample size would provide more than 95% power to detect the difference of adalimumab and placebo and approximately 90% power to determine the non-inferiority of adalimumab relative to MTX using a tolerance limit of 20%. Furthermore, this sample size also provides 80% power to detect a 20% difference between the two active arms, assuming the response rate in the adalimumab treatment group is 62%.

	was positive, the adalimumab treatment group was considered superior to the MTX treatment group. Subjects who did not have PASI assessments at Week 16 were imputed as non-responders in the primary analyses. **Secondary:** Summary statistics were provided for all secondary variables. Proportions were analysed using Fisher's Exact test to assess the potential treatment differences; exact binomial confidence interval were provided for each treatment group; the 95% confidence interval for the difference between the adalimumab treatment group and the MTX treatment group was calculated based on the normal approximation to the binomial distribution. Continuous variables were analysed using a one-way ANOVA. Time to event variables were analysed using the Log rank test. Analyses based on non-responder imputation, observed cases, and last observation carried forward (LOCF) were provided as appropriate. For the LOCF analyses, a Baseline value was carried forward if no post-Baseline value was available for a subject. A value from an unplanned timepoint was not carried forward if this value was the last observation. When adjustment for multiplicity was required, the secondary variables were analysed according to rank. Key efficacy variables were analysed with respect to demographics and Baseline Characteristics.		
M02-529	**Primary:** The primary analysis was the comparison between treatment groups using the CMH test adjusted for Baseline weight category of the proportion of subjects achieving clinical response as defined by ≥ PASI 75 response at Week 12. Subjects without Week 12 evaluations were classified as not achieving ≥ PASI 75 response. Summary statistics included point estimates of clinical response rate for each treatment group, the difference in proportion between each treatment group, and the corresponding 95% confidence intervals. A supportive analysis of the primary variable was to be performed using the Last Observation Carried Forward (LOCF) approach to impute missing values. **Secondary:** No adjustments for alpha level were needed for the secondary efficacy analyses. Continuous variables were to be analysed fitting a model including factors for weight strata and treatment. The CMH test adjusted for weight category was to be used for discrete	All statistical tests were two-sided. The centre effect was not included in any analyses since there were not enough subjects per treatment arm within each centre for a meaningful analysis. Unless otherwise stated, all statistical tests were to be conducted at an α=0.05 level (2-sided). The primary efficacy analyses were conducted on the Intent-to-Treat (ITT) population, which was defined as all randomised subjects who received at least one dose of study medication. The safety population consisted of all subjects who received at least one dose of the study medication.	Subjects who completed the lead-in study, Study M02-528, and who satisfied the inclusion/exclusion criteria were eligible for enrolment into this study.

	variables.		
M03-596	**Primary:** The primary efficacy variable was at least a 50% reduction in PASI score (≥ PASI 50 response) at Week 12 of M03-596 compared to the Week 0 PASI score in Study M02-538. The number and proportion that achieved ≥ PASI 50 response were summarised by original treatment group and the associated 95% confidence intervals (CIs) provided. The proportion achieving ≥ PASI 50 response were compared between original treatment groups using the Cochran-Mantel-Haenszel (CMH) test adjusted for Baseline PASI category. Because the results were conditional on relapsing after achieving an initial ≥ PASI 50 response at Week 12 of M02-538, additional logistic regression analyses included Baseline covariates if some were found to be important confounders. **Secondary:** Response variables among those with ≥ PASI 50 response at Week 12 were compared between the original active and placebo treatment groups. Continuous variables were analysed fitting an analysis of variance (ANOVA) model including factors for Baseline PASI strata and treatment. The CMH test adjusted for Baseline PASI category was used for variables that were discrete. Descriptive statistics were provided. Additional logistic regression and ANOVA analyses included Baseline covariates if some were found to be important confounders. The equality of the pattern of time to relapse from Week 12 up to Week 24 between treatment groups was assessed fitting a Cox proportional hazards model with factors for PASI strata and treatment. Those who discontinued from the study without documented relapse were to be censored. Time to PASI 50 response and time to PASI 75 response were similarly assessed. If few subjects had the episode recorded between scheduled visits, life-table analyses were performed instead. Additional models included Baseline covariates if some were found to be important confounders. Summaries of subjects with < PASI 50 response at Week 12 were detailed in the statistical analysis plan. Likewise, within-subject comparisons of responses during the first course of treatment to those during the second course were to be fully described.	All statistical tests were two-sided. The centre effect was not included in any analyses since there were not enough subjects per treatment arm within each centre for a meaningful analysis. Unless otherwise stated, all statistical tests were to be conducted at an α=.05 level (2-sided). The primary efficacy analysis was conducted using the intent-to-treat (ITT) population, which included all subjects initially randomised in Study M02-538 who received at least one dose of study medication in Study M03-596. The safety population consisted of all subjects who received at least one dose of study medication in Study M03 − 596.	Subjects randomised in Study M02-538 who relapsed and satisfied the inclusion/ exclusion criteria for this study were eligible for enrolment.
M03-658	The efficacy variables for this study are the PASI and PGA. The number and proportion of subjects who achieved ≥ PASI 50, ≥	Since this is an open-label continuation study which is currently ongoing, no formal statistical test will be	The sample size of this study was determined by the number of subjects who

	PASI 75, and ≥ PASI 90 will be summarised every 12 weeks. The number and proportion of subjects who were 'clear' or 'almost clear' as determined by the 7- point PGA will be summarised every 12 weeks up to and including Week 48. The number and proportion of subjects who were 'clear' or 'minimal' as determined by the 6- point PGA will be summarised every 12 weeks until study completion. Validation of the two PGA scales will be performed. The associated 95% confidence intervals will also be provided. The number and proportion of subjects who achieved ≥ PASI 50, ≥ PASI 75, and ≥ PASI 90 and PGA of 'clear' or 'minimal' among those who were dose escalated will be summarised.	conducted. Descriptive statistics will be provided. Continuous variables will be summarised by the number of observations, mean, standard deviation, 1st quartile (25^{th} percentile), median, 3rd quartile (75th percentile), minimum, and maximum; discrete variables were to be summarised by counts and percentages. The efficacy analyses will be conducted in the intent-to-treat (ITT) population, which is defined as all subjects who received at least one dose of study medication in Study M03-658 regardless of possible protocol deviations. The safety population will also consist of all subjects who received at least one dose of the study medication in M03-658.	were eligible based on the inclusion/exclusion criteria of this study and who participated in Studies M02-529, M02-538, M03-596 and the Phase III psoriasis studies, M03-656 and M04-716.

5.3.6 Critical appraisal of relevant RCTs

Critical Appraisal		Study Assessment					
		M02-528	**M02-538**	**M03-656**	**M04-716**	**M02-529**	**M03-596**
1	How was allocation concealed?	Randomisation schedules were kept sealed until unblinding of the study. Appropriate dummy products were administered to those in the placebo group. Abbott, the Investigator, site staff, and the subject remained blinded to the subject's treatment throughout the course of the study.	Randomisation schedules were kept sealed until unblinding of the study. Appropriate dummy products were administered to those in the placebo group. Abbott, the Investigator, site staff, and the subject remained blinded to the subject's treatment throughout the course of the study.	Randomisation schedules were kept sealed until unblinding of the study. Appropriate dummy products were administered to those in the placebo group. Abbott, the Investigator, site staff, and the subject remained blinded to the subject's treatment throughout the course of the study.	Randomisation schedules were kept sealed until unblinding of the study. Appropriate dummy products were administered to those in the placebo group. Abbott, the Investigator, site staff, and the subject remained blinded to the subject's treatment throughout the course of the study.	Randomisation schedules were kept sealed until unblinding of the study. Appropriate dummy products were administered to those in the placebo group. Abbott, the Investigator, site staff, and the subject remained blinded to the subject's treatment throughout the course of the study.	Randomisation schedules were kept sealed until unblinding of the study. Appropriate dummy products were administered to those in the placebo group. Abbott, the Investigator, site staff, and the subject remained blinded to the subject's treatment throughout the course of the study.
2	Which randomisation technique was used?	Computerised randomisation (Interactive Voice Response System [IVRS]) was used - this	Computerised randomisation (Interactive Voice Response System [IVRS]) was used - this	Computerised randomisation (Interactive Voice Response/ Interactive Web Response System	Computerised randomisation (Interactive Voice Response System [IVRS]) was used - this	Computerised randomisation (Interactive Voice Response System [IVRS]) was used - this	Computerised randomisation (Interactive Voice Response System [IVRS]) was used - this

		telephone-based system was provided by ClinPhone.	telephone-based system was provided by ClinPhone.	IVRS/IWRS) was used - this telephone-based system was provided by ClinPhone.	telephone-based system was provided by ClinPhone.	telephone-based system was provided by ClinPhone.	telephone-based system was provided by ClinPhone.
3	**Was follow-up adequate?**	Follow-up was adequate and concurs with EMEA recommendations[25].	Follow-up was adequate and concurs with EMEA recommendations[25].	Follow-up was adequate and concurs with EMEA recommendations[25].	Follow-up was adequate and concurs with EMEA recommendations[25].	Follow-up was adequate and concurs with EMEA recommendations[25].	Follow-up was adequate and concurs with EMEA recommendations[25].
4	**Were individuals undertaking the outcomes assessments aware of allocation?**	Protocol design ensured that those making measurements of outcome were kept fully blinded to treatment assignment and measurement techniques were not subject to observer bias.	Protocol design ensured that those making measurements of outcome were kept fully blinded to treatment assignment and measurement techniques were not subject to observer bias.	Protocol design ensured that those making measurements of outcome were kept fully blinded to treatment assignment and measurement techniques were not subject to observer bias.	Protocol design ensured that those making measurements of outcome were kept fully blinded to treatment assignment and measurement techniques were not subject to observer bias. Furthermore, to further conceal randomisation, the study had separate safety and efficacy assessors (so that potential LFT elevations, or GI complaints wouldn't alert the efficacy assessor.	Protocol design ensured that those making measurements of outcome were kept fully blinded to treatment assignment and measurement techniques were not subject to observer bias.	Protocol design ensured that those making measurements of outcome were kept fully blinded to treatment assignment and measurement techniques were not subject to observer bias.
5	**Was a justification of the sample size provided?**	Justification of the sample size was provided and detailed in Section 5.3.5. Trial had adequate power to test primary hypothesis.	Justification of the sample size was provided and detailed in Section 5.3.5. Trial had adequate power to test primary hypothesis.	Justification of the sample size was provided and detailed in Section 5.3.5. Trial had adequate power to test primary hypothesis.	Justification of the sample size was provided and detailed in Section 5.3.5. Trial had adequate power to test primary hypothesis.	Justification of the sample size was provided and detailed in Section 5.3.5. Patients completing M02-528 were eligible for entry in to this trial.	Justification of the sample size was provided in Section 5.3.5. The trial evaluated those patients who relapsed in M02-538.
6	**Was the design parallel or cross over? Is there risk, for cross over designs, of carry-over effect?**	Parallel design	Parallel design	Parallel design	Parallel design	Parallel design	Parallel design
7	**Was the RCT conducted in the UK?**	The study was multinational, conducted in the USA and Canada,	The study was multinational, conducted in the USA and Canada,	The study was multinational, conducted in the USA and Canada,	The study was multinational, conducted in Europe and Canada,	The study was multinational, conducted in the USA and Canada,	The study was multinational, conducted in the USA and Canada,

		but not in the UK.	but not in the UK.	but not in the UK.	but not in the UK.	but not in the UK.	but not in the UK.
8	**Do patients included in the RCT compare with patients likely to receive the intervention in the UK?**	Subjects in this RCT were broadly similar in terms of baseline disease severity and demographics to patients in England and Wales.	Subjects in this RCT were broadly similar in terms of baseline disease severity and demographics to patients in England and Wales.	Subjects in this RCT were broadly similar in terms of baseline disease severity and demographics to patients in England and Wales.	Subjects in this RCT were broadly similar in terms of baseline disease severity and demographics to patients in England and Wales. However, patients were MTX naïve as per inclusion criteria and are therefore slightly different to patients in the UK who will have failed systemic therapy, before initiating a biologic.	Subjects in this RCT were broadly similar in terms of baseline disease severity and demographics to patients in England and Wales.	Subjects in this RCT were broadly similar in terms of baseline disease severity and demographics to patients in England and Wales.
9	**Are dosage regimes within those cited in the summary of product characteristics?**	One of the active treatment arms of this trial employed the recommended dose in the draft summary of product characteristics.	In this trial subjects received 80 mg adalimumab at Week 0 and Week 1, followed by 40mg adalimumab weekly for the first 12 weeks (open-label). This dosing schedule differs to the draft summary of product characteristics (SmPC), however patients were then randomised to 40mg adalimumab eow as per the draft (SmPC).	Recommended dose in the draft summary of product characteristics was used in this trial.	Recommended dose in the draft summary of product characteristics was used in this trial.	Recommended dose in the draft summary of product characteristics was used in this trial.	In this re-treatment trial subjects received 80 mg adalimumab at Week 0 and Week 1, followed by 40mg adalimumab weekly for the first 12 weeks (open-label). This dosing schedule differs to the draft summary of product characteristics (SmPC), however patients were then randomised to 40mg adalimumab eow as per the proposed dosing regimen.
10	**Were study groups comparable?**	The study groups had similar demographic and clinical profiles.	The study groups had similar demographic and clinical profiles.	The study groups had similar demographic and clinical profiles.	The study groups had similar demographic and clinical profiles.	The study groups had similar demographic and clinical profiles.	No meaningful differences were observed in demographic data between the placebo and adalimumab 40 mg eow treatment groups; however, some differences were observed which are detailed in Section 5.3.2.

11	**Were statistical analyses performed appropriate?**	Statistical analyses of the trial were appropriate and intention-to-treat analyses were undertaken.	Statistical analyses of the trial were appropriate and intention-to-treat analyses were undertaken.	Statistical analyses of the trial were appropriate and intention-to-treat analyses were undertaken.	Statistical analyses of the trial were appropriate and intention-to-treat analyses were undertaken.	Statistical analyses of the trial were appropriate and intention-to-treat analyses were undertaken.	Statistical analyses of the trial were appropriate and intention-to-treat analyses were undertaken.

Note: Study M03-658, the open-label extension trial of the preceding phase II and phase III trials detailed in Section 5.3.1 is not included in the critical appraisal for the following reasons: the trial is currently ongoing; it is an open-label extension trial and as such does not contain any blinded periods; all subjects participating in this trial were enrolled in preceding adalimumab Ps trials.

5.4 Results of the relevant comparative RCTs

Results from the relevant RCTs in the adalimumab psoriasis clinical trial programme are presented in tabular form below in Sections 5.4.1 to 5.4.7.

5.4.1 Study M02-528[33, 34, 36, 37]

A total of 148 patients were randomised and 147 patients received at least one dose of study medication and were included in the efficacy analyses; one patient was randomised to the eow group, but did not receive study drug because of withdrawal of informed consent. The first subject was screened on 11 March 2003 and the last subject's final study visit occurred on 25 September 2003.

M02-528	**Primary Efficacy Outcome**
	At week 12, a significantly greater proportion of patients treated with adalimumab achieved the primary end point of PASI 75 than patients given placebo, with 53% (24 of 45) of patients in the 40 mg adalimumab eow group and 80% (40 of 50) of patients in the 40 mg adalimumab weekly arm achieving at least PASI 75 relative to baseline, compared with 4% (2 of 52) in the placebo group ($p<0.001$)[33, 37].
	Secondary Efficacy Outcomes
	• Statistically significant mean percentage improvements in PASI scores occurred as early as Week 1 after initiation of adalimumab vs. placebo ($p<0.001$), with a higher percentage of PASI 50 responders in both adalimumab treatment arms relative to placebo by Week 2, and a higher percentage of PASI 75 responders in both adalimumab treatment arms relative to placebo by Week 4[33]. • The proportion of patients in the eow and weekly adalimumab treatment arms achieving PASI 50 and PASI 90 scores at Week 12 were 76% and 88%, and 24% and 48%, respectively, compared to 17% and 0% in the placebo group[33, 37]. • The percentage of patients with a PGA of 'clear' or 'almost clear' in the every other week and weekly adalimumab treatment arms at Week 12 were 49% and 76%, respectively, compared to 2% of patients in the placebo group[33, 37]. • At Week 12, 11% of patients administered 40mg adalimumab eow and 26% of patients receiving 40mg adalimumab weekly achieved PASI 100 ($p<0.001$ for both groups vs. placebo) [33]. • At Week 12, patients in the eow and weekly adalimumab treatment groups had >10 point improvement in their mean DLQI scores (10.8 [95% CI of - 13.1, - 8.5] and 11.5 [95% CI of - 13.6, - 9.4], respectively) compared to patients in the placebo group who improved by a mean value of 1.3 points (95% CI of -3.3, 0.7) ($p<0.001$ for both treatment arms vs. placebo)[34]. Week 12 mean DLQI scores for the two adalimumab groups were < 3 points, whereas the placebo mean DLQI score was > 10 – a score that Khilji et al[64] described as consistent with severe psoriasis[34]. • Similarly, the improvements in both the EQ-5D Index and VAS scores were significantly greater for both adalimumab treatment groups than the improvements reported for the placebo group: 0.21 for the 40mg adalimumab eow ($p<0.001$) and 0.19 for the 40mg adalimumab weekly ($p=0.002$) groups vs. 0.01 for the placebo group for the EQ-5D Index score; and 17.9 and 10.7 points vs. 0.5 points on the VAS for the three groups, respectively ($p<0.001$ for adalimumab eow and $p=0.013$ for adalimumab weekly vs. placebo)[34]. • Both adalimumab treatment groups achieved statistically significantly greater improvements in the MCS component of the SF-36 in comparison to the placebo group (increases of 7.8 and 5.2 for the adalimumab eow and weekly groups, respectively, vs. a decrease of 0.1 for the placebo group) ($p<0.001$ for adalimumab eow and $p=0.017$ for adalimumab weekly vs. placebo). Both adalimumab treatment groups also achieved statistically significantly greater improvements compared to patients administered placebo in the Bodily Pain, Vitality, Social Function, Role-Emotional, and Mental Health domains[34].

	• Changes in PASI and PGA scores were significantly associated with changes in the health related quality of life scores. Baseline to Week 12 mean changes in PASI scores were correlated with changes in DLQI total scores (0.69, p<0.001); with EQ-5D Index scores (- 0.57, p<0.001); with SF-36 MCS scores (-0.45, p<0.001); and with SF-36 PCS scores (- 0.40, p<0.001). In addition, changes in PGA scores were correlated with DLQI total scores (0.71, p<0.001); with EQ-5D Index scores (- 0.44, p<0.001); with SF-36 MCS scores (-0.42, p<0.001); and with SF-36 PCS scores (- 0.25, p<0.01) [34].
	Post-hoc analysis[36]
	Gordon et al. performed a post-hoc analysis of M02-528 to test the hypothesis that patients who meet some of the criteria for biological therapy under BAD guidelines[3] have significant improvement in physician- and patient-reported outcomes upon adalimumab administration, with acceptable safety, compared to placebo. The post-hoc analysis was conducted among those patients with a baseline PASI score ≥ 10 and a baseline DLQI score of > 10. Of the 148 enrolled patients, 35% patients receiving placebo, 58% patients receiving 40mg adalimumab eow and 46% of patients receiving 40mg adalimumab weekly had baseline PASI score ≥ 10 and baseline DLQI score > 10. In this sub-group of patients, response rates at Week 12 were statistically significantly higher for patients randomised to active therapy compared to those on placebo, with a ≥ PASI 75 response achieved by 0% of patients in the placebo arm, 69% in the eow arm, and 74% in the weekly arm (p<0.001 vs. placebo for both treatment arms). Mean reductions in DLQI score at Week 12 relative to baseline were 2.3 for the placebo arm, 16.6 for the eow arm and 15.5 for the weekly arm (p<0.001 vs. placebo for both treatment arms). Among these patients, none in the placebo or eow arms, and 2 in the weekly arm, had serious adverse events after 12 weeks of treatment. It should be noted that these patients did not necessarily have failure on multiple systemic treatments, or contraindications, and therefore these results are not fully generalisable to the predicted patient experience of adalimumab patients under BAD guidelines.
	Conclusions
	In this multicentre, randomised, placebo-controlled, 12-week trial, adalimumab demonstrated statistically and clinically significant efficacy in the treatment of psoriasis as assessed by a variety of efficacy measures, including PASI 75 response rate and the proportion of patients with PGA of clear or almost clear. Furthermore, this study demonstrated that, relative to placebo, treatment with adalimumab 40mg eow or weekly resulted in significant improvements in the health-related quality of life of patients with moderate to severe plaque psoriasis.

5.4.2 Study M02-538[40, 41, 58]

A total of 148 patients were enrolled in M02-538, received at least on dose of the adalimumab 40mg weekly regimen, and were included in the efficacy and safety analysis; 136 of whom completed 12 weeks of open-label therapy and achieved at least a 50% improvement in PASI scores; a total of 96 subjects completed the blinded period from Week 12 to Week 24 (refer to Section 5.3.3 for the flow-chart of patient disposition throughout the study). The first subject's Screening visit occurred on 19 June 2003 and the last subject's final study visit occurred on 10 March 2005.

M02-538	**Primary Efficacy Outcome**
	The primary efficacy outcome in this study was the time to relapse beginning at Week 12 through to Week 24 in subjects who had achieved a ≥ PASI 50 response at Week 12 following 12 weeks of open-label therapy. Following 12 weeks of open-label therapy, 92% of patients achieved a PASI 50 response and were then randomised to 40mg adalimumab eow or placebo[41]. During the double-blind, placebo-controlled period (Weeks 12-24), subjects who underwent adalimumab dose decrease (40mg adalimumab eow) had approximately a 50% reduction in the risk of relapse than subjects who were withdrawn from adalimumab (placebo) (risk ratio 0.48; 16.2% *vs.* 30.9%, respectively). While clinically meaningful, this result was not statistically significant (p=0.060; 95% CI: 0.23, 1.03) [58]. The majority of patients in both groups sustained > PASI 50 scores vs. Baseline. Consequently, the median time to relapse during Weeks 12-24 could not be calculated[40]. The point estimate of the hazard ratio of the risk of relapse for subjects who discontinued from the study and were counted as relapsers continuing on adalimumab was 0.7 (95% CI of 0.37–1.34), with a hazard ratio below 1 signifying a lower risk of relapse for patients continuing on adalimumab vs. patients randomised to placebo[40]. The substantial number of patient discontinuations after week 24 precluded the ability to reliably estimate time to relapse for these groups past this time point[40].
	Secondary Efficacy Outcomes

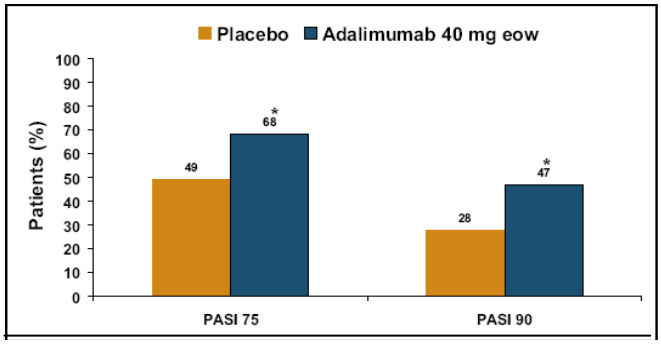
- The percentage of patients who achieved a PGA of “Clear” or “Almost Clear” at Week 12 following open-label therapy was 66.2% (98/148)[40].

- A greater percentage of patients randomised to adalimumab 40 mg eow (54.4% [37/68]) achieved PGA “Clear” or “Almost Clear” at Week 24 vs. patients who were withdrawn from adalimumab (39.7% [27/68]) (p=0.069)[40].

- At Week 12 following open-label therapy, PASI 75 and PASI 90 responses were achieved by 76.4% and 47.3% of patients, respectively[40].

- At Week 24, greater percentages of patients who had been randomised to adalimumab 40 mg eow sustained efficacy response, as assessed by several efficacy measures, compared with patients who had been randomised to adalimumab withdrawal (placebo). The differences in PASI 75 and PASI 90 response rates between patients randomised to adalimumab eow and patients randomised to placebo were statistically significant (Table 5.4.2.1)[40].

  Table 5.4.2.1: Percentages of patients achieving at least 75% and 90% improvements in PASI response at Week 24[40]



  *p<0.05 vs. placebo
  Patients with missing scores were considered non-responders.

- For patients in the adalimumab 40mg eow group, the percentage of patients with a PASI 50 score at Week 24 was 77.9% (53/68); and for patients in the placebo group the proportion with a PASI 50 score at Week 24 was 66.2% (45/68) (p=0.173)[40].

- For patients who achieved ≥ PASI 75 at Week 12, the relapse rate (loss of PASI 50 response relative to baseline) at week 24 was 17.2% for patients randomised to adalimumab eow and 23.6% for patients randomised to placebo[40].

- Patients who had received biologic agents within the last year had PASI 50 response rates similar to those of biologic naïve patients after 12 weeks open-label adalimumab treatment (12/14 patients exposed to etanercept, 4/4 patients exposed to infliximab, 6/6 exposed to alefacept, and 14/15 exposed to efalizumab all achieved ≥ PASI 50 responses at Week 12)[40].

- At each visit after Week 12, a smaller proportion of subjects in the adalimumab eow treatment group experienced relapse compared to subjects in the placebo treatment group. This trend continued up to the 360-day follow-up visit; however, the difference between treatment groups was statistically significant only at the 90-day follow-up visit (21.6% *vs.* 48.9%, p=0.011). Sensitivity analysis using non-responder imputation showed similar results[58].

- A statistically significantly greater proportion of subjects in the adalimumab eow treatment group had a ≥ PASI 75 response at the 30-day follow-up visit (80.4% *vs.* 55.6% respectively; p=0.015) and 90-day follow-up visit (52.9% *vs.* 20% respectively; p=0.001) than did those subjects in the placebo treatment group[58].

Conclusions

Weekly adalimumab therapy rapidly improved psoriasis during an initial 12-week period. Improvement was sustained in most, but not all patients, despite dosage reduction to every other week. Most patients in the trial maintained >PASI 50 improvement, relative to baseline, during the 3 months following adalimumab discontinuation. Overall, greater efficacy rates at Week 24 were observed for patients randomised to continuous adalimumab therapy than for patients who were withdrawn from therapy at Week 12.

5.4.3 Study M03-656 (REVEAL)[43, 44, 59]

A total of 1212 patients were randomised at the start of the study in Period A in a 2:1 fashion to receive either 40mg adalimumab eow (n=814) or placebo (n=398), of these patients 1138 completed the 16 week treatment period. Patients achieving at least a PASI 75 response at Week 16 then received open-label 40mg adalimumab eow from Week 17 to Week 31 in treatment Period B; of the 1138 subjects who completed Period A, 606 subjects received open-label therapy in Period B – 580 who were originally randomised to adalimumab and 26 subjects who were originally randomised to placebo. Patients achieving at least a PASI 75 response at Week 33 were then re-randomised to either 40mg adalimumab eow or placebo until Week 52 or to loss of an adequate response; 490 subjects were re-randomised in treatment Period C (refer to Section 5.3.3 for detailed information of subject's disposition throughout the trial). The first subject was screened on 13 December 2004, and the first subject was randomised on 21 December 2004. The last subject's final study visit occurred on 29 June 2006.

M03-656

Primary Efficacy Outcomes

There were two independent primary efficacy variables in this study:

- The first primary endpoint was the percentage of patients in treatment Period A achieving ≥PASI 75 response at Week 16 relative to Baseline PASI scores.
- The second primary endpoint was the percentage of patients in treatment Period C losing an adequate response after Week 33 and on or before Week 52.

1. The PASI 75 response rate at Week 16 was statistically significantly higher in the adalimumab treatment group compared with placebo ($p < 0.001$). Table 5.4.3.1 shows the proportion of subjects with ≥ PASI 75 at Week 16 for Period A (ITT Analysis Set). Subjects with missing responses at Week 16were imputed as non-responders[43].

Table 5.4.3.1: Proportion of subjects with ≥ PASI 75 at Week 16 for Period A (ITT Analysis Set) [43]

	Placebo N=398	Adalimumab N=814	Difference between treatment groups (%)	95% CI	p-value [a]
	n (%)				
Week 16	26 (6.5)	578 (70.9)	64.4	(58.4, 70.4)	< 0.001***

[a] Based on CMH test stratified by centre.
*** Statistically significant at the $p \leq 0.001$ level.

2. The proportion of subjects losing an adequate response was statistically significantly higher for subjects re-randomised to placebo compared with subjects re-randomised to adalimumab. A missing Week 52 PASI score was imputed as a loss of an adequate response if it resulted from premature discontinuation due to a lack of efficacy or study drug toxicity (including AE, unsatisfactory therapeutic effect, death, and IVRS required)[43].

Table 5.4.3.2: Proportion of subjects with loss of an adequate response after Week 33 and on or before Week 52 - Period C (ITT Analysis Set) [43]

	Placebo N=240	Adalimumab N=250	Difference between treatment groups (%)	95% CI	p-value [a]
	n (%)				
Week 33 to Week 52	68 (28.4)	12 (4.9)	-23.5	(-30.2, -16.9)	< 0.001***

[a] Based on CMH test stratified by centre.
*** Statistically significant at the $p \leq 0.001$ level.

	Secondary Efficacy Outcomes
	Period A: • PASI 75 response rates were statistically significantly higher in the adalimumab treatment group compared with placebo at Weeks 4, 8, and 12 using non-responder imputation ($p < 0.001$ at each visit; Fisher's Exact test). At Weeks 4, 8 and 12, 144 (18.9%), 440 (54.1%) and 551 (67.7%) of patients receiving adalimumab achieved $\geq$ PASI 75, respectively, compared to 5 (1.3%), 12 (3.0%) and 19 (4.8%) of patients in the placebo group[43]. • The proportions of subjects in the adalimumab treatment group achieving a PGA rating of clear or minimal were statistically significantly higher compared with placebo at Weeks 4, 8, 12, and 16 using non-responder imputation ($p < 0.001$ at each visit; Fisher's Exact test). At Weeks 4, 8, 12 and 16, 139 (17.1%), 389 (47.8%), 490 (60.2%) and 506 (62.2%) of patients in the adalimumab treatment arm achieved a PGA of clear or minimal, respectively, compared to 5 (1.3%), 9 (2.3%), 15 (3.8%) and 17 (4.3%) of patients in the placebo group[44]. • The response rates of subjects in the adalimumab treatment achieving PASI 50, as well as those achieving PASI 90, were statistically significantly higher compared with placebo at Weeks 4, 8, 12, and 16 using non-responder imputation ($p < 0.001$ at each visit; Fisher's Exact test). At Week 16, 671 (82.4%) of patients in the adalimumab treatment arm achieved $\geq$ PASI 50 response compared to 60 (15.1%) receiving placebo. Furthermore, at Week 16, 366 (45%) of patients receiving adalimumab achieved $\geq$ PASI 90 response compared to 7 (1.8%) in the placebo group[43]. • PASI 100 response rates in the adalimumab treatment group were statistically significantly higher compared with placebo at Weeks 8, 12, and 16 using non-responder imputation ($p < 0.001$ at each visit; Fisher's Exact test). At Weeks 4, 8, 12 and 16, 7 (0.9%; $p=0.285$), 58 (7.1%), 117 (14.4%) and 163 (20.0%) of patients in the adalimumab treatment arm achieved a PASI 100 response, respectively, compared to 1 (0.3%), 1 (0.3%), 1 (0.3%) and 3 (0.8%) receiving placebo[43]. • The proportions of subjects in the adalimumab treatment group achieving a DLQI total score = 0, i.e. no dermatology-specific impairment in quality of life, were statistically significantly greater compared with placebo at Weeks 4 and 16 using non-responder imputation ($p = 0.001$; Fisher's Exact test), with 73 (9.0%) and 258 (31.7%) of patients in the adalimumab treatment arm achieving a DLQI total score of 0 at Weeks 4 and 16, respectively, compared to 5 (1.3%) and 19 (4.8%) of subjects in the placebo group[59]. DLQI was not assessed at other study visits in Period A. • Subjects in the adalimumab treatment group demonstrated statistically significantly greater improvements in the mean changes from Baseline in the DLQI total scores compared to placebo at Weeks 4 and 16 using LOCF ($p < 0.001$). Patients in the adalimumab treatment group improved their mean DLQI score by 6.3 + 0.19 (+ SE) and 8.2 + 0.22 points from Baseline at Weeks 4 and 16, respectively, compared to 1.7 + 0.28 and 1.7 + 0.32 improvement for patients in the placebo arm[59]. • Subjects in the adalimumab treatment group demonstrated a statistically significantly greater improvement in the mean change from Baseline in the SF-36 PCS score compared with placebo at Week 16 using LOCF ($p < 0.001$). Subjects in the adalimumab treatment group also demonstrated statistically significantly greater improvements in the mean changes from Baseline the MCS score, and the scores of the eight scales of the SF-36 compared with placebo at Week 16 ($p < 0.001$ for all)[59].

Period B:

- During treatment with open-label adalimumab, PASI 75 response rates were maintained at Weeks 16, 24, and 33 in the majority of subjects originally randomised to either placebo or adalimumab, for example 89% of patients originally randomised to adalimumab achieved a ≥ PASI 75 response at Week 33[43]. PASI 90 response rates increased from Week 16 to Weeks 24 and 33 in subjects originally randomised to placebo, and were maintained in the majority of subjects originally randomised to adalimumab. Non-responder imputation was not used in this analysis.

- The proportions of subjects achieving a PGA rating of clear or minimal were increased at Weeks 16, 24, and 33 in subjects originally randomised to placebo, and were maintained in the majority of subjects originally randomised to adalimumab. [redacted][59].

- The proportions of subjects randomised to adalimumab in Period A who achieved a DLQI total score = 0 during period B increased from Week 16 to 33 [redacted][59].
  DLQI was not assessed at the Week 24 study visit.

- Improvements in the mean changes from Baseline in the SF-36 PCS and MCS scores, and the scores of the eight scales were observed at Week 33 in subjects originally randomised to placebo, and were maintained in subjects originally randomised to adalimumab. [redacted][59].

Period C:

- The time to loss of an adequate response was statistically significantly longer for subjects re-randomised to adalimumab compared with placebo using non-responder imputation (p = 0.001)[59].

- The time to loss of a PASI 75 response after Week 33 and on or before Week 52 was statistically significantly longer for subjects re-randomised to adalimumab compared with placebo (p < 0.001). Non-responder imputation was not used in this analysis. The median time to loss of a PASI 75 response was 134 days for subjects re-randomised to placebo, the median time to loss of a PASI 75 response was not observed in subjects re-randomised to adalimumab[59].

- The proportion of subjects achieving a PGA rating of clear or minimal was statistically significantly higher for subjects re-randomised to adalimumab compared with placebo at Weeks 40, 44, 48, and 52 using non-responder imputation (p = 0.041 at Week 40, and p < 0.001 thereafter; Fisher's Exact test). At Week 52, 170/250 (68.0%) of patients re-randomised to adalimumab had achieved a PGA of clear or minimal, compared to 67/240 (27.9%) of patients re-randomised to placebo[59].

- The proportions of patients achieving > PASI 50 and 90, or PASI 100 responses, at Week 52 were statistically significantly higher in subjects re-randomised to adalimumab than placebo (p<0.001 for all PASI responses; Fisher's Exact test). At Week 52, > PASI 50 and 90 response rates were reported in 218 (87.2%) and 134 (53.6%) of patients re-randomised to adalimumab, respectively, compared to 159 (66.3%) and 44 (18.3%) of patients receiving placebo. At Week 52, 80 (32.0%) of patients re-randomised to adalimumab had a PASI 100 response compared to 18 (17.5%) of patients who received placebo. Response rates were calculated following imputation of missing values as non-responders[59].

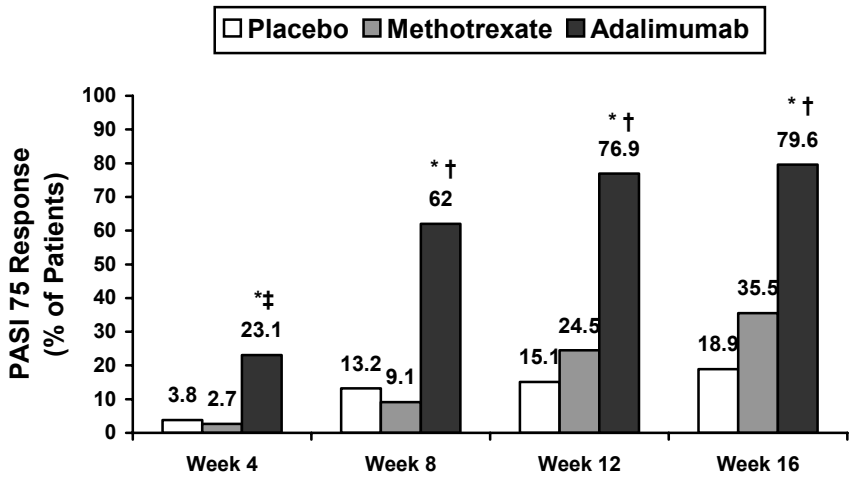
- The proportion of subjects achieving a DLQI = 0, i.e. no dermatology-specific impairment in quality of life, at Week 52 was statistically significantly higher in subjects re-randomised to adalimumab compared with placebo using non-responder imputation (p = 0.001), with 116 (46.4%) of patients re-randomised to adalimumab achieving a DLQI score of 0 at Week 52 in comparison to 31 (12.9%) of patients re-randomised to placebo[59].

- Subjects re-randomised to adalimumab demonstrated a statistically significantly greater mean improvement from Week 33 in the SF-36 PCS score at Week 52 compared with placebo using the LOCF approach (p = 0.002). Subjects re-randomised to adalimumab also demonstrated statistically significantly greater mean improvements from Week 33 in the SF-36 MCS score and scores of five of the eight scales (physical functioning, bodily pain, vitality, social functioning, and mental health) at Week 52 compared with placebo using the LOCF approach (p ≤ 0.017 for each scale)[59].

	Conclusions
	In this 52-week, pivotal phase III study consisting of three treatment periods (A, B and C), both the short-term (16 weeks) and long-term (52 weeks) clinical efficacy of adalimumab 40 mg eow sc was demonstrated by a reduction in the signs and symptoms of psoriasis as measured by the PASI score and PGA, and an improvement in the quality of life in subjects with moderate to severe chronic plaque Ps as measured by the DLQI and SF-36.

5.4.4 Study M04-716 (CHAMPION)[46, 47, 48, 49]

A total of 271 subjects were randomised in a 2:2:1 ratio to receive adalimumab (n=108), methotrexate (MTX) (n=110) or placebo (n=53). Of these 271 randomised patients, 256 completed the 16-week study [redacted]The 16-week study duration was considered by EMEA in their scientific advice to be adequate to assess the comparative efficacy of adalimumab and methotrexate and the dosing regimen for methotrexate is consistent with German guidelines on the use of methotrexate for psoriasis. A study by Heydendael *et al.* comparing MTX with ciclosporin in moderate to severe psoriasis patients over 16 weeks, started with a dose of MTX 15mg/week and increased after 4 weeks up to 22.5mg/week if there was less than a PASI 25 response.[65] After 16 weeks the PASI 75 response rate was 60%, however, there was no non-responder imputation, 28% of subjects discontinued the study due to LFT abnormalities, and 44% had nausea – this suggests that the methotrexate regimen was too aggressive from a dosage standpoint in this study. The Summary of Product Characteristics (SmPC) for methotrexate as a treatment of psoriasis suggests a 5-10mg test dose should be administered to identify and idiosyncratic adverse reactions, and then subsequently 10-25mg orally once a week should be given adjusted by the patient's response, which is in accordance with the MTX dosing regimen used in CHAMPION. The first subject was enrolled on 12 July 2005 and randomised on 27 July 2005. The last subject's final visit occurred on 17 May 2006.

M04-716	**Primary Efficacy Outcome**
	The primary outcome of study M04-716 (CHAMPION) was the proportion of subjects achieving clinical response, defined as at least a 75% reduction in PASI score, at Week 16 relative to the Baseline PASI score. At Week 16, 80% of subjects in the adalimumab treatment arm had achieved ≥ PASI 75 compared to 36% of patients receiving methotrexate and 19% of patients administered placebo (p<0.001, vs. both placebo and methotrexate) (see Figure 5.4.4.1)[46, 48, 49]. **Figure 5.4.4.1: Proportion of Subjects with ≥ PASI 75 Response Rates at Weeks 4, 8, 12, and 16 (ITT Analysis Set)**  ‡p=0.001, †p<0.001, both adalimumab and MTX vs. placebo; *p<0.001 adalimumab vs. MTX.

	Secondary Efficacy Outcomes
	• The proportions of subjects with a PGA rating of clear or minimal were higher in the adalimumab treatment group than in the placebo and MTX treatment groups from Week 4 through to Week 16. At Week 16, 73.1% of subjects in the adalimumab treatment group achieved a PGA rating of clear or minimal compared to 30.0% and 11.3% of subjects in the MTX and placebo treatment groups, respectively ($p<0.001$ at Weeks 12 and 16 for both adalimumab vs. placebo and adalimumab vs. MTX)[46]. • The proportions of subjects achieving $\geq$ PASI 75 response at Weeks 4,8 and 12 are presented in Figure 5.4.4.1 ($p<0.001$ for adalimumab vs. MTX at Weeks 4, 8 and 12; $p=0.001$ for adalimumab vs. placebo at Week 4, and thereafter $p<0.001$). • The proportions of patients achieving $\geq$ PASI 50 and $\geq$ PASI 90 response at Week 16 were statistically significantly greater in the adalimumab treatment arm than the methotrexate or placebo group ($p<0.001$; Fisher's Exact test), with 88% of patients in the adalimumab group achieving at least a PASI 50 response at Week 16, compared to 61.8% of patients receiving MTX and 30.2% of patients on placebo; and 51.9% of patients in the adalimumab treatment arm achieving at least a PASI 90 response at Week 16, compared to 13.6% and 11.3% of patients receiving MTX and placebo, respectively. PASI 100 response rates were higher in the adalimumab treatment group than in the placebo and MTX treatment groups at Weeks 12 and 8, respectively, through to Week 16[47, 49]. • The proportions of adalimumab-treated subjects with a DLQI total score = 0, i.e. no dermatology-specific impairment in quality of life, were statistically significantly higher compared with placebo-treated subjects at Week 12 ($p<0.001$) and Week 16 ($p<0.001$). At Week 16, the percentages of patients achieving a DLQI score of 0 were 33.3%, 21.8% and 5.7% for the adalimumab, MTX and placebo groups, respectively[49]. • Adalimumab-treated subjects demonstrated greater improvements in mean change from Baseline in their DLQI scores at Weeks 12 and 16 compared with placebo- and MTX-treated subjects ($p<0.001$ at Weeks 12 and 16 for both adalimumab vs. placebo and adalimumab vs. MTX). At Week 16, the mean change $\pm$ SD in DLQI from Baseline was -9.03 ± 6.68 for patients in the adalimumab treatment arm and -3.09 ± 6.00 and -5.35 ± 5.29 for subjects receiving placebo and methotrexate, respectively[49]. • At Week 16, the percentages of patients reporting good or complete disease severity control were 79%/57%/25% for patients treated with adalimumab/methotrexate/placebo ($p<0.001$ for all comparisons), respectively[47]. • Adalimumab patients achieved statistically significantly better mean EQ-5D Index scores vs. patients who received methotrexate and patients who received placebo, with patients in the adalimumab treatment arm achieving a mean EQ-5D score at Week 16 of 0.9 compared to 0.85 and 0.79 scores for patients given methotrexate and placebo, respectively ($p=0.004$ for adalimumab vs. MTX; $p=0.02$ for adalimumab vs. placebo). In addition, patients in the adalimumab treatment group achieved statistically significantly better mean EQ-5D VAS scores compared to patients receiving methotrexate or placebo ($p=0.004$ for adalimumab vs. MTX; $p<0.001$ for adalimumab vs. placebo)[48]. • Patients in the adalimumab treatment group achieved statistically significantly superior pain control compared with either MTX-treated patients or placebo-treated patients. At Week 16, the mean absolute improvements in Ps/PsA pain from Baseline was 25 points for patients in the adalimumab treatment group (Baseline score = 38), 10 points for MTX-treated patients (Baseline score = 37) and -3 for patients given placebo (Baseline score = 38) ($p<0.001$ for adalimumab vs. both MTX and placebo)[47]. • At Week 16, patients receiving adalimumab also achieved statistically significantly superior control of psoriasis-related pruritus. Patients given adalimumab demonstrated a mean percentage improvement of 70% from Baseline compared to 47% and 11% for patients administered MTX and placebo, respectively ($p<0.001$, adalimumab vs. placebo; $p=0.018$, adalimumab vs. methotrexate)[47].
	Post-hoc Sub-group Analysis – patients with Baseline BSA > 20% and/or Baseline PASI > 20

A post-hoc subgroup analysis of subjects participating in M04-716 who had greater than 20% body surface area (BSA) coverage of psoriasis and/or a Baseline PASI score of greater than 20 was performed to assess the efficacy of adalimumab in this more severe patient population (imputation of missing values as non-responders; ITT Analysis Set). Table 5.4.4.1 shows the PASI 50, PASI 75, PASI 90 and PASI 100 responses at Week 16 for this sub-group of patients receiving adalimumab, methotrexate or placebo.

Table 5.4.4.1: Proportion of subjects with Baseline BSA > 20% and/or Baseline PASI > 20 achieving PASI 50/ 75/ 90 and 100 Response Rates at Week 16 of M04-716 (ITT Analysis Set)

PASI	Treatment	N	Responder n (%)	Risk Difference	CI 95%*	P Value**
PASI 50	Placebo	32	10 (31.3)	0.608	(0.436, 0.779)	<0.001
	Methotrexate	69	43 (62.3)	0.297	(0.167, 0.427)	<0.001
	Adalimumab	75	69 (92.0)	-	-	-
PASI 75	Placebo	32	8 (25.0)	0.590	(0.419, 0.761)	<0.001
	Methotrexate	69	25 (36.2)	0.478	(0.337, 0.618)	<0.001
	Adalimumab	75	63 (84.0)	-	-	-
PASI 90	Placebo	32	4 (12.5)	0.462	(0.302, 0.622)	<0.001
	Methotrexate	69	11 (15.9)	0.427	(0.286, 0.568)	<0.001
	Adalimumab	75	44 (58.7)	-	-	-
PASI 100	Placebo	32	0	0.173	(0.088, 0.259)	0.009
	Methotrexate	69	6 (8.7)	0.086	(-0.022, 0.195)	0.145
	Adalimumab	75	13 (17.3)	-		-

* Based on the normal approximation of the binomial distribution
** Fisher's Exact test

Conclusions

The efficacy results from the M04-716 study demonstrate that adalimumab is an effective treatment for patients with moderate to severe psoriasis who are candidates for systemic or phototherapy. Adalimumab reduces the signs and symptoms of Ps, as measured by PASI 50, 75, 90 and 100 response rates, and improves the QoL in adults with moderate to severe chronic plaque psoriasis, as measured by the DLQI and the EQ-5D. This study demonstrates a favourable benefit-risk ratio for adalimumab in the treatment of moderate to severe psoriasis patients, both with respect to the comparison to placebo as well as the comparison to methotrexate as a conventional systemic therapy option for this condition. As adalimumab is the first biologic agent to demonstrate superiority to a traditional systemic agent for psoriasis, it is the logical biological choice for psoriasis patients who fail systemic therapy.

5.4.5 Study M02-529[33, 61]

Of the 147 subjects who received at least one dose of study drug in the lead-in study, M02-528, 137 entered the 12 week-blinded blinded period (Week 0 -12) and 132 entered the open-label period of this continuation study (refer to Section 5.3.3 for the flow-chart of patient disposition throughout the study). As study M02-529 was a continuation study of the lead-in study, screening had already occurred, thus the first enrolled subject was screened for M02-528 on 11 March 2003 and the last subject's final M02-529 study visit occurred on 17 June 2004.

M02-529

Primary Efficacy Outcome

The primary efficacy endpoint was the proportion of subjects achieving at least a PASI 75 response score relative to the Baseline value of the lead-in study M02-528 at Week 12 of M02-529 (i.e. Week 24 of M02-528). Figure 5.4.5.1 below shows the proportion of patients achieving $\geq$ PASI 75 response at Weeks 0, 12, 24 and 48. At Week 12, the $\geq$ PASI 75 response achieved by patients treated with placebo in M02-528 who began adalimumab (40 mg eow) at Week 0 in M02-529 was similar to the response achieved by the active-treatment 40-mg eow group at Week 12 of M02-528[33]. At Week 12, 55%, 67% and 77% of patients in the placebo/40 mg adalimumab eow, 40mg adalimumab eow and 40mg adalimumab weekly groups achieved $\geq$ PASI 75 response, respectively[33].

Secondary Efficacy Outcomes

Patients treated with adalimumab consistently experienced improvements in secondary efficacy variables.

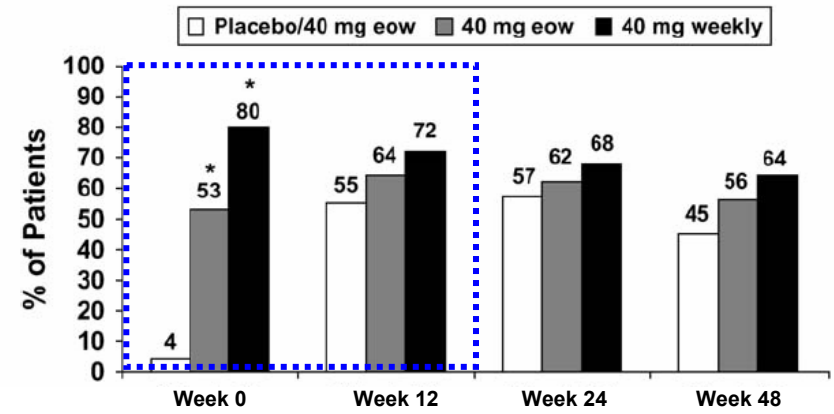
- For patients in the adalimumab eow and weekly arms, PASI 50 rates were 76% and 88% at Week 0 and 64% and 66% at Week 48, respectively. At Weeks 0 and 48, PASI 90 rates in these groups were 24% and 48% and 33% and 48%, respectively. Figure 5.4.5.1 illustrates the proportion of subjects achieving ≥ PASI 75 at Weeks 12, 24 and 48[33].

- The percentages of patients with PGA of clear or almost clear in the eow and weekly arms were 49% and 76% at Week 0 and 44% and 52% at Week 48, respectively[33].

- By Week 12, patients in the placebo/ adalimumab eow arm and the adalimumab eow arm had similar outcomes. For the former and latter arms, PASI 50 rates at Week 12 were 77% and 73%, percentages of patients with PGA of clear or almost clear were 45% and 64%, and 90% improvement in PASI rates were 32% and 42%, respectively[33].

- At Week 0, 11% of patients taking 40 mg of adalimumab eow and 26% of patients taking 40 mg/weekly of adalimumab achieved PASI 100 (p<0.001 vs. placebo), which was also sustained through to Week 48. At Week 12, the patients in the placebo/ eow group had a PASI 100 rate of 11%, compared with 13% for patients in the eow group[33].

Figure 5.4.5.1: Proportion of subjects achieving ≥ PASI 75 at Weeks 12, 24 and 48 in M02-529[33]



= blinded period

* p<0.001 vs. placebo.

Patients with missing scores were considered non-responders. Figure from Gordon et al 2006[33]. Note, Week 0 in Figure 5.4.5.1 corresponds to Week 12 of M02-528.

- Mean improvements in DLQI for the adalimumab eow and weekly groups demonstrated in the lead-in study M02-528, were maintained throughout the blinded period of M02-529 and the following 24 and 48 weeks of adalimumab treatment, a statistically significant improvement in change in DLQI from Baseline to Week 24 and to Week 48 was observed for all treatment groups[61].

- Upon analysis of the change from Baseline at Week 12 in SF-36 score by treatment group, subjects who received adalimumab 40 mg eow achieved statistically significant improvement (increase in score) in four of the eight domains of the SF-36, and subjects who received adalimumab 40 mg weekly achieved statistically significant improvement in seven of the eight domains of the SF-36 after receiving adalimumab treatment for 24 weeks (Week 12). Furthermore, all the treatment groups experienced a mean improvement from Baseline at Weeks 24 and 48 in the PCS and in the MCS of the SF-36[61].

- Statistically significant improvement (increase in score) in the EQ-5D Index from Baseline to Week 12 was demonstrated by subjects in all treatment groups with respect to change from M02-528 Baseline. The improvement in the EQ-5D Index was maintained through to Week 48 by subjects in all treatment groups[61].

Conclusions

The results of this study demonstrate that long-term treatment (up to 60 weeks) with adalimumab 40 mg eow or 40 mg weekly is highly effective and improves the quality of life of adult subjects with moderate to severe chronic plaque psoriasis.

5.4.6 Study M03-596[62]

The purpose of M03-596, which is an extension study of M02-538, was to determine whether those subjects who had achieved a PASI 50 response during the open-label portion (Weeks

0-11) of M02-538, and who experienced a relapse (<PASI 50 response) during the double-blind portion of M02-538 (Weeks 12-24), could achieve again a PASI 75 response if they received the identical dosing regimen that had been administered during M02-538. A total of 32 subjects, who were randomised and then relapsed on or before Week 24 of Study M02-538, participated in the open-label period of this study, during which they received loading doses of adalimumab 80 mg at Week 0 and at Week 1 followed by adalimumab 40 mg weekly from Week 2 to Week 11. Of these subjects, 8 discontinued the study in the open-label period. Twenty four subjects who had a ≥ PASI 50 response at Week 12 continued to participate in the double-blind period, during which they received either placebo or adalimumab 40 mg eow according to their randomised assignment in Study M02-538. A total of 15 subjects completed Study M03-596. The first subject's Screening visit occurred on 4 November 2003 the last subject's final study visit occurred on 2 September 2004.

M03-596	**Primary Efficacy Outcome**
	The majority of subjects (81.3%) achieved a ≥ PASI 50 response following 12 weeks of re-treatment with open-label adalimumab. No statistically significant difference was observed between treatment groups (subjects previously treated with either placebo or adalimumab 40 mg eow in the lead-in study, Study M02-538). However, a greater proportion of subjects previously treated with adalimumab 40 mg eow in Study M02-538 achieved a ≥ PASI 50 response following 12 weeks of retreatment with adalimumab 40 mg eow compared to subjects who previously received placebo (90.9% *vs.* 76.2%, respectively)[62].
	Secondary Efficacy Outcomes
	Secondary efficacy variables analysed in this study focused on clinical response (PASI response rates) and time to relapse from Week 12 to Week 24 in subjects who had achieved at least a PASI 50 response at Week 12[62]. <u>Relapse from Week 0 to Week 12 among subjects who had at least a PASI 50 response at Week 12 (n=24):</u> • A greater proportion of subjects from the adalimumab weekly/placebo treatment group experienced relapse at all visits after Week 12 than did subjects from the adalimumab weekly/adalimumab eow treatment group (43.8% *vs.* 37.5%, respectively). All early dropouts reached relapse. • For the time period beginning after Week 12 through to Week 24, subjects in the adalimumab weekly/adalimumab eow treatment group had a lower risk of relapse compared to placebo group; the risk of relapse in 40 mg eow treatment group was reduced by 57% compared to subjects in the adalimumab weekly/placebo treatment group (risk ratio 0.43; p = 0.2858; 95% CI: 0.09, 2.05). <u>Clinical response from Week 0 to Week 12 – all subjects (n=32):</u> • A greater proportion of subjects previously treated with adalimumab eow in M02-538 achieved a ≥ PASI 50/ 75/ 90 response than subjects previously treated with placebo in M02-538 (90.9%/ 72.7%/ 18.2% *vs.* 76.2%/ 38.1%/ 14.3%, respectively). No statistically significant difference was observed in the number (%) of subjects with a ≥ PASI 50/75/90 response at Week 12. • At Week 12, 25.0% of all subjects retreated with open-label adalimumab achieved PGA of clear/almost clear. • Subjects previously treated with open-label adalimumab followed by adalimumab eow required less time to achieve response: a statistically significantly difference in favour of adalimumab weekly/adalimumab eow for time to ≥ PASI 75 response was observed (median: 57 days *vs.* 86 days, respectively; p = 0.0494). In short, subjects who received continuous active treatment in both Study M02-538 and this study required a shorter time to response than subjects who took placebo after open-label adalimumab treatment in M02-538.
	Conclusions
	The results of this study demonstrate that adalimumab is effective in subjects with moderate to severe chronic plaque psoriasis who were retreated with adalimumab after loss of clinical response (< PASI 50 response) following adalimumab dose decrease or withdrawal. Furthermore, continuous dosing with adalimumab (open-label followed by dose decrease) was more effective than open-label adalimumab followed by placebo in terms of maintenance or regain of treatment response.

5.4.7 Study M03-658[55, 63]

As of 29 June 2006, [redacted] subjects had received at least one dose of adalimumab in study M03-658, the open-label extension trial evaluating the long-term safety and efficacy of adalimumab in patients with moderate to severe plaque psoriasis. Subjects entering study M03-658 had all participated in the preceding studies M02-528, M02-529, M02-538, M03-656 (REVEAL) and M04-716 (CHAMPION) which began and finished at quite different timepoints, as such, entry into this study varied significantly. For example, some subjects from the earlier phase II studies will have been enrolled in this study considerably longer than those patients who participated in either of the phase III studies, REVEAL or CHAMPION.

PASI response rates from the [redacted] subjects who had received at least 48 weeks of treatment with 40mg adalimumab eow are presented in tabular form below. In addition, data from subjects who took part in the phase II studies M02-528 and M02-529, who provide the most extensive long-term efficacy and safety data equating to over 120 weeks of continuous treatment with 40mg adalimumab eow, are also presented below. Of the 92 patients in the phase II studies who received at least one dose of adalimumab in the 40mg eow dosing regimen, 49 had evaluations up to Week 120. At the time of the analysis, 12 patients had discontinued the study; the remaining subjects had yet to be evaluated. Because this is an ongoing study and there is incomplete ascertainment of efficacy outcomes for all patients who had received adalimumab eow dosing in M02-528/529, this interim 120-week efficacy analysis was conducted as observed.

M03-658

48-Week Data

PASI 50, 75, 90 and 100 response rates for the [redacted] patients who had received 48 weeks treatment of 40mg adalimumab eow are shown in Table 5.4.7.1. PASI response rates in these subjects are similar to those reported following 12 Weeks of 40mg adalimumab eow treatment.

Table 5.4.7.1: PASI 50, 75, 90 and 100 response rates following 48 weeks of 40mg adalimumab eow[63]

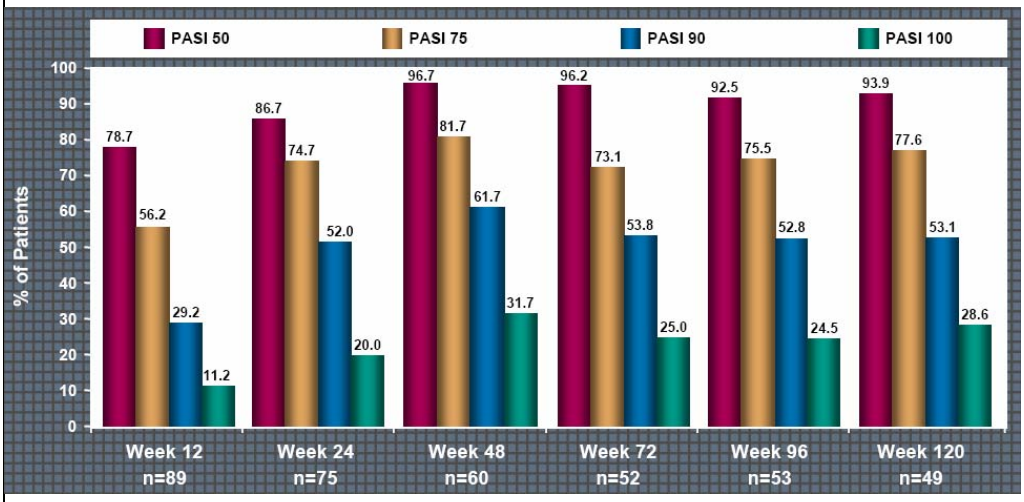
N = [redacted] n (%)	PASI 50 Responder	PASI 75 Responder	PASI 90 Responder	PASI 100 Responder
Week 48	[redacted]	[redacted]	[redacted]	[redacted]

Note: Response was derived using the percent change from the last evaluation prior to the first study drug administration (placebo or adalimumab) in Studies M02-528, M03-656 or M04-716.

120-Week Data

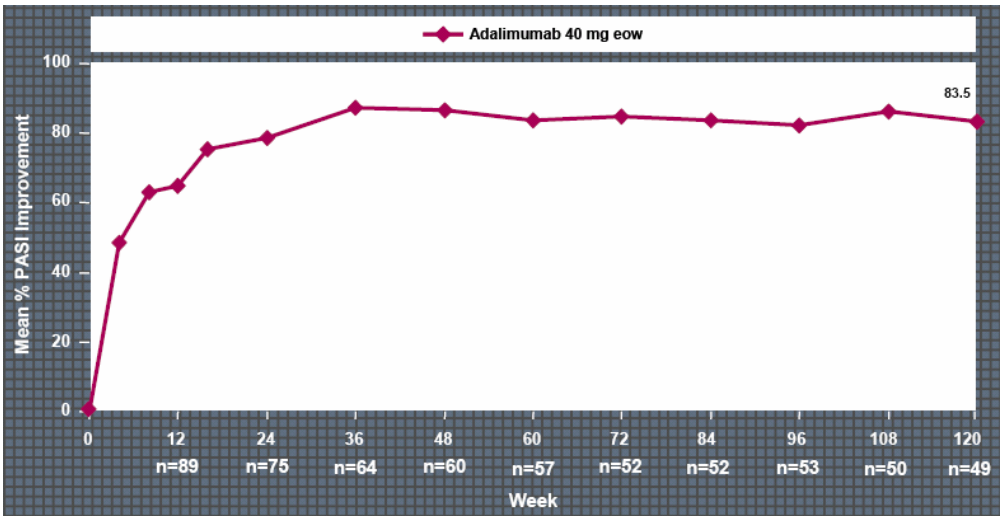
Figure 5.4.7.1 shows the PASI 50, 75, 90 and 100 response rates from Week 12 through to Week 120 in subjects participating in M03-658 who had taken part in the phase II studies M02-528 and M02-529. Among patients who continued to receive adalimumab 40 mg eow, PASI responses peaked at Week 48 and were generally maintained up to Week 120 of adalimumab therapy[55].

Figure 5.4.7.1: PASI 50, 75, 90 and 100 responses rates up to Week 120



Among patients who continued to receive adalimumab 40 mg eow, mean percentage PASI improvement peaked at Week 36 and was generally maintained to Week 120. Figure 5.4.7.2 shows the mean percentage PASI improvement from Baseline (baseline of M02-528) up to Week 120[55].

Figure 5.4.7.2: Mean Percentage PASI Improvement up to Week 120[55]



Conclusions

Patients with moderate to severe psoriasis achieved sustained efficacy up to Week 120 of treatment with adalimumab.

Overall Efficacy Conclusions

The five trials M02-528, M02-529, M03-656 (REVEAL), M04-716 (CHAMPION) and M03-658 form the evidence base for the efficacy of adalimumab in the treatment of moderate to severe plaque psoriasis. Studies M02-538 and M03-596 were also conducted as part of the psoriasis development programme, but the treatment regimen was different from that used in the five studies aforementioned, and data from these trials were not included in the evidence base demonstrating the efficacy of adalimumab for the EMEA submission. In the regulatory filing, no claim for efficacy was intended based on these two studies. These two studies have been included in this section because they are RCTs and provide data on time to relapse in

patients who had dose reduction or treatment withdrawal and also provided data concerning re-treatment with adalimumab in patients who had relapsed following dose reduction or treatment withdrawal.

The five trials mentioned above provide robust evidence demonstrating the short- and long-term efficacy of adalimumab in a large patient population. The trials have shown that adalimumab (40mg eow) successfully improves the signs and symptoms of Ps, yielding statistically significant improvements in:

- The signs and symptoms of Ps in patients with chronic plaque psoriasis - measured by the PASI 50, 75, 90 and 100 response rates and the Physician Global Assessment of Disease (PGA).

- The signs and symptoms of Ps in patients with chronic plaque psoriasis in a direct head-to-head comparison vs. methotrexate – as measured by the PASI 75 response as well as by secondary efficacy variables and patient reported outcomes.

- The quality of life of patients with Ps – measured by the DLQI, EQ-5D and SF-36.

Furthermore, data from 120 weeks of continuous 40mg adalimumab eow demonstrates that clinical response is maintained in the long-term.

5.5 Meta-analysis

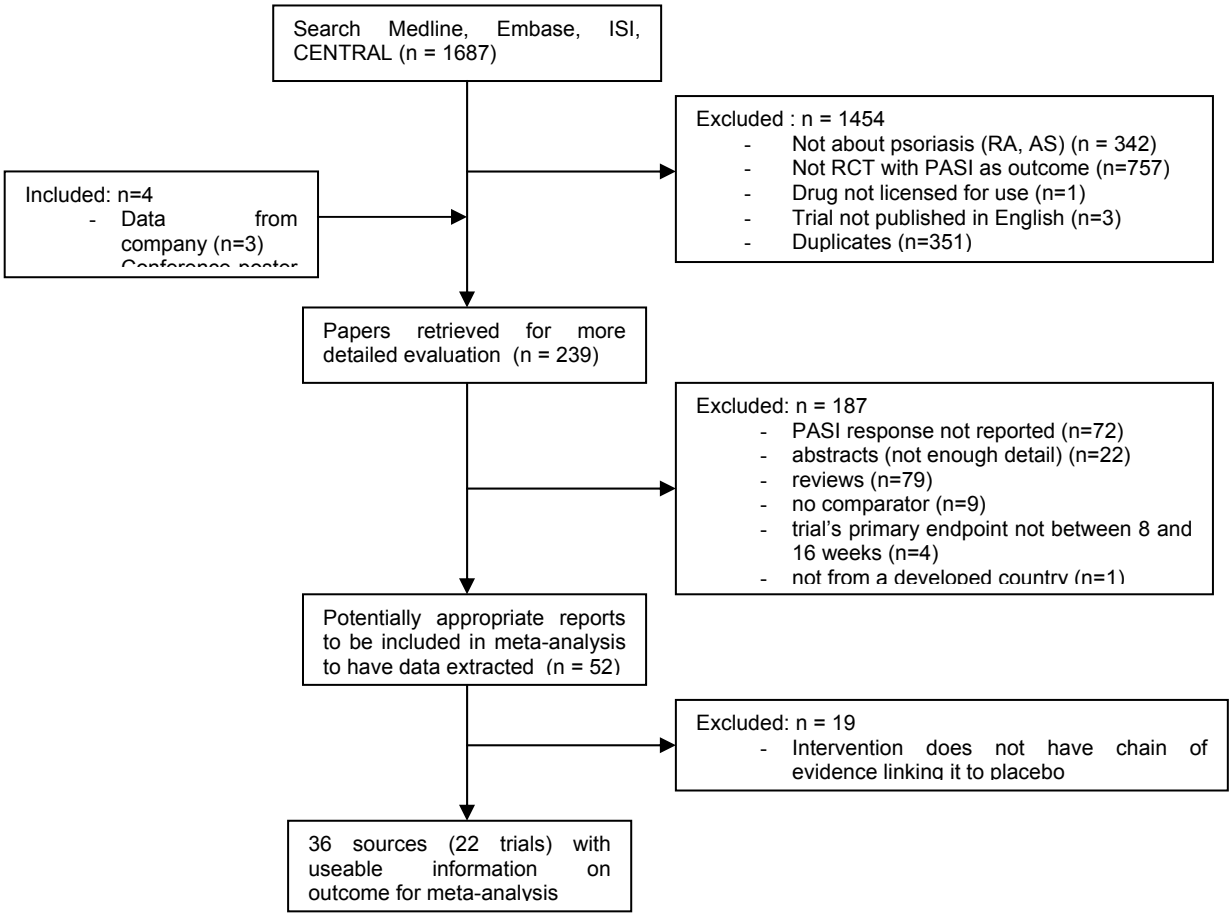
A meta-analysis was not conducted as Section 5.6 contains a mixed treatment comparison.

5.6 Indirect/mixed treatment comparisons

The evidence used for a mixed treatment comparison of the efficacy of systemic treatments efficacy in moderate-to-severe psoriasis was collected by a systematic search of the medical literature. Searches were undertaken with MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and ISI Science and Technology Proceedings (Web of Knowledge – http://wos.mimas.ac.uk) from their inception dates to September 2006. The search was supplemented with hand searching after the original systematic search. In addition, data from unpublished trials were used.

Only randomised controlled trials (RCTs) of patients with moderate-to-severe psoriasis were included. Trials had to have a primary endpoint of between 8 and 16 weeks, and to have taken place in a developed country. The patients must have inadequately responded to topical treatments alone and had received prior systemic therapy or phototherapy, or were candidates for such treatment. Trials must have also reported at least one of the PASI response values. All potential treatments for psoriasis with FDA or EMEA approval were initially considered eligible. This included the biologics (adalimumab, alefacept, efalizumab, etanercept, infliximab), non-biologic systemics (retinoids, methotrexate, ciclosporin) and other forms of therapy (phototherapy, combination therapy). Although adalimumab is not yet licensed at time of analysis, it has been included. Clinical trial data on adalimumab was supplemented to the results.

Figure 5.6.1: Literature search tree



The search identified 52 distinct RCTs providing evidence on the efficacy of 12 drugs (etanercept, infliximab, adalimumab, efalizumab, alefacept, ciclosporin, methotrexate, calcipotriol cream and PUVA, UVB phototherapy (narrowband and broadband), hydroxyurea, calcipotriol, and placebo). A majority of studies compared treatment to placebo, and not an active comparator. For the purposes of the analysis in comparing the cost-effectiveness of treatments for psoriasis, it is important to have estimates of the relative effects of each treatment. Standard meta-analytic techniques are unable to incorporate indirect comparisons, therefore the analysis utilised a mixed treatment comparison approach[66] within a Bayesian evidence synthesis framework[67].

Briefly, this approach links each treatment together through a link to placebo, either through direct comparison or through comparison with any other active agent compared to placebo. Some 19 papers were excluded because they could not be linked to placebo. Of the 22 trials (36 sources) that were finally used in the evidence synthesis, a majority (95%) compared a treatment to a placebo regimen. Only two included trials compared treatment to an active comparator, in this case, methotrexate (ciclosporin vs. methotrexate[65], and adalimumab vs. methotrexate [Champion]). A meta-analysis is then used to determine the average probability of each treatment achieving PASI response based on all the observed comparisons, having adjusted for variation in placebo response rates. This analysis used the methodology as set out by Woolacott et al[4].

The final analysis examined only treatments and dose regimens that are licensed and recommended for use in psoriasis patients in the UK. For example, two of the efalizumab trials administered efalizumab 1mg/kg (the licensed dose) as well as 2mg/kg (not licensed). In this case, only the 1mg/kg dose is estimated in the analysis. The treatments and dose regimens included in the final model are:

- Etanercept – 25mg twice weekly

- Etanercept High – 50mg twice weekly
- Efalizumab – 1mg/kg per week
- Infliximab – 5mg/kg weeks 0,2, and 6, and every 8 weeks thereafter
- Adalimumab – 40 mg every other week
- Ciclosporin – 3mg/kg per day*
- Methotrexate – varied dose daily (oral)

* Greater than 3mg/kg per day was determined to be related to high toxicities (personal communication S. Feldman, MD)

A list of studies included in the final analysis is given in Table 5.6.1.

Table 5.6.1: Studies included in the evidence synthesis

AUTHOR (YEAR)	COMPARATOR AND DOSE	N	AGE	% MALE	PS DUR (YRS)	BSA %	BASE PASI	PASI 50	PASI 75	PASI 90	END POINT (WKS)†
Papp, KA et. al. (2005) [68] (CONSORT)	Placebo	193	44	64%	18	20	16	9%	3%	1%	12
	Etanercept 25 mg BIW	196	46	65%	22	23	16.9	64%	34%	11%	
	Etanercept 50 mg BIW	194	45	67%	18	25	16.1	77%	49%	21%	
Gottlieb, AB et al. (2003) [69]	Placebo	55	47	67%	20	34	19.5	11%	2%	0%	12
	Etanercept 25 mg BIW	57	48	58%	23	30	17.8	70%	30%	11%	
Leonardi, CI, et al. (2003) [70]	Placebo	166	46	63%	18	29	18.3	14%	4%	1%	12
	Etanercept 25 mg OW	160	44	74%	19	28	18.2	41%	14%	3%	
	Etanercept 25 mg BIW	162	45	67%	19	29	18.5	58%	34%	12%	
	Etanercept 50 mg BIW	164	45	65%	19	30	18.4	74%	49%	22%	
Tyring, S, et al. (2006) [71]	Placebo	307	46	70%	20	27	18.1	14%	5%	1%	12
	Etanercept 50 mg BIW	311	46	65%	20	27	18.3	74%	47%	21%	
Gottlieb, AB et al. (2004) [72] (SPIRIT)	Placebo	51	45	61%	16	26	18	22%	6%	2%	10
	Infliximab 3mg/kg	99	45	71%	18	29	20	84%	72%	45%	
	Infliximab 5 mg/kg	99	44	74%	16	25	20	97%	88%	58%	
Reich, K et. Al. (2005) [73] (EXPRESS I)	Placebo	77	44	79%	17	34	22.8	8%	3%	1%	10
	Infliximab 5 mg/kg	301	43	69%	19	34	22.9	91%	80%	57%	
Chaudhari, U, et al (2001) [74] *	Placebo	11	45	73%	-	-	20.3	18%	18%	-	10
	Infliximab 5 mg/kg	11	51	64%	-	-	22.1	82%	82%	-	
	Infliximab 10 mg/kg	11	35	100%	-	-	26.6	91%	73%	-	
Menter, A, et al (2007) [75] (EXPRESS II)	Placebo	208	44	69%	18	28	19.8	-	2%	1%	10
	Infliximab 3 mg/kg	313	43	66%	18	28	20.1	-	70%	37%	
	Infliximab 5 mg/kg	314	45	65%	19	29	20.4	-	76%	45%	
Gordon, KB et al (2006) [33]	Placebo	52	43	65%	19	28	16	14%	4%	0%	12
	Adalimumab 40 mg EOW	45	46	71%	21	29	16.7	76%	53%	24%	
	Adalimumab 40 mg OW	50	44	66%	18	25	14.5	88%	80%	48%	
Saurat, J et al. (2006) [46] (CHAMPION)	Placebo	53	41	66%	19	28	19.2	30%	19%	11%	16
	Adalimumab 40 mg EOW	108	43	65%	18	34	20.2	88%	80%	52%	
	Methotrexate	110	42	66%	19	32	19.4	62%	36%	14%	
Abbott (2006) [42] (REVEAL)	Placebo	398	45	65%	19	26	19.01	15%	7%	2%	16
	Adalimumab 40 mg EOW	814	44	67%	19	26	18.83	83%	71%	45%	
Gordon (2003) [76]	Placebo	187	45	71%	19	27	19	14%	4%	1%	12
	Efalizumab 1 mg/kg OW	369	45	68%	19	28	19	59%	27%	5%	
Dubertret L, et al. (2006) [77] (CLEAR)	Placebo	264	45	67%	21	36	23	14%	4%	-	12
	Efalizumab 1 mg/kg OW	529	44	67%	19	37	23.6	54%	31%	-	
Papp, KA et. al. (2006) [78]	Placebo	236	46	59%	18	27	18.69	14%	3%	-	12
	Efalizumab 1 mg/kg OW	450	46	67%	18	28	19.14	52%	26%	-	

Leonardi et al. (2005) [79]	Placebo	170	42	73%	19	29	19	15%	2%	1%	12
	Efalizumab 1 mg/kg OW	162	45	73%	19	30	18.6	61%	39%	12%	
	Efalizumab 2 mg/kg OW	166	46	71%	17	30	18.9	51%	27%	5%	
Lebwohl et al. (2003) [80]	Placebo	122	-	-	-	-	-	16%	5%	1%	12
	Efalizumab 1mg/kg OW	232	-	-	-	-	-	52%	22%	4%	
	Efalizumab 2 mg/kg OW	243	-	-	-	-	-	57%	28%	6%	
Meffert (1997) [81]	Placebo	43	38†	64†	-	-	15.6	10%	5%	-	10
	Ciclosporin 1.25 mg/kg/day	41	38†	64†	-	-	16.7	21%	10%	-	
	Ciclosporin 2.5mg/kg/day	44	38†	64†	-	-	15.1	58%	29%	-	
Heydendael (2003) [17]	Methotrexate	43	41.6	65%	-	-	13.4	-	60%	40%	16
	Ciclosporin 3-5 mg/kg/day	42	38.3	69%	-	-	14	-	71%	33%	

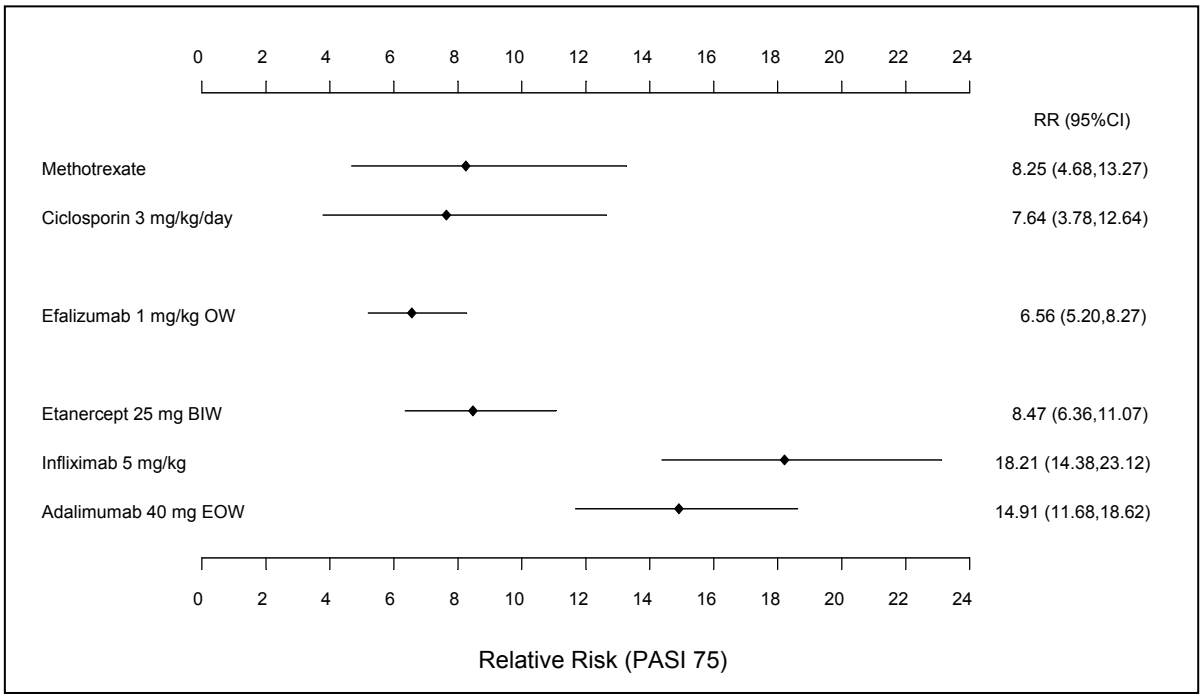
† Where possible, the endpoint that matches the trial period was chosen. However this was limited to what endpoints were measured in each trial. For example, there were no assessments from a 14-week endpoint for infliximab, which is specified as the time to assess response in its European label.
BIW = twice weekly, EOW = every other week, OW = once weekly

The results of the evidence synthesis are shown in Table 5.6.2. The synthesis shows that the probability of PASI response was greater for either infliximab or adalimumab in comparison to both doses of etanercept by a statistically significant margin. Both doses of etanercept gave higher probabilities of PASI response compared to efalizumab and the non-biologic systemics.

Table 5.6.2: Results of evidence synthesis

Treatment	Probability of a Response			Relative Risks		
	Mean	2.50%	97.50%	Mean	2.50%	97.50%
PASI 50 Response						
Supportive Care	15%	12%	17%	1.00	1.00	1.00
Etanercept 50 mg BIW	75%	67%	82%	5.21	4.42	6.18
Etanercept 25 mg BIW	63%	53%	71%	4.34	3.60	5.22
Efalizumab 1 mg/kg	54%	47%	60%	3.72	3.15	4.38
Infliximab 5 mg/kg	94%	90%	96%	6.49	5.45	7.70
Methotrexate	61%	45%	78%	4.24	2.96	5.72
Ciclosporin 5 mg/kg/day	76%	54%	93%	5.30	3.50	6.98
Ciclosporin 3 mg/kg/day	58%	39%	76%	4.04	2.59	5.58
Adalimumab 40 mg EOW	86%	80%	90%	5.93	4.98	6.95
PASI 75 Response						
Supportive Care	5%	4%	6%	1.00	1.00	1.00
Etanercept 50 mg BIW	52%	43%	60%	11.60	9.16	14.78
Etanercept 25 mg BIW	38%	29%	47%	8.47	6.36	11.07
Efalizumab 1 mg/kg	29%	24%	35%	6.56	5.20	8.27
Infliximab 5 mg/kg	81%	75%	87%	18.21	14.38	23.12
Methotrexate	37%	22%	55%	8.25	4.68	13.27
Ciclosporin 5 mg/kg/day	55%	29%	79%	12.29	6.07	19.49
Ciclosporin 3 mg/kg/day	34%	18%	53%	7.64	3.78	12.64
Adalimumab 40 mg EOW	67%	57%	74%	14.91	11.68	18.62
PASI 90 Response						
Supportive Care	1%	0%	1%	1.00	1.00	1.00
Etanercept 50 mg BIW	24%	17%	31%	34.80	24.48	49.44
Etanercept 25 mg BIW	14%	9%	20%	20.83	13.64	30.91
Efalizumab 1 mg/kg	10%	7%	13%	13.97	9.98	19.32
Infliximab 5 mg/kg	55%	46%	64%	81.17	57.82	114.70
Methotrexate	14%	6%	26%	20.62	8.59	41.97
Ciclosporin 5 mg/kg/day	27%	9%	51%	40.45	12.69	84.39
Ciclosporin 3 mg/kg/day	12%	5%	24%	18.31	6.24	38.77
Adalimumab 40 mg EOW	37%	28%	45%	54.40	37.92	75.43

Figure 5.6.2: Estimates of the relative risk of PASI 75 response from evidence synthesis



5.7 Safety

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

5.7.1 Safety Overview

The safety of adalimumab in psoriasis was determined through an evaluation of Adverse Events (AEs), Serious Adverse Events (SAEs), anti-TNF AEs of interest (malignancy, lymphoma, tuberculosis/granulomatous infections, demyelination, drug-induced lupus, and congestive heart failure), clinical laboratory evaluations, physical examinations, and vital signs. Safety data presented in this section are derived from two analysis sets of the clinical trial patient population – the Placebo-Controlled Study Set and the All Adalimumab Treatment set, criteria for which are outlined below. These data are from the Clinical Summary of Safety[82] (CSS) provided to the US FDA and EMEA with the regulatory filing. Safety data from the individual trials are available from manuscripts, posters and abstracts for studies M02-528[33], M02-529[33], M02-538[40], M03-656[43,44,45], M03-658[55] and M04-716[46,47,48,49,50]; however, Abbott felt it would be prudent to present pooled safety data from all the studies in order to provide a comprehensive, but brief overview.

- The Placebo–Controlled Study Set (N=1469) – Subjects who were enrolled and received at least one dose of study medication in Studies M02-528, M04-716, and Period A of Study M03-656. The Placebo–Controlled Study Set includes subjects who received at least one dose of study drug as follows: 1) Study M02-528: Subjects in the placebo and adalimumab eow treatment groups. Data from Weeks 0 to 12 are included. (Subjects in the adalimumab weekly treatment group are not included); 2) Study M03-656: Subjects in the placebo and adalimumab eow treatment groups in Period A only. Data from Weeks 0 to 16 are included; 3) Study M04-716: Subjects in the placebo and adalimumab eow treatment groups. Data from Weeks 0 to 16 are included. (Subjects in the MTX group are not included.) Note, while Period C of Study M03–656 was also placebo–controlled, subjects participating in Period C were not included in the Placebo–Controlled Study Set because they had received open–label adalimumab in Period B.

- The All Adalimumab Treatment Set (N=[redacted]) - which includes subjects who received at least one adalimumab injection in Studies M02-528, M02-529, M02-538, M03-596, M03-656, M03-658, or M04-716. All adalimumab treatment regimens (40 mg eow and weekly) are included in the All Adalimumab Treatment Set. The All Adalimumab Treatment Set contains data from 198 subjects who received 40 mg weekly as their initial dose in Study M02–528 or Study M02–538.

- The safety of adalimumab has also been assessed in the context of the current prescribing information that is based on global clinical studies in rheumatoid arthritis (RA) and spontaneous post-marketing reports in the USA[83], information from which are also presented in this section to provide additional evidence of the use of adalimumab in a large patient population.

Data from all these sources support the fact that adalimumab is generally well tolerated with a favourable risk/benefit profile in patients with moderate to severe plaque psoriasis, virtually all of the key safety findings observed in the psoriasis clinical trials are currently described in the prescribing information, and no new safety concerns have arisen.

5.7.2 Placebo-Controlled Study Set (N=1469)

- Adalimumab was generally safe and well–tolerated when administered to subjects with moderate to severe chronic plaque Ps at a dose of 40 mg eow sc for up to 16 weeks.

- Adalimumab was generally safe and well–tolerated as demonstrated by the incidence and severity of treatment–emergent AEs. The most commonly reported individual treatment–emergent AEs in adalimumab–treated subjects (nasopharyngitis, upper respiratory tract

infection and headache) are consistent with the current safety profile as observed in subjects receiving adalimumab for treatment of other indications, and do not represent new safety findings.

- The incidence of AEs at least possibly–related to study drug overall occurred at a statistically significantly higher incidence in the adalimumab treatment group than in the placebo treatment group; however, the most commonly reported individual treatment–emergent AEs at least possibly–related to study drug in adalimumab–treated subjects (injection site reaction and headache) are consistent with the current safety profile as observed in subjects receiving adalimumab for treatment of other indications, and do not represent new safety findings.

- The incidence of severe AEs was low and comparable in the adalimumab and placebo treatment groups. Only two individual severe AEs (headache and cellulitis) were reported by ≥ 2 adalimumab–treated subjects.

- No deaths occurred.

- The overall incidences of SAEs and AEs leading to discontinuation of study drug were low and comparable in the adalimumab and placebo treatment groups. The most commonly reported individual treatment–emergent SAE in adalimumab–treated subjects (cellulitis) is consistent with the current safety profile as observed in subjects receiving adalimumab for treatment of other indications, and does not represent a new safety finding. No individual AE leading to discontinuation of study drug was reported in more than one adalimumab–treated subject.

- Non–serious infections overall occurred at a statistically significantly higher incidence in the adalimumab treatment group than in the placebo treatment group; however, this difference is consistent with the current safety profile and does not represent a new safety finding. The incidence of serious infections was comparable in the adalimumab and placebo treatment groups.

- The overall incidence and exposure–adjusted rate of treatment–emergent non−melanoma skin cancers appeared to be higher in the adalimumab treatment group (0.5%; 1.7 E/100 PY) than in the placebo treatment group (0.2%; 0.7 E/100 PY). The between-group difference was not statistically significant. The numerically elevated rate results are consistent with the current safety profile as observed in subjects receiving adalimumab for treatment of other indications, and do not represent new safety findings.

- Injection site reactions occurred at a slightly higher incidence in the adalimumab treatment group than in the placebo treatment group; however, the difference was not statistically significant. Injection site reactions are consistent with the current safety profile and do not represent new safety findings.

- Congestive heart failure, allergic reactions, haematologic events, and hepatic events occurred at comparable or lower incidences in the adalimumab treatment group than in the placebo treatment group.

- Data from the Ps clinical programme do not suggest an increased risk of malignancies as a result of treatment with adalimumab, with the exception of non-melanoma skin cancers.

- No adalimumab– or placebo–treated subjects reported AEs in any of the following special interest categories related to the administration of TNF antagonists like adalimumab: lymphoma, demyelinating disorders, opportunistic infections (excluding TB), TB, and lupus–like syndrome.

5.7.3 All Adalimumab Treatment Set (N=[redacted])

- Adalimumab was generally safe and well–tolerated when administered to subjects with moderate to severe chronic plaque Ps for up to three years.

- Adalimumab was generally safe and well–tolerated as demonstrated by the incidence and severity of treatment–emergent AEs and by the incidence of AEs at least possibly related to study drug (i.e., treatment–related). The most commonly reported individual treatment–emergent AEs, irrespective of relation to study drug [redacted] and treatment–related AEs [redacted] in the All Adalimumab Treatment Set are consistent with the current safety profile as observed in subjects receiving adalimumab for treatment of other indications, and do not represent new safety findings.

- [redacted]

- The overall incidences and exposure–adjusted rates for SAEs [redacted] and AEs leading to discontinuation of study drug [redacted] were relatively low. The most commonly reported individual treatment–emergent SAEs [redacted] and AEs leading to discontinuation of study drug [redacted] are either consistent with the current safety profile and do not represent new safety findings [redacted] are associated with the underlying disease (Ps and psoriatic arthropathy), and/or are not considered to be clinically relevant [redacted]

- The overall incidence and exposure–adjusted rate for infections were [redacted] and [redacted], respectively; the overall incidence and exposure–adjusted rate for serious infections were [redacted] and [redacted], respectively. The most commonly reported individual treatment–emergent infections [redacted] and serious infections [redacted] are consistent with the current safety profile as observed in subjects receiving adalimumab for the treatment of other indications, and do not represent new safety findings. [redacted]

- The overall incidence and exposure–adjusted rate for injection site reactions were [redacted] Injection site reactions are consistent with the current safety profile and do not represent new safety findings.

- The overall incidence and exposure–adjusted rate for hepatic events were [redacted] and [redacted], respectively. [redacted]

- [redacted]

- [redacted]

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5.7.4 Safety Analysis of the RA Clinical Trial Safety Database

As of 31 August 2002, 2,468 patients with RA had received adalimumab in clinical trials, representing 4,870 patient years of exposure. Up to 15 April 2005, 10,050 patients (12,506 PYs) had participated in adalimumab RA clinical trials, more than 300 of whom have had at least 5 years of exposure to adalimumab. Patients in the pivotal trials had moderately or severely active, long standing disease (average duration of approximately 11 years), and the majority had failed treatment with prior DMARDs. The rates for SAEs of interest reported in the clinical trial safety database (RCTs/open-label extensions, Access to Therapy trial {Act} and Research in Active RA trial {ReAct}) as of April 2005 were compared with the rates reported 2.5 years earlier in August 2002 (Table 5.7.4.1).

Table 5.7.4.1: Rates of selected Adverse Events from the RA Clinical Trial Safety Database[83]

	All RA trials as of 31 August 2002 (E/100 PYs) N = 2468, 4780 PYs	**All RA trials as of 15 April 2005 (E/100 PYs) N = 10 050, 12 506 PYs.**
Tuberculosis	0.27	0.27
Histoplasmosis	0.06	0.03
Demyelinating diseases	0.08	0.08
Lymphoma	0.21	0.12
SLE/Lupus-like syndrome	0.08	0.10
Congestive heart failure	0.28	0.29

E/100 PYs = events per 100 patient years

The rate of serious infections in the clinical trial safety database as of April 2005 was 5.1/100 PYs. This rate is nearly identical to that observed in August 2002 (4.9/100 PYs) and is similar to rates reported for the general RA population.

5.8 Non-RCT evidence

Sections 5.3 and 5.4 provide considerable evidence from well-conducted RCTs demonstrating the short- and long-term efficacy of adalimumab for the treatment psoriasis. As such, non-RCT evidence is not required for this submission. However, data from a recently published study evaluating open-label adalimumab in 30 patients with severe psoriasis and psoriatic arthritis previously treated with other biologics are shown below to further demonstrate the efficacy of adalimumab in a difficult to treat patient population [84].

5.8.1 Summary of methodology of relevant non-RCTs

Patients:
30 patients (20 males and 10 females; aged between 30 and 75) with plaque psoriasis and Baseline PASI scores ranging from 3 to 67.2 (median PASI = 16.4; PASI interquartile range = 14.5) enrolled in this 24-week study. Of these patients, 19 also had PsA.

All patients were unresponsive to or had contraindications to conventional systemic treatments (methotrexate, ciclosporin, retinoids, PUVA). Furthermore, all patients had failed to respond to all other available biologic agents - infliximab and efalizumab (at the standard SPC recommended doses) and etanercept 50mg twice weekly. Of these 30 patients, 19 had failed 2 prior biologics and 11 had failed 3 biologics. The reasons for stopping a prior biological were primary inefficacy [defined as a lack of response i.e. patients not achieving PASI 50 from Baseline score at 12 weeks for etanercept and efalizumab and 22 weeks for infliximab], long-term inefficacy [defined as relapse greater than 50% of Baseline PASI score in patients who had achieved a complete response at Week 12 (Week 14 for infliximab)], or adverse events. Patients were not allowed to participate if they had a history of active infectious disorders, opportunistic infections or demyelinating diseases.

Methods:
Clinical and laboratory assessments were performed at Screening, Baseline, and every 4 weeks thereafter. Patients were administered 40mg adalimumab weekly based on dose-finding data from M02-528 and because of the failure of all other biologics. No systemic agents affecting PASI score or arthritis indexes were permitted. Efficacy was evaluated at Baseline and then every 4 weeks by calculating the PASI score, the DLQI and Psoriasis Disability Index (PDI) were also evaluated in all patients.

The primary efficacy endpoint was the proportion of patients who achieved at least a PASI 75 response at Week 12 and at Week 24. Secondary endpoints included the improvement in score of the DLQI and PDI at Weeks 12 and 24.

5.8.2 Results of the relevant non- RCTs

Twenty-seven patients completed the 24-week treatment. Three patients withdrew form the study due to lack of efficacy (PASI 50 not achieved or maintained beyond Week 12). In those 27 patients who continued adalimumab treatment, significant improvement in PASI score was seen as early as Week 4 (reduction of mean PASI score from 19.2 to 8.9) and the efficacy continued to improve through to Week 8.

Week 12 Results
At Week 12, 27 (90%) of patients achieved $\geq$ PASI 50 response, 26 (97%) achieved $\geq$ PASI 75, and 21 (70%) reached an improvement of at least 90% of their baseline PASI score (PASI 90). The mean PASI score improved from 19.2 to 2.5, corresponding to an 87% improvement. Patients' quality of life was significantly improved as demonstrated by an improvement in the DLQI and PDI from Baseline (see Table 5.8.2.1).

Week 24 Results
At Week 24, 25 (83%) of patients achieved $\geq$ PASI 50, 25 (83%) achieved $\geq$ PASI 75 and 23 (77%) of patients achieved at least a 90% improvement in their PASI score from Baseline. Furthermore, the mean PASI score at Week 24 2.2, corresponding to an 88.5% improvement from Baseline. Patients' quality of life was significantly improved as demonstrated by an improvement in the DLQI and PDI from Baseline (see Table 5.8.2.1).

Table 5.8.2.1: Evaluation of DLQI and PDI scores at Baseline and at Weeks 12 and 24

Measure	Baseline	Week 12	Week 24
DLQI	12.4 $\pm$ 6.4 (4.0-28.0)	3.2 $\pm$ 4.8 (0-21.2)	3.9 $\pm$ 5.2 (0-19)
PDI	33.3 $\pm$ 15.6 (13.0-74.0)	3.3 $\pm$ 8.7 (0-27)	6.3 $\pm$ 11.0 (0-35)

DLQI, Dermatology Life Quality Index; PDI, Psoriasis Disability Index;
Results presented as mean $\pm$ SD (range).

Interestingly, the authors noted that no differences in efficacy were observed based on the type of previous biologic treatments used. Moreover, there were no differences in efficacy among the patients depending on the cause of cessation (lack of efficacy vs. long-term lack of efficacy) of the previous treatment.

Conclusions
This small study demonstrates that adalimumab is an effective treatment of severe psoriasis in patients who have failed treatment with both conventional systemic therapies and biological agents. The responses seen in these difficult-to-treat patients at Week 12 and Week 24 are comparable to those seen in the adalimumab RCT programme. However, the authors do note that the dosing used in this study is higher than the dose likely to be stipulated in the licence (40mg adalimumab eow).

5.9 Interpretation of clinical evidence

5.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The following points outline key areas for consideration of the relevance of the evidence base for the decision problem:

Severity of psoriasis

Adalimumab has demonstrated clear efficacy in the treatment of moderate to severe psoriasis. Furthermore, subgroup analyses have indicated that adalimumab is highly efficacious in the most severe group of psoriasis patients (BSA >20% in the CHAMPION trial; Table 5.4.4.1). In the two pivotal phase III adalimumab clinical trials, M04-716 (CHAMPION) and M03-656 (REVEAL), the mean baseline PASI and DLQI scores of subjects fulfilled the criteria of severe disease suggested by NICE and the trial subjects were comparable to patients with active severe psoriasis in England and Wales. Furthermore, when the PASI response rates for all patients were compared to a sub-group of subjects who have a Baseline DLQI of greater than 10, the response rates were very similar (Table 5.9.1.1), which suggests that although the trials were conducted in patients with moderate to severe psoriasis, adalimumab is just as effective in the severe patient population for which it is likely to be used in the UK. This evidence provides reassurance that the benefits observed in the clinical trials are likely to be applicable for the treatment of severe patients in clinical practice with adalimumab.

Table 5.9.1.1: PASI Responses at Weeks 12 and 16 in All patients vs. those patients with a Baseline DLQI score of greater than 10 in M02-528, M03-656 and M04-716

Trial	Treatment group	PASI response Level	Week	All Patients	Baseline DLQI > 10
M02528	Placebo	1:PASI 90+	12	0 (0%)	0 (0%)
		2:PASI 75-90	12	2 (4%)	0 (0%)
		3:PASI 50-75	12	7 (14%)	4 (17.4%)
		4:PASI 50-	12	41 (82%)	19 (82.6%)
	Adalimumab 40mg eow	1:PASI 90+	12	11 (25.6%)	10 (37%)
		2:PASI 75-90	12	13 (30.2%)	8 (29.6%)
		3:PASI 50-75	12	10 (23.3%)	6 (22.2%)
		4:PASI 50-	12	9 (20.9%)	3 (11.1%)
	Adalimumab 40mg weekly	1:PASI 90+	12	24 (50%)	16 (57.1%)
		2:PASI 75-90	12	17 (35.4%)	7 (25%)
		3:PASI 50-75	12	4 (8.3%)	3 (10.7%)
		4:PASI 50-	12	3 (6.3%)	2 (7.1%)
M04-716	Adalimumab	1:PASI 90+	12	52 (49.5%)	27 (51.9%)
		2:PASI 75-90	12	31 (29.5%)	15 (28.8%)
		3:PASI 50-75	12	15 (14.3%)	7 (13.5%)
		4:PASI 50-	12	7 (6.7%)	3 (5.8%)
	Methotrexate	1:PASI 90+	12	10 (9.4%)	3 (6.7%)
		2:PASI 75-90	12	17 (16%)	6 (13.3%)
		3:PASI 50-75	12	33 (31.1%)	14 (31.1%)
		4:PASI 50-	12	46 (43.4%)	22 (48.9%)
	Placebo	1:PASI 90+	12	4 (8.2%)	3 (13%
		2:PASI 75-90	12	4 (8.2%)	2 (8.7%)
		3:PASI 50-75	12	6 (12.2%)	2 (8.7%)
		4:PASI 50-	12	35 (71.4%)	16 (69.6%)
M03-656	Adalimumab	1:PASI 90+	16	366 (47.2%)	187 (49.1%)
		2:PASI 75-90	16	212 (27.3%)	102 (26.8%)
		3:PASI 50-75	16	93 (12.0%)	42 (11%)
		4:PASI 50-	16	105 (13.5%)	50 (13.1%)

	Placebo	1:PASI 90+	16	7 (2.0%)	4 (2.3%)
		2:PASI 75-90	16	19 (5.4%)	11 (6.4%)
		3:PASI 50-75	16	34 (9.6)	17 (9.9%)
		4:PASI 50-	16	293 (83%)	140 (81.4%)
M04-716	Adalimumab	1:PASI 90+	16	56 (53.8)	30 (55.6%)
		2:PASI 75-90	16	30 (28.8%)	15 (27.8%)
		3:PASI 50-75	16	9 (8.7%)	5 (9.3%)
		4:PASI 50-	16	9 (8.7%)	4 (7.4%)
	Methotrexate	1:PASI 90+	16	15 (14.6%)	5 (11.9%)
		2:PASI 75-90	16	24 (23.3%)	10 (23.8%)
		3:PASI 50-75	16	29 (28.2%)	13 (31.0%)
		4:PASI 50-	16	35 (34.0%)	14 (33.3%)
	Placebo	1:PASI 90+	16	6 (12.5%)	5 (22.7%)
		2:PASI 75-90	16	4 (8.3%)	1 (4.5%)
		3:PASI 50-75	16	6 (12.5%)	1 (4.5%)
		4:PASI 50-	16	32 (66.7%)	15 (68.2%)

Prior treatment history

In NICE technology appraisal TA 103 of etanercept and efalizumab for psoriasis, the Appraisal Committee noted that the inclusion criteria for the RCTs did not wholly reflect the population for which these technologies are currently licensed because their psoriasis had not necessarily failed to respond to other treatment options. This implies that the clinical trials may represent a population that is easier to treat than that which is set out in the license, namely patients who have previously failed on systemic therapies. There is limited published evidence in psoriasis that response rates vary for treatments according to prior treatment exposure. The limited available data indicate that there is no difference in efficacy according to whether patients have received prior systemic therapy or not. In the European Post Assessment Report (EPAR) for etanercept, the CHMP stated in the scientific discussion that a subgroup analysis of PASI 75 response at 12 weeks by prior systemic therapy was presented for all 3 etanercept studies. There was little difference in PASI 75 response between patients who had received previous systemic therapy and those who had not[85]. Furthermore, in the Schering Plough submission of infliximab for the treatment of psoriasis, the manufacturer presented analyses by prior systemic therapy from the EXPRESS I and EXPRESS II trials that showed that the benefit achieved with infliximab was consistent, irrespective of the type of prior therapy and whether patients had received at least two prior systemic therapies[86]. Although, the data presented were commercial in confidence and cannot be verified by Abbott.

Post-hoc sub-group analyses from the Placebo-Controlled Analysis set described in Section 5.7 (i.e. subjects enrolled in Studies M02–528, M04-716, and Period A of Study M03-656), which amounts to 1,459 patients administered 40mg adalimumab eow, support the findings that treatment response is not affected by prior Ps treatments. Table 5.9.1.2 shows the PASI 50, 75, 90 and 100 response rates at Week 16 for the placebo-controlled set by patients who received systemic biologic therapy vs. those who did not within the last 12 months, and subjects who received systemic non-biological therapy vs. those who did not within the last 12 months. Data from the adalimumab trials indicate no significant difference in PASI 75 outcome by prior treatment exposure:

Table 5.9.1.2: PASI 50, 75, 90 and 100 response rates at Week 16 for the placebo-controlled set by patients who received systemic biologic therapy vs. those who did not within the last 12 months, and subjects who received systemic non-biological therapy vs. those who did not within the last 12 months

	History of Systemic Biologic Therapy within last 12 months				History of Systemic Non-Biologic Therapy within last 12 months			
	Placebo n (%)		Adalimumab n (%)		Placebo n (%)		Adalimumab n (%)	
Response	Did not receive N=322	Received N=55	Did not receive N=695	Received N=99	Did not receive N=273	Received N=104	Did not receive N=579	Received N=215
PASI 50	58 (18)	7 (13)	577 (83)	84 (85)	54 (20)	11 (11)	490 (85)	171 (80)
PASI 75	26 (8)	5 (9)	501 (72)	78 (79)	27 (10)	4 (4)	430 (74)	149 (69)
PASI 90	11 (3)	0	327 (47)	47 (47)	11 (4)	0	281 (49)	93 (43)
PASI 100	4 (1)	0	138 (20)	19 (19)	4 (1)	0	122 (21)	35 (16)

Note: Response rates calculated following imputation of missing values as non-responders.
Visits are relative to the first dose of study drug in the double-blind period of Studies M02-528, M03-656 or M04-716.
Baseline = Baseline 1, last assessment prior to first study drug injection.
PASI was not to be collected at Week 16 in Study M02-528 and non-responder imputation was not applied to these subjects.

Section 5.3.2 of this submission reports the Baseline Demographics and Disease characteristics of the subjects in the clinical trial programme, including previous Ps treatments within the last 12 months. Treatment history for this time period have been presented because there is a degree of scepticism about how reliable recollections are concerning which systemic treatment was used in a patient 10 years ago, and that data within the past year are considerably more reliable. For this reason, Table 5.9.1.2 presents PASI response rates in patients who have had systemic therapy vs. those who have not within the last 12 months. However, psoriasis treatment history recorded in subjects from M04-716 (CHAMPION) from more than 12 months ago show that on average [redacted]% of subjects in this trial had received unspecified systemic therapies, which would be comparable to the intended patient population in England and Wales.

Intermittent vs. continuous therapy

Currently, etanercept is recommended by NICE in TA103 for use up to 24 weeks, i.e. intermittent use in line with its license. However, the available data indicate that patients receiving intermittent therapy are less likely to maintain/ re-achieve a PASI 75 response[75,87,88], which clearly has implications for the management of Ps. In the Schering Plough submission of infliximab for psoriasis, the manufacturer stated that based on evidence from large centres in the UK, the use of etanercept in the treatment of psoriasis is continuous, and that etanercept treatment is not stopped if a patient is responding, due to concerns regarding potential relapse. In addition, there is evidence that etanercept is used at 50mg twice weekly in order to achieve the desired level of response[86]. The ERG's clinical advisor also concurred that etanercept is given continuously in patients in whom it is effective and that some patients in the UK are treated with 50mg twice weekly. For this reason, continuous use of etanercept was included as a treatment option in the economic model to better accurately reflect current management of Ps in the UK. The adalimumab Ps clinical trial programme demonstrated that continuous treatment with 40mg adalimumab eow was an effective therapeutic option for patients with moderate to severely active psoriasis. This was supported by data from REVEAL (M03-656), where the co-primary outcome measured was time to loss of response after Week 33 and on or before Week 52 in patients re-randomised to receive adalimumab eow or placebo.

Relative efficacy of adalimumab versus systemic therapy

The CHAMPION trial provides evidence in a head to head RCT that adalimumab is more efficacious than systemic therapy. This is the first RCT to indicate superior efficacy of a biologic agent over systemic therapy in the treatment of psoriasis and can therefore be considered robust evidence of the effectiveness of adalimumab.

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

The adalimumab clinical trial programme included a comprehensive range of clinical outcome measures alongside Patient Reported Outcomes. The PASI clinical measure is not an ideal tool for assessment of the impact of psoriasis on patients, as the impact of psoriasis on a patient will depend on a number of factors. However, analyses have indicated that changes in the PASI score are significantly associated with changes in the SF-36 MCS scores, SF-36 PCS scores, DLQI total scores and the EQ-5D index scores. Section 6 outlines in detail the observed relationship between PASI response and EQ-5D index scores. Given the correlation between these measures it can be observed that the main clinical outcomes assessed in the adalimumab trials are useful in estimating the clinical benefits experienced by patients in clinical practice. In addition, it should be noted that the goal of therapy for patients is complete control of their disease. In this respect it should be noted that the proportion of patients in the adalimumab clinical trial programme that had a PASI 100 response suggests a significant benefit for adalimumab.

Furthermore, the outcomes assessed using the SF-36, EQ-5D and DLQI measures indicate directly that patients value the benefits of adalimumab treatment for psoriasis. Patient reported outcomes assessing specific symptoms of psoriasis such as the percentage of patients reporting psoriasis/ psoriatic arthritis pain and psoriasis-related pruritus were also significantly improved for patients receiving adalimumab. For example, in the CHAMPION trial, at Week 16, the percentages of patients reporting good or complete disease severity control were 79%/57%/25% for patients treated with adalimumab/methotrexate/placebo ($p<0.001$ for all comparisons), respectively[47].

5.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

As outlined in section 5.9.1 the patient population included in the adalimumab clinical trial programme is broadly similar in terms of baseline disease severity to NICE recommendations for etanercept and efalizumab and the recommendations of the BAD as to which patients should receive anti-TNF therapy for psoriasis.

Potential issues relating to the conduct of the trials compared with clinical practice have been discussed in brief below.

Methotrexate (MTX) dosing in CHAMPION study

MTX dosing in psoriasis in Europe is widely variable. The MTX dosing used in CHAMPION had to be aggressive enough to achieve a representative response by the completion of the study, but could not be too aggressive to lead to an excessive number of dropouts in the MTX arm due to the known myelosuppressive, gastrointestinal and hepatic toxicities associated

with the drug. The study design of CHAMPION required that adalimumab superiority be demonstrated prior to establishing non-inferiority vs. MTX, which posed a limitation as to the duration of the randomised, double-blind study due to the increasing difficulties of conducting extended placebo-controlled studies in psoriasis, i.e. the duration of the study that could be ethically conducted was limited.

According to country-specific SmPCs reviewed, the recommended MTX starting dose in Europe ranges from 2.5 to 10 mg per week. Based on publications and feedback from practicing dermatologists, the MTX starting dose generally ranges between 7.5 mg to 15 mg per week, although extreme doses of 2.5 mg and 30 mg per week are also mentioned. A starting dose of 7.5 mg per week in Study M04-716 ensured retention of subjects in the study without undue numbers of dropouts due to safety reasons. Heydendael's study[17] evaluating MTX and ciclosporin for psoriasis used a high MTX starting dose of 15 mg, which led to a dropout rate (28%, 12/43) that was not considered an acceptable comparison to adalimumab which is generally well tolerated with drop-out rates well below 5%. The maximum MTX dose in the majority of approved European SmPCs reviewed is 25 mg/week, which equates to the maximum dose used in CHAMPION. Furthermore, the increments of 2.5 mg at Week 2, 5 mg at Week 4, 5 mg at Week 8, and 5 mg at Week 12 in Study M04-716 meant that a dose generally regarded as therapeutic (15 mg) was reached as early as Week 4, with the endpoint 12 weeks later. In addition, those subjects with a sub-therapeutic response to MTX could have their dose escalated up to 25 mg by Week 12.

High placebo response in M04-716 (CHAMPION)

Nineteen percent of patients administered placebo in CHAMPION achieved $\geq$ PASI 75 response at Week 16, which is unusually high for Ps trials where the expected proportion of patients achieving $\geq$ PASI 75 response in the placebo arm is typically between 3-8%. CHAMPION is the first trial to directly compare a biologic with an active comparator, methotrexate. There are relatively few studies that have addressed folate supplementation with the use of MTX for the treatment of Ps[89], however BAD guidelines recommend that folic acid supplementation is provided to Ps patients on MTX treatment to prevent some of the adverse effects associated with MTX treatment. Due to the double-dummy design of the trial, all patients participating in CHAMPION received folates to maintain the blind of patients randomised to MTX. Folic acid is a cofactor for homocysteine metabolism, which induces interleukin-8 and MCP-1 secretion by monocytes. It is known that plasma homocysteine levels positively correlate with psoriasis severity. Giving folate to patients with low folate levels leads to decreased homocysteine and therefore decreased chemokine production and hence anti-inflammation. Therefore the high proportion of placebo responders observed in CHAMPION could be attributed to the potential benefit folates provide to those patients in the placebo arm with low folate levels at Baseline. Furthermore, as all of the patients in the study received folates, the superior efficacy of adalimumab in comparison to MTX at Week 16 cannot be attributed to folate supplementation. In addition, to maintain blinding, all patients in the placebo arm received placebo injections and placebo tablets due to the three-arm nature of the study. It is possible that this could have accentuated the placebo effect in this study.

Long-term efficacy data for adalimumab

There is limited data available on the long-term efficacy of any of the biologics. Etanercept is licensed for use up to 24 weeks because there is a paucity of data past six months demonstrating efficacy at its licensed dose (25mg twice weekly). Collecting long-term efficacy data is complicated by the fact that it is considered unethical to compare any Ps treatment to placebo in an RCT setting any longer than 16 weeks (all the biologics use placebo as the comparator in their clinical trials; adalimumab is the first biologic to be compared directly to an active comparator). As such long term randomised data for any of the biologics are unavailable. However, there are 120-week data available for patients receiving 40mg adalimumab eow (24 weeks were randomised), albeit in a small proportion of patients (n=49). These data (presented in Section 5.4.7) show that patients receiving 40mg adalimumab eow sustain clinical response, defined as $\geq$ PASI 75 response for 2 years.

Adalimumab dosing

The five trials M02-528, M02-529, M03-656 (REVEAL), M04-716 (CHAMPION) and M03-658 form the evidence base for the efficacy of adalimumab in the treatment of moderate to severe plaque psoriasis. All of these trials have demonstrated the efficacy of adalimumab at a maintenance dose of 40 mg eow and the vast majority of the clinical data from these trials are available for the 40 mg eow maintenance dose, which is the anticipated dose in the licensed indication for adalimumab for the treatment of psoriasis.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

A systematic search of the economic literature was conducted. The aim of the search was to identify published cost-effectiveness studies of therapies used in the treatment of psoriasis excluding topical treatments. Given the limited number of available treatments in this therapeutic area and *a priori* knowledge of the paucity of economic studies in psoriasis, a deliberately wide search strategy was conducted as outlined in Appendix 9, Section 9.3.

6.1.2 Description of identified studies

Only six published studies met the inclusion criteria of being comparative economic evaluations[90, 91, 92, 93, 94, 4]. The other identified studies did not contain comparative economic evaluations. Of the six studies meeting the inclusion criteria, one study was developed by the assessment group for the appraisal of etanercept and efalizumab for Ps by NICE. As the details of this study have been outlined elsewhere, this section does not provide further information. The interested reader is referred to the previously published HTA report for further information on methods and results. Section 6.3.4.1 explores in detail the differences between the methods and results of Woolacott et al and the de novo economic model developed for this appraisal.

Ellis et al. Cost-effectiveness comparison of therapy for psoriasis with a methotrexate-based regimen versus a rotation regimen of modified cyclosporine and methotrexate.

This cost-effectiveness study assesses two systemic strategies for psoriasis treatment. The target population for this model is patients with moderate to severe chronic plaque psoriasis. Costs included are related to medication, laboratory and physician fees and also cost of treating adverse events. The point of view taken is the payer's. The simulation has been run for ten years in order to include the cost of adverse events. The effectiveness outcome used is "year(s) clear of psoriasis". Finally sensitivity analyses were performed.

In the first strategy, virtual patients are given methotrexate for the length of the study unless they fail. If that happens, patients would then be given cyclosporine alternating yearly with a maintenance treatment. If again patients fail with this treatment then they would be given the maintenance treatment for the remaining time of the study. In the second strategy, patients are given alternatively cyclosporine or methotrexate every year unless patients fail one or both of them. Maintenance treatment would then be given alternatively with cyclosporine if resistance to methotrexate should occur and methotrexate would be given continuously if resistance to cyclosporine should occur. Maintenance treatment would be given the rest of the study if both resistances should occur.

The total cost of the methotrexate strategy over 10 years is $33,000 provided approximately 2 years clear of psoriasis and the cost of the cyclosporine strategy is $38,000 provided approximately 4 years clear of psoriasis. Hence the incremental cost-effectiveness of rotational strategy is $2,700 per year clear of psoriasis over methotrexate strategy. The sensitivity analysis showed that this ratio would vary from $2,700 to $4,100 when relative efficacy of the two treatments varies from 1 to 20.

Critical appraisal:

The authors do not consider the PASI evaluation in the outcomes measured and only consider "clear or almost clear" state. Adjustments on the quality of life of patients are not

included in the cost-effectiveness ratio. This analysis therefore does not consider the whole impact of the treatments on patients.

This article highlights the fact that adverse events of methotrexate and cyclosporine occur with long-term exposure and therefore it is important to consider a lifetime perspective.

D.J. Pearce et al. The cost-effectiveness and cost of treatment failures associated with systemic psoriasis therapies.

The objective of the study is to assess the cost-effectiveness of 9 therapies:

- PUVA
- narrowband UVB phototherapy
- acitretin
- cyclosporine
- methotrexate
- alefacept
- efalizumab
- etanercept
- infliximab

The target population is patients with moderate-to-severe plaque psoriasis. Only direct costs are included: drugs, physician and nurse fees, laboratory fees, tuberculosis and chest X-rays. The average patient weight is 80kg. The prices/ costs are taken from 2003 Drug Topics Red Book and 2003 Medicare median national reimbursement. The timeframe of the model was set at 12 weeks.

This study relies on bibliographic searches. In order to obtain the cost of treating psoriasis and the cost of the failures for each strategy, the authors take all the costs involved in a strategy and divide it by the percentage of PASI 75 responders of the strategy to give the cost per PASI 75 responder.

The PASI 75 responses for the anti-TNF agents are 49% and 82% respectively for etanercept and infliximab compared to methotrexate efficacy of 70%. Cyclosporine and PUVA are also associated with high response rates, 82% and 84% respectively. The cost per PASI 75 responder is $1,926 and $8,319 for anti-TNF, respectively for infliximab and etanercept. Other biologics have higher cost-effectiveness ratios, $12,897 for efalizumab and $50,383 for alefacept. Methotrexate shows the lowest cost per responder with $187 followed by cyclosporine $505 and PUVA $767.

Critical appraisal:

The use of a disease-specific outcome measure for the cost effectiveness ratio is an important limitation of the comparison. Patients may perceive a significant improvement of their quality of life with a PASI score lower than 75.

The time frame is relatively short and does not consider adverse events nor long term toxicity and thus does not include cost of managing those events. This timeframe does not take into consideration the long-term effectiveness of the different therapies considered.

S.C. Feldman et al. Strategy to manage the treatment of severe psoriasis: considerations of efficacy, safety and cost.

This review includes a comparative cost-effectiveness analysis. Use of a number of different therapies has been modelled (Methotrexate, Acitretin, Cyclosporine, Etanercept, Infliximab, Alefacept and PUVA). Patients with moderate-to-severe psoriasis were included; their average weight was 75kg. The time frame was 12 months. Direct (third-party payer) and indirect costs (lost work time) were included to incorporate the patient's perspective. The costs include drugs, office visits, lab work, radiological studies, procedures (liver biopsy) and infusions.

Etanercept at 25 or 50 mg twice weekly were assumed to be given continuously for 52 weeks and Infliximab was assumed to be given as six infusions a year. Annual cost and annual cost per treatment success were calculated. PASI 75 was the outcome chosen for treatment success.

Methotrexate was found to be the least costly with $1,600 annually. Etanercept 25mg and 50mg twice-weekly cost respectively $16,900 and $33,000 per year and Infliximab 5mg/kg costs $18,000 per year.

Methotrexate is still among the least costly when considering the annual costs per treatment success with $5,400. Etanercept 25mg twice weekly was costly with $35,900 and Infliximab was relatively less costly in this analysis, with $22,500 for 5mg/kg, due to its high efficacy.

Critical appraisal:

The point of view is the patient's and thus the figures estimated are not directly useful for NHS decision makers but comparisons between the therapies are still informative.

QALY are not used taking patients' quality of life out of the comparison.

The one-year timeframe does not allow consideration of long-term adverse events.

C.S. Hankin et al. A cost comparison of treatments of moderate to severe psoriasis

This cost-effectiveness study assesses 9 treatments (UV-B, PUVA, acitretin, cyclosporine, methotrexate, alefacept, efalizumab, etanercept and infliximab) and two combinations (acitretin with PUVA or UV-B). The managed health care system perspective has been used. The target population is patients with moderate to severe psoriasis. The efficacy end-point chosen is PASI percentage improvement. The cost-effectiveness outcome presented is the ratio of annualised cost for each treatment (including medication, monitoring and administration) with PASI percentage improvement. Costs of adverse events have been annualised and included in the model except for biologics.

The results of this study are that systemic agents and UV therapies alone or combined with acitretin are more cost-effective than biologics. Although efficacy may be high for biologics, especially for infliximab, their high costs induce cost-effectiveness ratios greater than $23,946.

Critical appraisal:

The studies used to estimate the efficacy of the treatments are not homogeneous regarding sample sizes. Narrowband UV-B, PUVA + acitretin, UV-B + acitretin, infliximab and methotrexate sample sizes are respectively 11, 34, 17, 33 and 48 while the other treatments' sample sizes range from 145 to 1153.

QALYs are not used here; therefore the data are of limited interest to NHS decision makers assessing the cost effectiveness of psoriasis treatments compared to other therapeutic areas.

N. Woolacott et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review.

This study is discussed in detail in sections 6.2 and 6.3 below

L. Hakkaart-van Roijen et al. The cost-effectiveness of tapered versus abrupt discontinuation of oral cyclosporine microemulsion for the treatment of psoriasis.

This cost-effectiveness study relies on an open label, multicentre, international clinical trial performed in Canada (97 patients), Spain (35), Turkey (33) and the UK (47). Patients included are over 18 years old with chronic plaque of psoriasis inadequately controlled with topical therapies. The societal point of view used includes direct (medication, dermatologist

visits, laboratory test) and indirect costs (loss of productivity based on a patient questionnaire). The timeframe is one year. The outcome measured is systemic therapy-free days (STFDs).

After 12 weeks of treatment with cyclosporine 51% will abruptly stop their treatment and 41% will decrease by 1 mg/kg/day until cessation. All currencies are converted to 1997 US $. The follow up of patients is one year and patients could receive up to 4 treatment courses.

The total direct costs for the UK are $3,853 and $3,861 (USD 1997) respectively for tapered and abrupt while it is $3,314 and $3,573 respectively for the total population. The STFDs are 236 for tapered and 197 for abrupt discontinuation. For the total population the results are respectively 257 and 225 STFDs. Tapered discontinuation dominates the abrupt discontinuation treatment strategy.

Critical appraisal:

This study is limited only to comparison of cyclosporine strategies.

The outcome measure does not facilitation comparison of cost effectiveness results with other studies and does not capture impact of treatment on patient quality of life.

6.2 De novo economic evaluation(s)

6.2.1 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

The use of adalimumab is modelled in line with the anticipated licensed indication for psoriasis:

- For the treatment of moderate to severe psoriasis in patients who have failed systemic therapy or for patients for whom systemic therapy is contraindicated or inappropriate.
- Adalimumab dosing of 80mg at baseline then 40mg eow from week 1.
- Used as a monotherapy.
- Patients not responding to adalimumab stop treatment at 16 weeks in line with the proposed recommendation in the licence that continued therapy should be carefully considered in patients not responding after 16 weeks of therapy. Response is defined as PASI 75 response in the base case model analysis and PASI 50 response in sensitivity analyses.
- For continuous use as a maintenance therapy in patients responding to adalimumab.

Guidance from both the British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005[3] and the NICE Final Guidance TA103 of efalizumab and etanercept for the treatment of adults with psoriasis[5] state that biologic therapies are appropriate for use when a patient has severe psoriasis. This is defined as when baseline

PASI is greater than or equal to 10 and baseline DLQI is greater than 10. In addition, patients can only continue on treatment if they show adequate response, defined as a PASI 75 response or a combination of PASI 50 response and a 5-point reduction in DLQI from when treatment started. Since the actual numbers achieving these eligibility criteria for trials of most therapies is unknown, this analysis focussed solely on PASI 75 response as the indicator for success in the base case analysis. Nevertheless, in clinical practice less than 75% improvement in PASI may be considered adequate and an analysis using PASI 50 as the response indicator is performed in the sensitivity analysis. The time at which response is assessed for each drug is defined in their respective labels and varies between 12 weeks and 16 weeks for the different treatments (16 weeks for adalimumab). Where this information is not defined in the label, the primary endpoints of the RCTs were used.

6.2.2 Patients

6.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The base case analysis considered the treatment of moderate to severe psoriasis in patients who have failed systemic therapy or for patients for whom systemic therapy is contraindicated or inappropriate. The base case analysis applied utility data from patients with severe psoriasis (DLQI >10).

6.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

The base case analysis used the utility scores from the subgroup of severe patients from the adalimumab trials. A sensitivity analysis was also conducted using the utility scores from all patients in the trials.

6.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

Treatment of the subgroup of patients who have failed a previous biologic agent has not been considered in this analysis. Based on data for other indications for adalimumab, it is hypothesised that use of adalimumab in psoriasis patients who have failed prior biologic therapy is likely to be of considerable therapeutic benefit. However, it has not been possible to quantify the cost-effectiveness of adalimumab in this subgroup of patients because there are insufficient data currently available for modelling the effectiveness of adalimumab for this subgroup of patients.

6.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients enter the evaluation at the time of receiving therapy. Patients not responding to a particular treatment move onto the next therapy in the treatment sequence. Patient entry and exit points from the evaluation do not differ between treatment regimens.

6.2.3 Comparator technology

The model included only treatments and dose regimens that are licensed and recommended for use in psoriasis patients in the UK. For example, two of the efalizumab trials administered efalizumab 1mg/kg (the licensed dose) as well as 2mg/kg (not licensed). In this case, only

the 1mg/kg dose is estimated in the analysis. The treatments and dose regimens included in the final model are:

- Etanercept – 25mg twice weekly
- Etanercept High – 50mg twice weekly
- Efalizumab – 1mg/kg per week
- Infliximab – 5mg/kg weeks 0,2, and 6, and every 8 weeks thereafter
- Adalimumab – 40 mg every other week
- Ciclosporin – 3mg/kg per day[i]
- Methotrexate – varied dose daily (oral)

As per the York Assessment Group model previously developed for TA103 (hereafter referred to as the York model), it was not possible to include acitretin, hydroxycarbamide and PUVA in the evidence synthesis and economic modelling, as the appropriate data are not available.

6.2.4 Study perspective

The base case analysis was conducted in accordance with NICE's reference case.

6.2.5 Time horizon

The model considers the use of standard and biologic therapies over time as per the York model. Each treatment is trialed for a set period of time, after which patients are only eligible to continue therapy if the patient has achieved a predetermined improvement in their disease severity. Those who do not reach the desired level of improvement (non-responders) go on to trial the next available treatment in the sequence. The expected costs and benefits expressed as QALYs for patients are estimated for the time spent on each therapy. Costs and QALYs are divided by the average time spent on therapy. This modelling structure assumes that the long term effectiveness and safety of different agents do not differ between therapies. The strengths and weakness of this model structure are outlined in Section 6.3.4.3.

6.2.6 Framework

a) Model-based evaluations

6.2.6.1 Please provide the following:

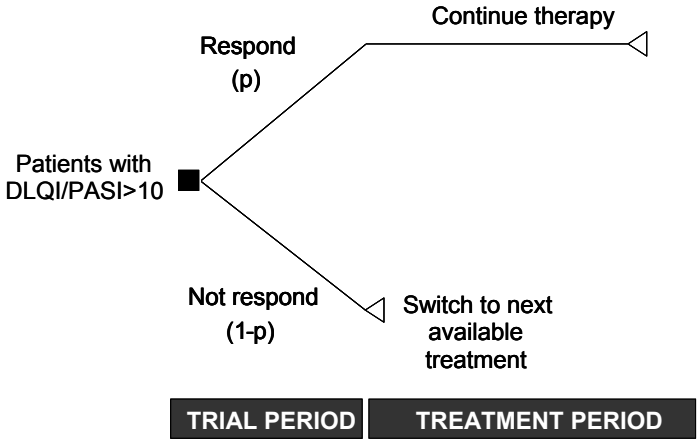
- ***A description of the model type.***
- ***A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.***

The base-case analysis considers patients with moderate to severe psoriasis. The model follows a clinical pathway set out by established guidelines[5,3]. Each treatment is trialed for a set period of time, after which patients are only eligible to continue therapy if the patient has achieved a predetermined improvement in their disease severity (Figure 6.2.6.1). Those who do not reach the desired level of improvement (non-responders) go on to trial the next available treatment in the sequence. The expected costs and benefits expressed as Quality

[ii] Greater than 3mg/kg per day was determined to be related to high toxicities (personal communication S Feldman, MD)

Adjusted Life Years (QALYs) for UK patients are estimated for the time spent on each therapy. A National Health Services (NHS) perspective is adopted for the base case analysis, and a societal perspective is examined in a sensitivity analysis.

Figure 6.2.6.1. Clinical pathway used in model structure



A previous analysis, the York model, was further developed to include the new evidence on the anti-TNF agent adalimumab. After applying a set of assumptions, the authors from York decided to utilise a simple decision tree structure to represent the sequential nature of treating psoriasis. The assumptions are: once severe, the disease is not progressive and the chances of obtaining clear, controlled skin remain possible[ii]; each treatment effect is independent of order; and, failure of one treatment does not preclude the use of any another treatment.

Instead of analysing each combination of treatments separately, the model examines all potential systemic treatment options used in this patient group both simultaneously, and compared to supportive care.[iii] Each treatment is then ranked in terms of its incremental cost-effectiveness ratio (ICER) to supportive care. The treatments with ICERs less than set threshold values for cost-effectiveness are then selected. The ranking of selected therapies determines the most cost-effective sequence of treatments[iv].

Benefits from treatments are determined by examination of their impact on disease severity. PASI 50, PASI 75 and PASI 90 responses are defined as a ≥ 50%, ≥ 75% and ≥90% reduction from baseline PASI respectively. In the base case model, patients need to achieve a PASI 75 response to be classified as a responder and remain on the therapy. In sensitivity analysis, the lower threshold of PASI 50 response is also considered. Data on the effectiveness of different agents in the treatment of psoriasis was taken from the results of the mixed treatment comparison outlined in section 5.6.

[ii] This would contrast with a disease such as rheumatoid arthritis, where joint erosions mean patients cannot always return to perfect health and a Markov or patient level model would be required to incorporate changes in transitions.
[iii] Supportive care is considered equivalent to placebo (no systemic therapy). No significant additional treatment costs are associated with supportive care compared to the other treatments. Patients receiving supportive care are assumed to have two outpatient visits annually.
[iv] An alternative approach is to model each possible sequence of treatments and compare the expected costs and benefits of the whole sequence, but given the number of potential combinations (over 100,000), this is inefficient and ultimately gives the same result

A list of all variables that includes their value, range (distribution) and source.

Table 6.2.6.1. Key Model parameters and assumptions

Variable	Value	Description of parameter and distribution (source)
PASI Response, % probability	*(50/75/90)*	
Supportive Care	15/5/1	Values generated from evidence synthesis. Simulated conjugate distribution from MCMC analysis. (section 5.6)
Methotrexate	61/37/14	
Ciclosporin 3 mg/kg/day	58/34/12	
Efalizumab 1 mg/kg	54/29/10	
Etanercept 50 mg BIW	75/52/24	
Etanercept 25 mg BIW	63/38/14	
Infliximab 5 mg/kg	94/81/55	
Adalimumab 40 mg EOW	86/67/37	
Health Utilities	*(change(se))*	
No response (<PASI 50)	0.06 (0.03)	From analysis of M02-528 and M04-716 trial data. Normal distribution. (section 6.2.7.3)
Moderate response (≥PASI 50 to <PASI 90)	0.18 (0.02)	
Good response (≥PASI 90)	0.31 (0.03)	
Total Costs	*£ (trial/annual post trial)**	
Supportive Care	0/117	Includes Drug costs, monitoring and administration. (section 6.2.9). Fixed
Methotrexate	337/471	
Ciclosporin	770/1238	
Efalizumab	2495/9055	
Etanercept High Intermittent	3454/8852	
Etanercept	2433/9540	
Infliximab	7102/11508	
Adalimumab	3925/9540	
Etanercept Intermittent	2433/8406	
Intermittent rates	*(% of continuous dose per annum)*	
Ciclosporin	44	From Ho et al,[95] and IHCIS data. Normal distribution (Appendix 9.4)
Etanercept 25 mg	88	
Etanercept 50 mg (trial/annual)	74/46	
Length of stay for inpatient	*(days (se))*	Woolacott et al, Normal distribution.
Number of days for each admission	21 (2.55)	
Average Daily Salary	*(£)*	
Male	118	2006 Annual Survey of Hours and Earnings[96]. Fixed.
Female	91	

A separate list of all assumptions and a justification for each assumption.

The following list outlines the assumptions applied in the model and the justification for each assumption.

- It is assumed that once severe, the disease is not progressive and the chances of obtaining clear, controlled skin remain possible. This assumption means that long term modelling of effectiveness and baseline risks of disease progression using a Markov or patient-level model are not required. This assumption was previously utilised in the York model.

- It is assumed that the treatment effect for each treatment is independent of order. Furthermore, it is assumed that failure of a particular treatment does not preclude the use of any other subsequent treatments. These assumptions were also previously utilised in the York model. These assumptions allow the modelling of the cost effectiveness of treatment sequences. As these assumptions will likely affect all treatments equally, they are unlikely to have a major impact on the ICERs presented for adalimumab.

- Benefits from treatments are determined by examination of their impact on disease severity, specifically their impact on PASI response. It is assumed that the PASI response discriminates all the benefits of treatment. In other words a PASI 75 responder will have the same improvement in utility regardless of the treatment received. This analytical approach was also employed in the York model and a previous model for adalimumab in the treatment of RA[97]. This approach is

conservative for adalimumab and infliximab because some patients with psoriasis have other conditions such as PsA, AS or Crohn's disease (around 30% of patients with severe psoriasis have psoriatic arthritis). Adalimumab and infliximab would be expected to improve these conditions whereas efalizumab is not licensed for the treatment of these conditions. In this respect it can also be observed that etanercept is licensed for the treatment of PsA and AS but not Crohn's disease.

- The model excludes adverse effects of treatment from the calculation of costs and QALYs. This assumption was also previously employed in the York model. This assumption is discussed in detail in section 6.2.7.4.

6.2.6.2 Why was this particular type of model used?

On reviewing the economic evaluations identified in TA103, the model structure previously developed by the University of York was considered an appropriate model structure for use in the current appraisal. Consideration of the choice of analytic framework for psoriasis therapies has previously been set out in detail[4]. Use of this model structure has the benefit that the appraisal committee has considered this framework appropriate for presenting the cost effectiveness of etanercept and efalizumab, and should also ensure consistency in the analysis of the cost effectiveness of biologics for the treatment of psoriasis across different technology appraisals.

6.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

As outlined above the chosen structure was based on the York model. It is assumed that by the time that patients are considered eligible for adalimumab treatment, the disease is not progressive. Therefore, it is not of primary importance to model the long-term course of the disease, and the main analytical focus is on the short-term in the modelling of effectiveness.

6.2.6.4 What were the sources of information used to develop and inform the structure of the model?

The model structure was informed by previous research on the cost-effectiveness of etanercept and efalizumab in NICE TA103.

6.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

It is argued that all key features of the condition relevant to the decision problem are reflected in the model structure, with the exception of two areas where data are limited, as outlined in section 6.3.4.3.

6.2.6.6 **For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?**

The model uses a trial period, which is the time taken to assess response then a treatment period which is the time that responders remain on treatment.

6.2.6.7 Was a half-cycle correction used in the model? If not, why not?

Due to the modelling structure employed, a half cycle correction was not required.

6.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

The model assumes that patients responding at the end of the trial period (trial period as defined in the model) remain responders while they remain on treatment. This assumption is applied equally for all treatments. It is argued that this assumption is conservative for adalimumab, as the available data suggest that treatment response is maintained over time for adalimumab, although long-term randomised data are not available. However, available data for infliximab suggests that the initial high response rates are not maintained up to week 50 in controlled trials. In addition, as noted by the SMC, if an intention to treat analysis were to be conducted the response rates would be further reduced (see section 5.9.2 in clinical efficacy for further details of these data). The available data indicate that patients receiving intermittent therapy are less likely to maintain/ re-achieve a PASI 75 response[75,87,88]. Therefore, it is argued that the PASI response rates applied for intermittent etanercept in the model may not be achievable in clinical practice over the long term.

b) Non-model-based economic evaluations

A model-based evaluation was conducted therefore the questions in section b are not applicable.

6.2.7 Clinical evidence

6.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

No data are available to indicate a progressive worsening of patient status over time, for patients with severe psoriasis. Therefore, severe psoriasis is assumed not to be progressive.

6.2.7.2 How were the relative risks of disease progression estimated?

Not applicable (see section 6.2.7.1 above).

6.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

QALYs are used to assess the final health outcomes achieved with treatment. Treatments are assumed not to affect survival; therefore no linking between disease severity and life expectancy is included in the model. This is an area for future development if data become available which suggest a link between treatment of severe patients and life expectancy.

Evidence for linking the change in health utilities to PASI response types is limited, and has previously been estimated through indirect sources. Research was conducted to assess the responsiveness of changes in EQ-5D scores by PASI response over 16 weeks using new evidence from trials of adalimumab.

Methods

Two studies were combined in order to increase the sample size and to include patients from different countries. The first study (M04-716) was a 16-week, randomised, double-blind, placebo-controlled clinical trial. 271 patients in 28 centres in 8 European countries (23

centres) and Canada (5 centres) participated in this study. The second study (trial M02-528) was a Phase II, randomised, double-blind, placebo-controlled, multi-centre clinical trial in which the objective was to assess the clinical efficacy and safety of subcutaneously administered adalimumab vs. placebo using two dosage regimens for 12 weeks in the treatment of patients with moderate-to-severe plaque psoriasis. 147 patients in 18 centres in the USA participated in this study.

The analysis was conducted on the intention-to-treat (ITT) population, which was defined as all randomised patients who completed the baseline EQ-5D assessment. In the analysis of continuous variables, a patient with missing data for a visit, or who was discontinued prior to a visit, had the last observation carried forward. In the analysis of categorical variables (e.g., PASI response categories), a patient with missing data for a visit, or who was discontinued, was counted as a non-responder at that visit.

Pooling the data from the two trials, a mixed model with repeated measures of analysis of covariance was used to assess the relationship between changes in EQ-5D and clinical response. The analyses were blinded to the assigned treatment groups of patients. The mixed model included the categorical variables for PASI response, baseline DLQI, and PASI response by baseline DLQI interaction. The response categories for PASI change were <50%, 50%-75%, 75%-90%, and ≥90% and the categories for baseline DLQI were ≤10 and >10. The interaction term between PASI response and baseline DLQI was included in the model to assess whether the responsiveness of changes in EQ-5D to PASI response was different between the two groups. The model also included a random effect for the intercept.

Results

The EQ-5D was measured at baseline, week 12 and week 16 in trial M04-716 and at baseline and week 12 in trial M02-528. A total of 252 patients in trial M04-716 and 145 patients in trial M02-528 completed the EQ-5D at baseline and thus were included into the analysis.

The relationship between utility changes and PASI response was assessed using the pooled data from the two trials. PASI-50-75 and PASI 75-90 groups were combined as they provided similar estimates. Results indicated that the responsiveness of changes in EQ-5D to PASI response was significantly different between patients with baseline DLQI>10 and those with baseline DLQI≤10 (p=0.01) (Figure 6.2.7.1). Among patients with baseline DLQI>10, the PASI 50-75 and PASI 75-90 groups were also combined as a result of similar estimates. Once combined, all of the pairwise group differences were statistically significant, with the greater improvements in EQ-5D responding to the higher PASI response. The mean changes were 0.308, 0.178 and 0.063 for the PASI≥90% category, the 50%≤PASI<90% category and the PASI<50% category, respectively.

Table 6.2.7.1. Changes of EQ-5D by PASI response combining PASI 50-90

	Δ EQ-5D[a]		**P Values[b]**	
PASI Response	**Mean**	**SE**	**Versus PASI 50-90**	**Versus PASI 50-**
PASI 90+	0.219	0.021	0.004	<0.001
PASI 50-90	0.140	0.016	N/A	<0.001
PASI 50-	0.054	0.017	<0.001	N/A

NA: not applicable.
[a]P<0.001 for test of differences between PASI response categories from a mixed model with repeated measures analysis of covariance. [b]Pairwise comparisons between means were performed using Scheffe's test adjusting for multiple comparisons.

Figure 6.2.7.1. Changes of EQ-5D by PASI response for baseline DLQI >10

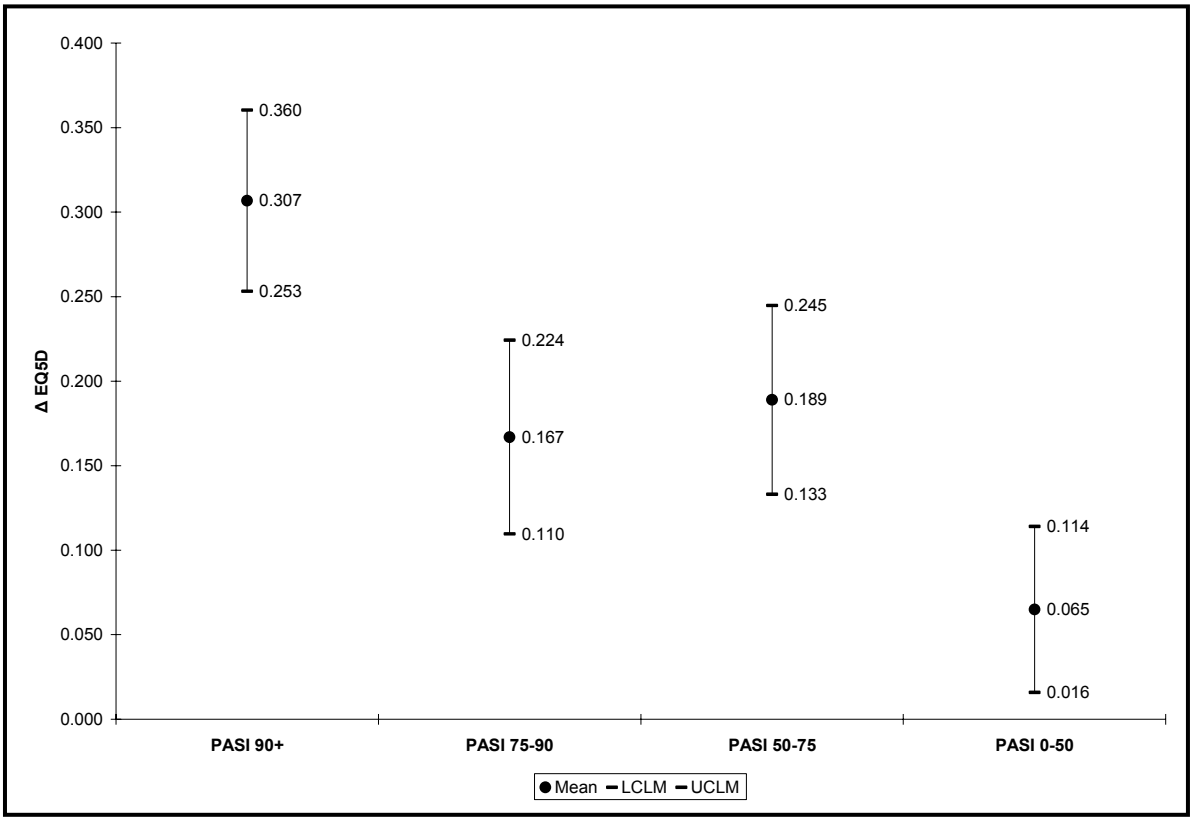


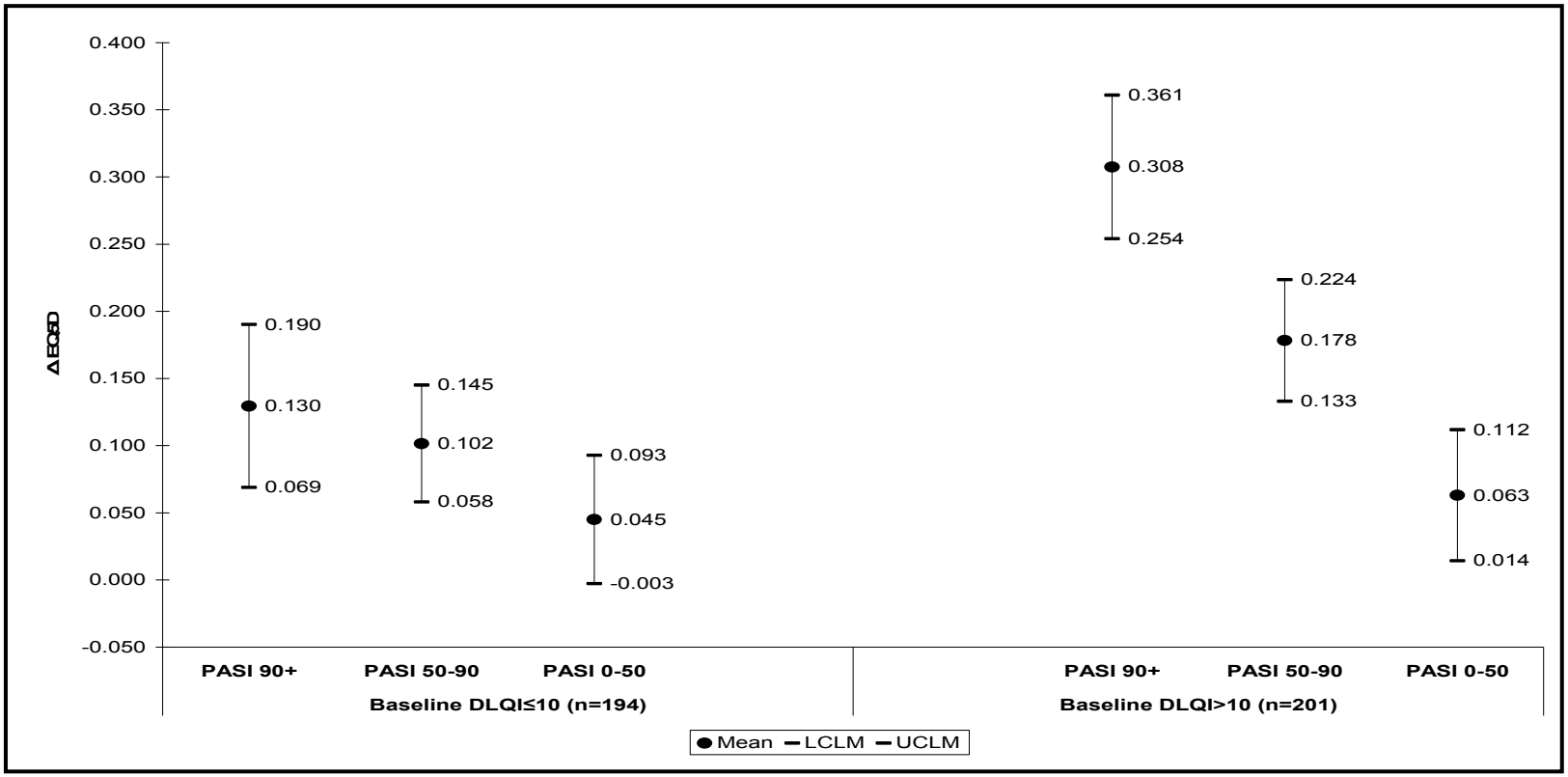
Table 6.2.7.2 Changes of EQ-5D by PASI response and baseline DLQI

Baseline DLQI	PASI Response	Δ EQ-5D[a]	SE	P Values[b]	
				Versus PASI 50-90	Versus PASI 50-
≤10 (n=194)	PASI 90+	0.130	0.031	0.982	0.436
	PASI 50-90	0.102	0.022	N/A	0.605
	PASI 50-	0.045	0.024	0.605	N/A
>10 (n=201)	PASI 90+	0.308	0.027	0.008	<0.001
	PASI 50-90	0.178	0.023	N/A	0.014
	PASI 50-	0.063	0.025	0.014	N/A

NA: not applicable.
[a]P=0.01 for test of overall PASI response categories by baseline DLQI interaction from a mixed model with repeated measures analysis of covariance. [b]Pairwise comparisons between means were performed using Scheffe's test adjusting for multiple comparisons.

Figure 6.2.7.2. Changes of EQ-5D by PASI response and baseline DLQI

- LCLM: lower 95% confidence limit; UCLM: upper 95% confidence limit.
- P=0.01 for test of overall PASI response categories by baseline DLQI interaction from a mixed model with repeated measures analysis of covariance.



The model links the response estimates from the evidence synthesis to the utility estimates provided above to calculate QALYs for each intervention.

To account for the difference in utility between continuous and intermittent therapy, a disutility assumption was built into the model to reflect the fact that recommencement of treatment and the effect of treatment are not instantaneous. Patients are likely to experience a reduction in utility upon the occurrence of each flare while they wait for the treatment to take effect. The mean time to effects of ciclosporin and etanercept (70 days and 35 days respectively)[95, 88,] were used to calculate the amount of time within the mean treatment period that a patient would experience the negative effects of a flare (Figure 6.2.7.3). During this time, patients are assumed to experience health utilities associated with non-response.

Figure 6.2.7.3. Estimation of flares on intermittent therapy*

ETANERCEPT		
Year 1	1st tx	84
	time off tx	39.6
	FLARE	
	2nd tx	84
	time off tx	39.6
	FLARE	
	3rd tx	84
	time off tx	39.6
Year 2	time off tx	40
	FLARE	

CICLOSPORIN		
Year 1	1st tx	80
	time off tx	109
	FLARE	
	2nd tx	81
	time off tx	60
	FLARE	
	3rd tx	35
	time off tx	40
Year 2	time off tx	52
	FLARE	
	4th tx	64

***All numbers are in days**

6.2.7.4 Were the health effects of adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

The health effects of adverse events associated with each of the treatments for psoriasis were not included in the economic modelling. All treatments for psoriasis may be associated with adverse events of differing severity. Little is known about the frequency of adverse events when systemic agents are used in clinical practice. Evidence from Pearce et al found that ciclosporin was most frequently associated with toxicities compared to methotrexate and biologic therapies[98]. However, many events were classified as minor such as a headache, which has a correspondingly minor impact on the costs or benefits of a treatment. When events were classified into serious or not serious, the chart review in this small sample found no serious toxicities associated with biologic agents (Table 6.2.7.3).

Table 6.2.7.3. Adverse events associated with psoriasis treatment

	Patients (N)	Adverse events (N)	Patients with an adverse event (N, and % affected)	Ratio of events per patient year (%)[v]	No. of 'significant' adverse events	Patients with 'significant' adverse events (N and % affected)
Methotrexate	181	135	91 (50)	28	65	61 (34)
CIclosporin	16	19	12 (75)	100	10	10 (63)
Biologics	29	3	3 (10)	20	0	0 (0)

As per the York model, toxicities have not been incorporated into the model. This will underestimate the costs associated with methotrexate and cyclosporine, and overestimate benefits somewhat, but not by an amount that would influence the results of the analysis.

6.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Expert opinion was used to determine the maximum dose that would be used in clinical practice for treatment with ciclosporin. Dr Steven Feldman, Professor of Dermatology at the Wake Forest University School of Medicine indicated that a maximum dose of 3mg/ kg per day is an appropriate maximum dose for ciclosporin in the evidence synthesis and economic modelling. Above this dose it was indicated that ciclosporin would be associated with high toxicity.

6.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

No further assumptions were made regarding the clinical evidence.

6.2.8 Measurement and valuation of health effects

6.2.8.1 Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The health effects associated with the different treatments were measured according to the PASI response criteria achieved for each treatment, as estimated using the mixed treatment comparison evidence synthesis.

6.2.8.2 Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?

The methods used for valuation of health effects using the PASI response score and EQ-5D utility scoring are provided above in section 6.2.7.3.

6.2.8.3 Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?

The health effects were mapped to the EQ-5D, which represents UK population valuations for health states in line with NICE's reference case.

[v] Further information obtained from authors of study. Numbers are a high estimate as they are based on the minimum time spent on therapy.

6.2.8.4 Were any health effects excluded from the analysis? If so, why were they excluded?

As highlighted in section 6.2.7.4 the health effects of adverse events for patients receiving all psoriasis treatments were not included in the analysis. The analysis assumes that the health benefits of treatments can be captured through analysis of their impact on PASI scores. It is argued that this may provide an underestimate of a treatment's impact on a patient's quality of life if other systemic improvements occur with effective treatment that are not captured via the observed relationship between PASI score and EQ-5D utility assessment.

Another important aspect that has not been included is the impact of different treatments on mortality. Anti-TNF therapy improves the cardiovascular risk profile of patients with RA by improving the lipid profile (higher HDL-cholesterol and decreased LDL:HDL ratio) and decreasing inflammation[99]. A study of mortality among RA patients treated with anti-TNF agents has been conducted in the US using the National Data Bank for Rheumatic Diseases (63,811 patient years of follow up)[100]. This study indicated that the use of anti-TNF agents was associated with a reduction in the mortality risk, despite patients having more severe RA at onset (Hazard Ratio 0.72, 95% CI 0.62 to 0.84). Anti-TNF therapy was most strongly associated with reduced cardiovascular mortality (0.55 to 0.69). This analysis suggests that use of anti-TNF agents has a beneficial impact in reducing mortality for patients with RA, however it is not known whether this is also a possibility for patients with psoriasis.

6.2.8.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Not applicable.

6.2.9 Resource identification, measurement and valuation

6.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

Costs were calculated for a trial period and a mean treatment period. The trial period refers to the time spent on treatment before assessment of response. This parameter was informed using the European labels of the drugs, where available, or the primary endpoint of the respective RCTs. Etanercept, efalizumab and the lower dose of ciclosporin had a trial period of 12 weeks. Adalimumab and methotrexate both had trial periods of 16 weeks and the infliximab label states to assess response at 14 weeks. Treatment periods were obtained from the York Assessment report[4]. Mean treatment periods of 75 weeks for ciclosporin and 186 weeks for all other drugs were calculated using a Markov model with an annual cycle. An assumed drop-out rate of 0.2 for all patients and a maximum assumed treatment period of 2 years for ciclosporin and 10 years for all other drugs, based on published guidelines, were used in their model. Discount rates were incorporated into the model by discounting treatment durations by 3.5 % per annum for both costs and effects, in accordance with NICE guidelines.

Drug Costs

Unit costs for all drugs were obtained from the British National Formulary 53[101]. All drugs are assumed to be taken continuously except for ciclosporin in which there is a potential for irreversible hepatotoxicity with continuous use,[102] and etanercept, where the summary of product characteristics (SmPC) specifies that treatment should only continue until remission is achieved[103]. The cost for intermittent etanercept was calculated as 88% of the cost of continuous therapy, as guided by evidence from the IHCIS data (see Appendix 9.4). The cost for ciclosporin was calculated with the assumption that intermittent treatment consists of 161 days of therapy in a year (44%), as reported in the PISCES study[95]. No drug cost was assumed for supportive care.

A mean weight of 80 kg is assumed for the calculation of costs, as per the York model. Sensitivity analyses are run using both lower (60 kg) and higher (90 kg) weights. The high weight assumption only affects the cost of infliximab, requiring one extra vial for each administration. The low weight assumption affects infliximab and ciclosporin, requiring one less vial per administration. For all drug dosages that are weight dependent, such as ciclosporin, efalizumab and infliximab, it is assumed that excess drug from the vial that is not administered is wasted. For example, even though an average patient may only need 240 mg of ciclosporin in one administration, it is assumed that 3 vials are used, as the drug comes in 100 mg vials.

Table 6.2.9.1. Drug unit costs

Drug	Price per mg	Price per tablet/vial	Source
Adalimumab	£8.94	£357.50	BNF 53
Ciclosporin, 25 mg	£0.02	£0.44	BNF 53
Ciclosporin, 100 mg	£0.02	£1.75	BNF 53
Efalizumab, 125 mg	£0.35	£169.20	BNF 53
Etanercept, 25 mg	£3.58	£89.38	BNF 53
Infliximab	£4.20	£419.62	BNF 53
Methotrexate, 2.5 mg	£0.05	£0.12	BNF 53

Table 6.2.9.2. Drug costs for the trial and treatment period

Treatment	Vials/tabs (assume 80 kg)	Trial doses	Annual doses	Total trial cost	Total annual cost
Adalimumab		10	26	£3,575	£9,295
Etanercept intermittent		24	91	£2,145	£8,161
Etanercept High intermittent		18	48	£3,166	£8,607
Etanercept		24	104	£2,145	£9,295
Efalizumab	1	13	52	£2,200	£8,799
Ciclosporin	3	84	161	£441	£845
Methotrexate	9	16	52	£17	£56
Infliximab	4	4	6.5	£6,714	£10,910

Monitoring and Administration Costs

Part of the total cost of treatment is attributed to monitoring, administration and outpatient visits. Regular laboratory tests are performed in order to screen for adverse effects both before and during treatment. Costs of tests performed to determine eligibility were not included in our calculations as there is not enough evidence. The schedule of laboratory tests for monitoring during treatment was taken from the York assessment report (see Table 6.2.9.3). They assumed that clinician and nurse time for such examinations were included in the care covered by a standard outpatient visit. Cost of administration of the biologics was calculated. For etanercept, efalizumab and adalimumab, it was assumed that to educate patients to self-inject would involve three 1-hour sessions of nurse time during the trial period. Infliximab infusion costs were based on the BSR guidelines, which recommend the monitoring period of the first four 2-hour infusions to be 2 hours and then reduced to 1 hour thereafter[104]. Unit costs for laboratory tests and outpatient visits were obtained from the York NHS Trust[4] and the NHS Reference Costs and National Tariff[105]. Where current costs were unavailable, the PSSRU inflation index was used to update costs to 2005/2006 levels[106].

Table 6.2.9.3: Schedule of annual laboratory tests

	FBC	Liver Biopsy	LFT	PIIINP	Serum creatinine	Total protein	U&E
Adalimumab	2-4					2-4	2-4
Ciclosporin					6 -14		6-14

Efalizumab	4-8				4-8	4-8
Etanercept Continuous	2-4				2-4	2-4
Etanercept Intermittent	2-4				2-4	2-4
Infliximab	4		4			4
MTX No PIIINP	4-5	0.28/pt/year	4-5	0		4-5*

* U&E, FBC and LFT: expert opinion suggests 8-9 tests in the first year of treatment, reducing to 4-5 annually thereafter.
FBC = Full blood count with differential, PIIINP = serum procollagen III aminopeptide (test), U&E = urea and electrolytes

Table 6.2.9.4: Schedule of outpatient visits

	Number of visits Week 0 to week12	Number of visits Annually (maintenance)
Adalimumab	4	4
Ciclosporin, continuous	5 to 6	6 to 7
Efalizumab	3	4
Etanercept, intermittent	3	4
Infliximab*	4 to 5	5 to 6
Methotrexate	4 to 5	4 to 5
Supportive care	-	2

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

Table 6.2.9.5. Laboratory unit costs (2003/2004)

Test	Cost/test	Source
Blood glucose	£0.43	York NHS Trust[4]
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	Chalmers et al, 2004 (mean)
Liver function test	£0.61	York NHS Trust
PIINP (serum procollagen III aminopeptide)	£21.64	Chalmers et al, 2004; York NHS Trust
Serum creatinine	£0.31	York NHS Trust
Total Protein	£0.43	York NHS Trust
U&E	£1.12	York NHS Trust

Table 6.2.9.6. Hospital visit unit costs

	Category	Source	2005/2006 Costs*
Cost/inpatient day*	Elective inpatient HRG data, major dermatological conditions. Weighted average of J39(>69 or wcc) and J40(<70 or w/o cc)	NHS Reference Costs and National Tariff	£256
Cost/outpatient visit*	Major dermatological conditions; other attendance without other investigation or procedure (J10op)	NHS Reference Costs and National Tariff	£58
Cost/outpatient visit*	Major dermatological conditions; other attendance with other investigation or procedure (J09op)	NHS Reference Costs and National Tariff	£80
Cost/patient educational hour	Cost per patient related hour, staff nurse	PSSRU Unit Costs of Health and Social Care	£35

* Updated to 2005/06 prices using PSSRU inflation index

Table 6.2.9.7. Monitoring, administration and outpatient visit Costs for Trial and Treatment Periods

	Monitoring Costs		Administration Costs		Outpatient Visit Costs	
Treatment	**Trial Period**	**Treatment Period**	**Trial Period**	**Treatment Period**	**Trial Period**	**Treatment Period**
Supportive Care	-	-	-	-	£0	£117
Adalimumab	£12	£12	£105	£0	£233	£233
Etanercept 25 mg intermittent	£8	£12	£105	£0	£175	£233
Etanercept 50 mg intermittent	£8	£12	£105	£0	£175	£233
Etanercept continuous	£8	£12	£105	£0	£175	£233
Efalizumab	£16	£24	£105	£0	£175	£233
Ciclosporin licensed	£9	£14	£0	£0	£320	£379
Methotrexate	£58	£153	£0	£0	£262	£262
Infliximab	£8	£17	£322	£523	£58	£58

Resource Utilisation

An important component of the York model was that patients who failed to respond to treatment consumed resources not directly related to the primary drug. Therefore, the cost of drugs that induced response was partially offset by reduced utilisation of other healthcare resources. The other resources were inpatient care, outpatient care and other treatments (like OTC drugs). A search was conducted for other sources of evidence on these items of resource utilisation.

The added cost of being a non-responder to treatment is reflected in the model using the number of days of hospitalisation as a parameter. The York Assessment report estimates the number of inpatient days to be 21 based on a combination of data from the Department of Health Hospital Episode Statistics for psoriasis (2002-2003) and evidence from audits of two local hospitals. It also runs a sensitivity analysis assuming 0 days of hospitalisation for non-responders. A study conducted in Germany gives data on treatment patterns, and resource consumption within the last 12 months and during current flares[107]. In this study, disease severity is categorised as moderate (10-20% affected body surface area) or severe (>20% affected body surface area). It found the average length of hospital stay to be 16.8 days in a year and 19 days during a current flare. A poster presented at a dermatology conference also found average length of hospital stay for patients to be 16 days[108]. In addition, Feldman et al linked resources to severity, but the study was from the early 90s and unlikely to be relevant to today's healthcare setting[109]. As well, this study did not report any data on average length-of-stay. In the absence of further data, the model uses 21 days of hospitalisation for the base case since the data comes from hospitals in the UK as well as the Department of Health, Hospital Episode statistics for psoriasis, while other estimates were based on other countries. A normal distribution around the mean, using 16 as the lower bound and 39 as the upper bound, is used to reflect uncertainty in this value. Sensitivity analyses assuming 0, 16 and 39 days of hospitalisation are run. The unit cost of an inpatient day was obtained from the NHS Reference Costs and National Tariff[105] and inflated to 2005/2006 using the PSSRU inflation indices.

Table 6.2.9.8. Evidence in literature informing number of days of hospitalisation

Source	**Annual number of days in hospital (mean)***	**Patient characteristics**
Sato (2006) [108]	16	Survey of European dermatologists. Mean BSA=20% in 175 hospitalisations
Munro (1999) [110]	16	Survey of inpatient dermatology wards in Scotland. 78% of 143 hospitalised patients were admitted due to severity of disease

Berger (2005) [107]	17	Study of dermatology departments in Germany. 106 patients with BSA 10-20%; 82 patients with BSA>20%
Woolacott (2006) 4	21	Average of UK DoH Hospital Episode Statistics (19.6 days), and audit of two local hospitals (22.3 and 22.7 days)
Caporis (2007) [111]	23	Survey of large dermatology wards of severe psoriasis patients in the UK
Schöffski (2007) [112]	39	Study of dermatology departments in Germany. Mean BSA=28.9%; Mean PASI=18.2; Mean DLQI=10.6 in 184 patients with psoriasis

*Mean number of days calculated using only those patients who were hospitalised

6.2.9.2 How were the resources measured?

See Section 6.2.9.1.

6.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

No disease progression was included in the model. No cost data were available from the trials used in the evidence synthesis for the estimation of effectiveness.

6.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

The model structure considers drug treatment sequences over the lifetime of patients. As per the estimation of effectiveness it is assumed that it is possible to extrapolate short-term costs over the long term for all treatments.

6.2.9.5 What source(s) of information were used to value the resources?

See Section 6.2.9.1.

6.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?

Adalimumab costs £357.50 per 40mg injection. This is the listed price reported in section 1.

6.2.9.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

The resources were measured and valued in a manner consistent with the reference case.

6.2.9.8 Were resource values indexed to the current price year?

The PSSRU inflation index was used to update costs to 2005/2006 levels.

6.2.9.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

It is assumed that effective treatment of psoriasis does not have an impact in reducing the number of GP/ consultant visits and concomitant medication that a patient requires. This assumption was made in the absence of published data on the relationship between PASI severity levels and resource utilisation for these cost offsets. This assumption is likely to

adversely affect the ICER estimates for adalimumab and infliximab, which are associated with the highest levels of PASI response.

6.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Costs and health benefits occurring in future years were discounted at 3.5% as per NICE's reference case. It should be noted that the ICERs presented in the present analysis will not be comparable with those previously generated for TA103 which used discount rates of 6% for costs and 1.5% for outcomes.

6.2.11 Sensitivity analysis

6.2.11.1 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

The uncertainty in model parameters was characterised using Probabilistic Sensitivity Analysis using second order Monte Carlo simulation. Distributions for model variables were specified to represent the uncertainty in these estimates A number of univariate sensitivity analyses were also conducted on key model parameters across a range of plausible values and assumptions, including those previously applied in the York model.

Table 6.2.11.1 outlines the parameters examined in the univariate sensitivity analysis.

Table 6.2.11.1 Univariate sensitivity analyses

Parameter	Basecase	In Sensitivity Analysis	Value	Source
Hospitalisation days for non responder	York model (21 days)	Alternative published estimates	0, 16, 39 days	Various, see table 6.2.9.8
Disutility for intermittent therapy	Included	No disutility included	-	York model
High dose for ciclosporin therapy	>3mg/ kg not included due to toxicity potential	5 mg/ kg data Included	Ciclosporin 5 mg/ kg PASI 50: 76%/ PASI 75: 55%/ PASI 90: 27%	Heydendael 2003
Continuous ciclosporin use	Intermittent use	Continuous use	-	Assumption
Etanercept intermittent dose	88% of continuous use	74% of continuous use	74% of continuous use	York model
PASI response required to remain on therapy	PASI 75 response	PASI 50 response	See section 5.6 for estimated PASI 50 response rates	Various see section 5.6
Utility values for PASI improvement	Adalimumab trial patients with DLQI >10 at baseline	York model values	Utility improvement by PASI response: <50%: 0.12; ≥50% and <75%: 0.29; ≥75% and <90%: 0.38; ≥90%: 0.41	York model
Utility values for PASI improvement	Adalimumab trial patients with DLQI >10 at baseline	Adalimumab trial patients with DLQI ≤ 10	Utility improvement for patients with DLQI ≤ 10: PASI <50%: 0.045; PASI > 50% <90%: 0.102; PASI > 90%: 0.13;	M02-528 and M04-716 Adalimumab trials
Utility values for PASI improvement	Adalimumab trial patients with DLQI >10 at baseline	All adalimumab trial patients	All adalimumab trial patients: PASI <50%: 0.054; PASI > 50% <90%: 0.140; PASI > 90%: 0.219	M02-528 and M04-716 Adalimumab trials
Mean patient weight	80 kg	Mean weights associated with lower and higher infliximab vial requirements	60kg , 90kg	York model
Productivity costs for non-responders who are hospitalised	Excluded	Included	£118 daily cost for males and £91 for females	2006 annual survey of hours and earnings
Proportion of non-responders hospitalised	100%	Alternative published estimate	40% (49 days in hospital)	Schoffski 2007

PASI response rates for adalimumab	M02-528 phase II adalimumab trial included	M02-528 adalimumab phase II trial excluded	PASI 50%: 88%; PASI 75%: 71%; PASI 90%: 41%	M02-528 adalimumab trial

6.2.11.2 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Probabilistic sensitivity analysis was conducted as outlined above. Table 6.2.6.1 lists key model variables, their distributions and sources.

6.2.11.3 Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

See section 6.2.11.1.

6.2.12 Statistical analysis

6.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

Not applicable.

6.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

It has been assumed that psoriasis is not progressive. Furthermore, it is assumed that the treatment effect of all treatments is maintained over the long term and is independent of the order in which treatments are used. Section 6.4.3.4 discusses the strengths and weaknesses of these assumptions and the evidence underpinning them.

6.2.13 Validity

The model has been tested for validity in terms of replicating the results of the previously published York model. Appendix 9.5 provides details of this validation. Furthermore, the model has been validated through development in two alternative software formats (R and Microsoft Excel). No differences in the model results were identified via the construction of the Excel replica, and no errors were identified in the programming code via this replication exercise. As such, it is considered that the model structure and results have been thoroughly validated.

6.3 Results

6.3.1 Base-case analysis

6.3.1.1 What were the results of the base-case analysis?

The infliximab strategy was found to give the most incremental QALYs in comparison to supportive care (0.18 QALYs [95%CI, 0.13-0.24]) closely followed by the adalimumab strategy (0.16 QALYs [95%CI, 0.11-0.22]). The continuous etanercept regimen gave slightly more QALYs than the intermittent regimens (0.13 QALYs versus 0.11 and 0.12 QALYs for the 25mg and 50mg doses respectively). Methotrexate and ciclosporin gave the lowest benefits of all the systemic therapies (0.13 and 0.08 QALYs respectively).

The disutility associated with intermittent therapy reduces the QALYs gained from etanercept from 0.13 to 0.11. However, since the cost of intermittent therapy is reduced (£4,114 vs £5,058), the ICERs compared to supportive care are both similar (around £37,000 per QALY). The disutility is also the reason for the lower QALYs gained from ciclosporin compared to methotrexate.

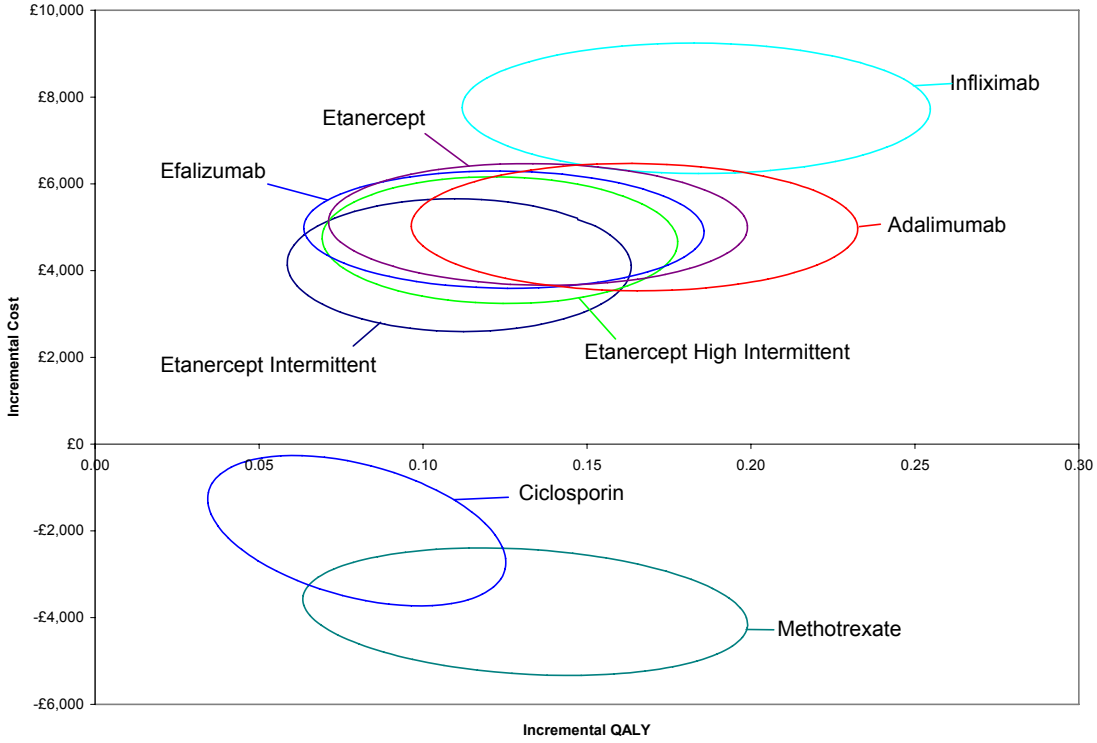
Table 6.3.1.1. Results of base case scenario (annualised)*

	Mean QALY (95% CI)	Mean Cost (£) (95% CI)	ICER vs. biologics only‡	ICER vs. Supportive Care
Methotrexate	0.129 (0.078 - 0.185)	-3,844 (-5,049 - -2,722)		-29,759
Ciclosporin	0.079 (0.044 - 0.116)	-1,987 (-3,313 - -597)		-25,135
Supportive Care	0 (0 - 0)	0 (0 - 0)	-	-
Etanercept Intermittent†	0.110 (0.070 - 0.153)	4,114 (2,862 - 5,335)	Extended Domination**	37,284
Etanercept High Intermittent†	0.123 (0.081 - 0.166)	4,699 (3,532 - 5,865)	Extended Domination**	38,358
Efalizumab	0.124 (0.077 - 0.173)	4,942 (3,855 - 6,002)	Extended Dominated**	39,948
Adalimumab	0.164 (0.110 - 0.219)	4,993 (3,806 - 6,157)	30,538	30,538
Etanercept	0.134 (0.085 - 0.186)	5,058 (3,928 - 6,169)	Dominated	37,676
Infliximab	0.182 (0.126 - 0.240)	7,736 (6,515 - 8,945)	147,906	42,492

* See section 6.2.3 for details of drug dosages and frequency
† Denotes intermittent use – where use is stopped upon remission and restarted upon relapse
** Extended domination refers to cases where the ICER is higher than that of another drug even though one of either costs or QALYs is more favourable
‡ Only biologics and supportive care compared. This excludes methotrexate and ciclosporin from the analysis

In terms of costs, both methotrexate and ciclosporin were found to be cost-saving. This is because the costs saved through reduced hospitalisations were greater than the drug-related costs. Consequently, the mean ICERs for both strategies dominate supportive care (more benefit with less costs). The uncertainty in these values is demonstrated in figure 6.3.1.1. Here, the 95% confidence interval for both treatments remains below the x-axis, resulting in a negative ICER, thus meaning it is likely the treatments are cost-saving. For the purposes of comparisons described herein, these two treatments were taken out of the options, allowing focus on what the next most cost-effective treatment would be.

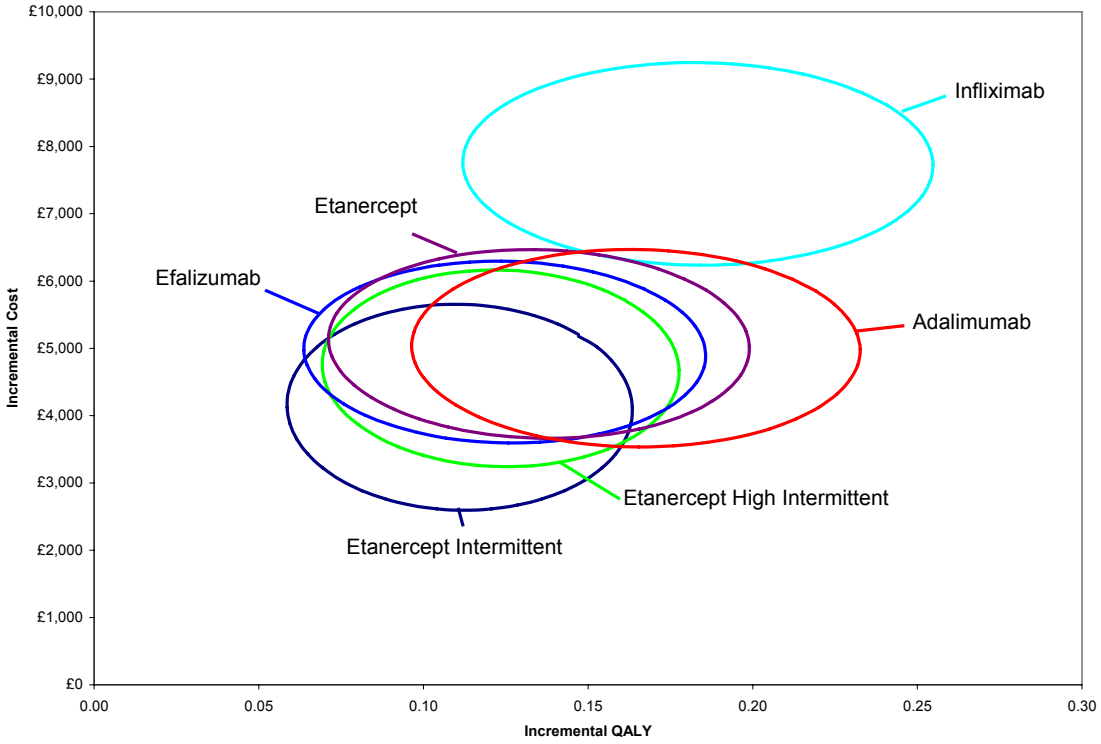
Figure 6.3.1.1. 95% confidence interval contour plots of the cost-effectiveness of all treatments*



*See section 6.2.3 for doses considered

The infliximab strategy costs the most (£7,736 [95%CI, 6,515-8,945]) resulting in an ICER of £42,000 per QALY compared to supportive care. The adalimumab strategy is the most cost-effective biologic strategy with additional costs of £4,993 (95%CI, 3,806-6,157) resulting in an ICER of £30,500 per QALY. All other treatments have ICERs between £37,000 and £40,000 per QALY. The horizontal spread in the ellipses describes the uncertainty in the PASI response parameters, and the relationship between utilities and response. The spread in the vertical axis is predominantly associated with risk and the cost of hospitalisations (figure 6.3.1.2).

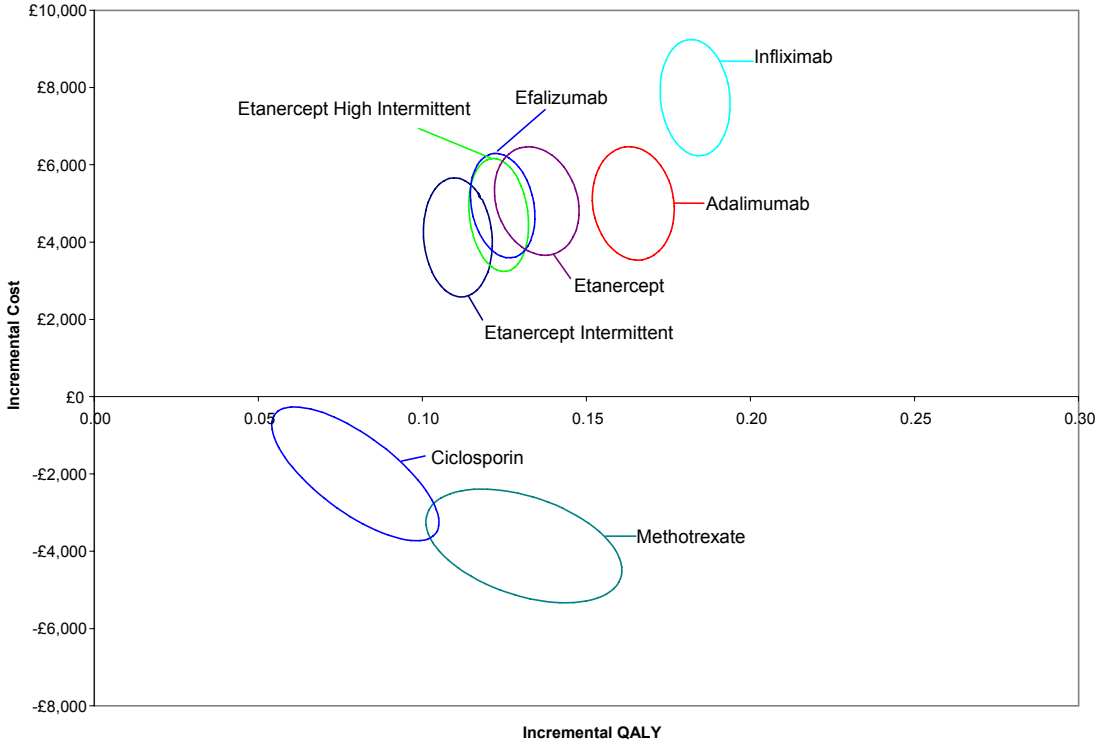
Figure 6.3.1.2. 95% confidence interval contour plots of the cost-effectiveness of biologic treatments*



*See section 6.2.3 for doses considered

Through additional analysis, it can be seen that the majority of the uncertainty in incremental QALYs comes from the relationship between utilities and PASI response, and not the uncertainty in PASI response estimates (Figure 6.3.1.3). In this analysis, it was assumed that there was no distribution around the mean utility values, so that the only uncertainty in incremental QALYs is a result of the uncertainty in PASI response parameters. Corresponding with the results from the evidence synthesis, the new ellipses of adalimumab and infliximab do not overlap any of the other treatments.

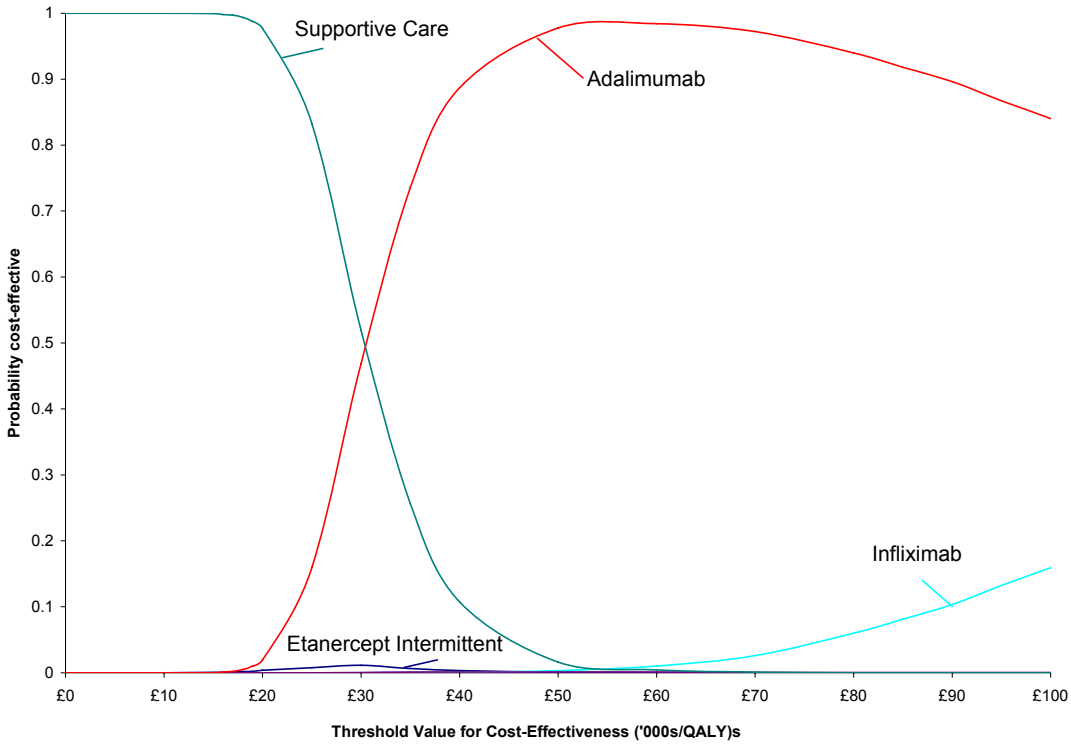
Figure 6.3.1.3. 95% confidence interval contour plots of the cost-effectiveness of all treatments assuming no uncertainty in utility to PASI response relationship



See section 6.2.3 for doses considered

Further analysis of the uncertainty is found in the acceptability curve (Figure 6.3.1.4). This represents the probability that each treatment is the most cost-effective at different threshold values of cost-effectiveness. This clearly shows that as this threshold increases, adalimumab has the highest probability of being cost-effective in comparison to supportive care. Once the threshold value for cost-effectiveness increases above £30,000 per QALY, adalimumab becomes the most cost-effective option compared to supportive care. Even at a threshold of £100,000 per QALY, adalimumab has a higher probability in comparison to infliximab.

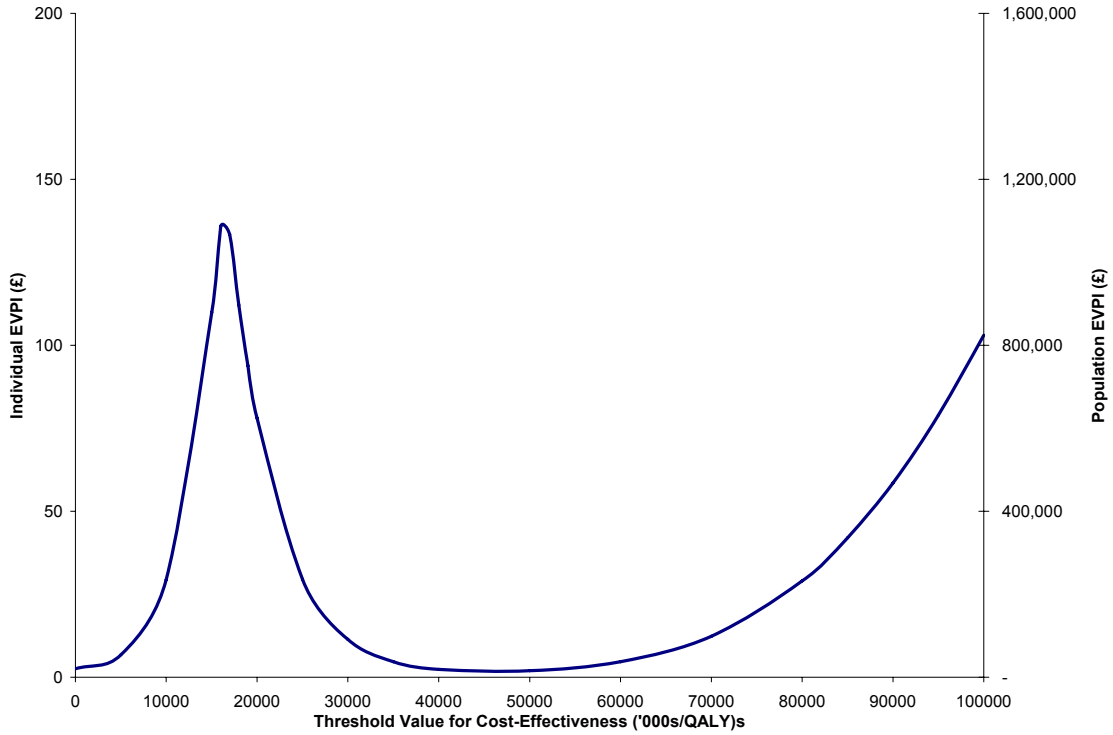
Figure 6.3.1.4. Cost-effectiveness acceptability curves for biologics*



* Other treatments not shown (they have probabilities of cost-effectiveness of 0)

The value of information analysis (Figure 6.3.1.5) peaks at a threshold of cost-effectiveness equal to £17,000 per QALY. The annual population EVPI is around £1 million, which, even if the decision has long-term consequences, would be less than the cost of performing a large randomised controlled trial of competing systemic therapies for psoriasis. It would, however, probably be sufficient for performing an observational study, but without a partial EVPI analysis, it is unclear whether this design could reduce decision uncertainty.

Figure 6.3.1.5. Annual Expected Value of Perfect Information per individual and population



Population is defined as the 8189 patients in England who would be eligible for biologic treatment based on their diagnosis of severe psoriasis.

Sequences

The most cost-effective sequencing of treatments is shown in Table 6.3.1.2. Note that the length of time spent on each treatment is not defined, so it is plausible that patients might not move through all of the treatments in the sequence. However, the use of each treatment in such an order would ensure the most cost-effective management strategy. Again, since the effects of the treatments are assumed to be independent of each other, the most cost-effective sequence changes depending on the threshold value of cost-effectiveness. Up until the threshold reaches £30,500 per QALY, the most cost-effective strategy is methotrexate followed by ciclosporin. Below this, no other treatments are determined to be cost-effective and therefore supportive care would be the only available option. If payers were willing to pay more for additional benefit, it can be observed that instead of supportive care, adalimumab should be incorporated into the sequence. As the threshold continues to increase, all treatments are included in order of their cost-effectiveness ratios.

Table 6.3.1.2. Most cost-effective ordering of therapies as a function of cost-effectiveness threshold

Threshold value of cost-effectiveness (£)	1st in sequence	2nd in sequence	3rd in sequence	4th in sequence	5th in sequence	6th in sequence	7th in sequence	8th in sequence	9th in sequence
0	Methotrexate	Ciclosporin	Supportive Care						
5000	Methotrexate	Ciclosporin	Supportive Care						
10000	Methotrexate	Ciclosporin	Supportive Care						
15000	Methotrexate	Ciclosporin	Supportive Care						
20000	Methotrexate	Ciclosporin	Supportive Care						
25000	Methotrexate	Ciclosporin	Supportive Care						
30000	Methotrexate	Ciclosporin	Supportive Care						
35000	Methotrexate	Ciclosporin	Adalimumab	Supportive Care					
40000	Methotrexate	Ciclosporin	Adalimumab	Etanercept	Etanercept intermittent	Etanercept high intermittent	Efalizumab	Supportive Care	
45000	Methotrexate	Ciclosporin	Adalimumab	Etanercept	Etanercept intermittent	Etanercept high intermittent	Efalizumab	Infliximab	Supportive Care
50000	Methotrexate	Ciclosporin	Adalimumab	Etanercept	Etanercept high intermittent	Etanercept intermittent	Infliximab	Efalizumab	Supportive Care
55000	Methotrexate	Ciclosporin	Adalimumab	Etanercept	Infliximab	Etanercept high intermittent	Etanercept intermittent	Efalizumab	Supportive Care
60000	Methotrexate	Ciclosporin	Adalimumab	Infliximab	Etanercept	Etanercept high intermittent	Etanercept intermittent	Efalizumab	Supportive Care
65000	Methotrexate	Ciclosporin	Adalimumab	Infliximab	Etanercept	Etanercept high intermittent	Efalizumab	Etanercept intermittent	Supportive Care
70000	Methotrexate	Ciclosporin	Adalimumab	Infliximab	Etanercept	Etanercept high intermittent	Efalizumab	Etanercept intermittent	Supportive Care
75000	Methotrexate	Ciclosporin	Adalimumab	Infliximab	Etanercept	Etanercept high intermittent	Efalizumab	Etanercept intermittent	Supportive Care

6.3.2 Subgroup analysis

6.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

No further subgroup analyses were conducted other than those identified in the sensitivity analyses outlined in section 6.3.3.

6.3.3 Sensitivity analyses

6.3.3.1 What were the main findings of the sensitivity analyses?

Key parameters were varied in the one-way sensitivity analysis. Changing the number of days hospitalised due to non-response to treatment had an important effect on the resulting ICERs. For example, the adalimumab strategy increased by approximately £7,000 per QALY when the number of days was decreased from 21 (base case) to 16 days (estimate of average length of stay from a German study)[107]. It increased by nearly £30,000 per QALY (to £61,000 per QALY) if it was assumed that non-responders did not require hospitalisations. However, the ICER reduced to £5,000 per QALY when the number of days was varied to a high estimate of 39 inpatient days.

Modifying parameters on intermittent therapy improved the results for etanercept. If no disutility was assumed due to flares (e.g. the strategy gives the same benefit to continuous therapy) then the ICER of etanercept decreased from £37,000 to £31,000 per QALY. If the frequency of dosing is taken from the trial of intermittent therapy, the ICER improved to £28,000. Sensitivity analyses on methotrexate and ciclosporin do not change the magnitude of their results. Using an alternative source of utility values (used in Woolacott et al) decreases the utility values marginally. Assuming patients have less severe psoriasis impairment at baseline (DLQI ≤10), the utility benefits associated with response decrease, and therefore, the cost-effectiveness of all treatments decreases (higher ICERs). Using all patients to estimate utility benefits, regardless of severity of psoriasis impairment at baseline, also decreases cost-effectiveness, though to a lesser degree. Assessing response using PASI 50 increases all ICERs as it means patients remain on treatment for longer, thus increasing costs. It has not been possible to consider the impact of using a stopping rule of PASI 50 response combined with DLQI improvement of 5 points, as data are not available to indicate how many patients would achieve this level of response for each treatment. When the average weight of a patient is assumed to be higher, at 90 kg, only the ICER of infliximab is increased owing to the added cost of one extra vial of medication. When a low patient weight is assumed (60 kg), both the ICERs of infliximab and ciclosporin decrease due to the decrease in cost of medication. Including the costs of lost productivity while hospitalised increases the cost-effectiveness of all treatments due to the added cost to society. Assuming that only 40% of non-responders incur hospitalisation costs, but those that do spend 49 days in hospital, marginally increases the ICERs. The reduction in the number of hospitalisations is cancelled out by the extra days spent in hospital per patient. Lastly, the M02-528 adalimumab phase II trial has a primary endpoint earlier than that of the other adalimumab trials. However, the base case assumes the primary endpoints are the same in order to use all available evidence. Excluding adalimumab's phase II trial increases the efficacy of adalimumab slightly, thus lowering the ICER.

Table 6.3.3.1. ICERs from sensitivity analyses changing key parameters†

	£ per QALY (rank in optimum treatment sequence at £30,000 threshold)±							
	Methotrexate	Ciclosporin	Etanercept intermittent	High Etanercept intermittent	Efalizumab	Adalimumab	Etanercept	Infliximab
Base Case*	-29,759 (1)	-25,135 (2)	37,284	38,358	39,948	30,538	37,676	42,492
Hospitalisation Days = 16	**-21,559 (1)**	**-13,301 (2)**	**47,322**	**47,782**	**48,506**	**37,718**	**45,912**	**45,063**
Hospitalisation Days = 39	**-59,176 (1)**	**-67,635 (2)**	**1,374 (4)**	**4,558 (5)**	**9,253 (7)**	**4,782 (3)**	**8,138 (6)**	**18,790 (8)**
Hospitalisation Days = 0	**4,608 (1)**	**24,495 (2)**	**79,281**	**77,850**	**75,813**	**60,629**	**72,190**	**70,184**
No disutility on intermittent therapy	**-29,759 (1)**	**-17,117 (2)**	**30,660**	**31,489**	**39,948**	**30,538**	**37,676**	**42,492**
High doses of ciclosporin	**-29,759 (1)**	**-22,271 (2)**	**37,284**	**38,358**	**39,948**	**30,538**	**37,676**	**42,492**
Continuous ciclosporin use	**-29,759 (1)**	**-10,950 (2)**	**37,284**	**38,358**	**39,948**	**30,538**	**37,676**	**42,492**
Etanercept dose = 74% of continuous	**-29,759 (1)**	**-25,135 (2)**	**27,585 (3)**	**80,927**	**39,948**	**30,538**	**37,676**	**42,492**
Alternative Utility values	**-33,266 (1)**	**-27,716 (2)**	**41,844**	**45,597**	**43,264**	**38,679**	**42,304**	**57,946**
PASI Response assessed using PASI 50	**-31,607 (1)**	**-32,280 (2)**	**42,308**	**43,854**	**43,103**	**35,243**	**42,838**	**46,836**
Utility values of patients with DLQI≤10	**-72,741 (1)**	**-60,66 (2)**	**91,389**	**97,168**	**95,920**	**80,124**	**92,387**	**116,073**
Utility values of all patients	**-42,081 (1)**	**-35,454 (2)**	**52,770**	**54,772**	**56,209**	**44,005**	**53,330**	**61,911**
Patients with high weight (assume 90 kg)	**-29,759 (1)**	**-25,135 (2)**	**37,284**	**38,358**	**39,948**	**30,538**	**37,676**	**59,118**
Patients with low weight (assume 60 kg)	**-29,759 (1)**	**-30,195 (2)**	**37,284**	**38,358**	**39,948**	**30,538**	**37,676**	**25,866 (3)**
Include lost productivity while hospitalised	**-40,036 (1)**	**-39,976 (2)**	**24,736 (4)**	**26,549 (5)**	**29,223 (7)**	**21,540 (3)**	**27,356 (6)**	**34,211**
Only 40% of non-responders hospitalised (49 days in hospital)	**-27,447 (1)**	**-21,806 (2)**	**40,119**	**41,016**	**42,362**	**32,562**	**40,000**	**44,355**
Adalimumab phase II trial excluded	**-29,606 (1)**	**-25,833 (2)**	**37,671**	**38,564**	**39,856**	**29,399 (3)**	**37,970**	**42,644**

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

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

Table 6.3.3.2. Incremental costs from sensitivity analyses changing key parameters

	£							
	Methotrexate	Ciclosporin	Etanercept intermittent	High Etanercept intermittent	Efalizumab	Adalimumab	Etanercept	Infliximab
Base Case*	-3,844	-1,987	4,114	4,699	4,942	4,993	5,058	7,736
Hospitalisation Days = 16	**-2,784**	**-1,051**	**5,222**	**5,853**	**6,001**	**6,167**	**6,164**	**8,939**
Hospitalisation Days = 39	**-7,643**	**-5,348**	**151**	**558**	**1,144**	**782**	**1,092**	**3,420**
Hospitalisation Days = 0	**595**	**1,937**	**8,749**	**9,537**	**9,380**	**9,913**	**9,692**	**12,777**
No disutility on intermittent therapy	**-3,844**	**-1,987**	**4,114**	**4,699**	**4,942**	**4,993**	**5,058**	**7,736**
High doses of ciclosporin	**-3,844**	**-2,188**	**4,114**	**4,699**	**4,942**	**4,993**	**5,058**	**7,736**
Continuous ciclosporin use	**-3,844**	**-1,271**	**4,114**	**4,699**	**4,942**	**4,993**	**5,058**	**7,736**
Etanercept dose = 74% of continuous	**-3,844**	**-1,987**	**3,044**	**9,914**	**4,942**	**4,993**	**5,058**	**7,736**
Alternative Utility values	**-3,844**	**-1,987**	**4,114**	**4,699**	**4,942**	**4,993**	**5,058**	**7,736**
PASI Response assessed using PASI 50	**-3,799**	**-2,377**	**4,226**	**4,855**	**4,926**	**5,318**	**5,235**	**8,056**
Utility values of patients with DLQI≤10	**-3,844**	**-1,987**	**4,114**	**4,699**	**4,942**	**4,993**	**5,058**	**7,736**
Utility values of all patients	**-3,844**	**-1,987**	**4,114**	**4,699**	**4,942**	**4,993**	**5,058**	**7,736**
Assume high weight	**-3,844**	**-1,987**	**4,114**	**4,699**	**4,942**	**4,993**	**5,058**	**10,762**
Assume low weight	**-3,844**	**-2,387**	**4,114**	**4,699**	**4,942**	**4,993**	**5,058**	**4,709**
Include lost productivity due to hospitalisation	**-4,799**	**-2,832**	**3,118**	**3,658**	**3,987**	**3,934**	**4,061**	**5,210**
Only 40% of non-responders hospitalised (49 days in hospital)	**-3,545**	**-1,724**	**4,427**	**5,025**	**5,241**	**5,324**	**5,370**	**8,075**
Adalimumab Phase II trial excluded	**-3913**	**-2103**	**2893**	**3548**	**3871**	**3752**	**3942**	**6547**

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

Table 6.3.3.3. Incremental QALYs from sensitivity analyses changing key parameters

	QALY							
	Methotrexate	Ciclosporin	Etanercept intermittent	High Etanercept intermittent	Efalizumab	Adalimumab	Etanercept	Infliximab
Base Case*	0.129	0.079	0.110	0.123	0.124	0.164	0.134	0.182
Hospitalisation Days = 16	**0.129**	**0.079**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
Hospitalisation Days = 39	**0.129**	**0.079**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
Hospitalisation Days = 0	**0.129**	**0.079**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
No disutility on intermittent therapy	**0.129**	**0.116**	**0.134**	**0.149**	**0.124**	**0.164**	**0.134**	**0.182**
High doses of ciclosporin	**0.129**	**0.098**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
Continuous ciclosporin use	**0.129**	**0.116**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
Etanercept dose = 74% of continuous	**0.129**	**0.079**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
Alternative Utility values	**0.116**	**0.072**	**0.098**	**0.103**	**0.114**	**0.129**	**0.120**	**0.134**
PASI Response assessed using PASI 50	**0.119**	**0.074**	**0.100**	**0.111**	**0.114**	**0.151**	**0.122**	**0.172**
Utility values of patients with DLQI≤10	**0.053**	**0.033**	**0.045**	**0.048**	**0.052**	**0.062**	**0.055**	**0.067**
Utility values of all patients	**0.091**	**0.056**	**0.078**	**0.086**	**0.088**	**0.113**	**0.095**	**0.125**
Assume high weight	**0.129**	**0.079**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
Assume low weight	**0.129**	**0.079**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
Include lost productivity due to hospitalisation	**0.129**	**0.079**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
Only 40% of non-responders hospitalised (49 days in hospital)	**0.129**	**0.079**	**0.110**	**0.123**	**0.124**	**0.164**	**0.134**	**0.182**
Adalimumab Phase II trial excluded	**0.132**	**0.081**	**0.110**	**0.122**	**0.124**	**0.168**	**0.134**	**0.182**

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

6.3.4 Interpretation of economic evidence

6.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The model facilitated a comprehensive cost-effectiveness analysis of all potential treatments for moderate-to-severe psoriasis. Methotrexate and ciclosporin were found to be the most cost-effective treatments for severe psoriasis in line with the conclusions of the York model. However, neither treatment appears to be very well tolerated. Guidelines and consensus statements from the BAD and the British Journal of Dermatology recommend other therapies due to the fact that currently available standard systemic therapies lack consistent efficacy over time and are associated with the potential for major long-term toxicity; thus the importance of the newly developed biologic therapies.

Of the available biologic therapies, adalimumab was found to be the most cost-effective when compared to supportive care (around £30,000 per QALY). Infliximab gave the most benefit, as seen in the evidence synthesis. However, the cost of the drug and the related infusions outweigh the benefit that it provides with an ICER of £42,000 per QALY compared to supportive care. When analysed with other biologics only, the ICER of infliximab compared to adalimumab becomes £148,000 per QALY - far above typical threshold values of cost-effectiveness. Only when the weight of a patient was less than 60kg (e.g. 3 vials instead of 4) was infliximab a potentially cost-effective treatment. However, since the average weight in the clinical trials of psoriasis patients was closer to 90kg, it is more likely that a higher dose of infliximab (e.g. 5 vials instead of 4) is required which results in an ICER versus supportive care of £60,000 per QALY. In addition, the long-term effectiveness of infliximab therapy is considered uncertain.

The intermittent etanercept strategies are potentially appealing due to their reduced costs. However, the evidence synthesis found etanercept produced the least PASI responders of all anti-TNF agents, and when the disutility associated with a disease flare was included, these strategies produced lower QALY gains. The resultant ICERs were close to £40,000 per QALY compared to supportive care. When looking only at biologics, all three etanercept strategies are weakly dominated by adalimumab due to the greater benefit that adalimumab can provide. That is, the ICER for adalimumab is lower than the ICER for etanercept in spite of its higher cost.

The one-way sensitivity analysis found the assumptions regarding hospitalisations to be the most influential on the cost-effectiveness of all treatments. The assumption is based on a limited evidence base, and assumes that patients who do not respond to treatment incur an annual hospitalisation cost. Assessing the plausibility of this assumption is difficult, but the paper by Munro et al. allows some validation[110]. In this, a number of dermatology wards in the UK were surveyed in the month of March, 1997. They found 143 patients were admitted for inpatient stays in that one-month period with a median length of stay equal to 15 days (range 2 to 52 days). The prevalence of patients with severe psoriasis in the catchment area of these wards can be estimated to be nearly 1200 persons.[vi] This equates to 12% of the severe population being hospitalised in one month. Seasonal variation of psoriasis flares means that annual rates are unlikely to simply be the multiplication of the monthly rate by 12. However, the rates appear to broadly concord with model prediction rates of 40% hospitalisations (PASI 50 rates of 60% for methotrexate and ciclosporin) per annum for non-biologic systemic treatments, which would commonly have been used at the time of this survey.

[vi] The population served by the dermatology clinics is quoted at 6.6 million. The prevalence of psoriasis is estimated to be 1.5%, and the prevalence of severe psoriasis (DLQI >10) in psoriasis patients has been estimated at 1.2%. This equates to 1188 patients with severe psoriasis in the area.

The adverse events associated with each treatment are not explicitly modelled in our analysis. This is because biologic agents have been proven to be relatively safe[113], with very few toxicities seen in clinical trials or clinical practice. Since the frequencies of events are so low, it is unlikely that the incorporation of toxicities into the model will modify the ICER results to any extent, except perhaps to reduce the relative cost-effectiveness of methotrexate and ciclosporin.

An important assumption in the developed model is the independence of effects with sequential treatments. The model assumes that the benefits of a given treatment will be the same if trialed before or after any number of alternative treatments. There is some evidence to suggest that certain drugs may induce a resistance to other drugs, such as in the study by Costanzo et al., which suggests infliximab, but not efalizumab, induces resistance to etanercept[114]. The incorporation of this element would require detailed and, to date, non-existent evidence for each combination of treatments, and more complex economic modelling.

The model also assumes that once a patient responds, that response is maintained for the duration of treatment. While this assumption will require longitudinal studies to test its validity, initial evidence suggests that this is particularly problematic for infliximab treated patients, where PASI 75 response rates had halved by 26 weeks from the 10 week maximum[75]. Similarly, data from the same study indicates that maintenance of response is less likely for patients receiving intermittent therapy. This has not been incorporated into the analysis.

Developments of the existing model:

A number of developments were made to the York model described in Woolacott et al[4]. These are detailed below:

- *Evidence synthesis*. Trials which were completed after the existing analysis were incorporated into the evidence synthesis. In particular, evidence on adalimumab was included. Also included were trials on infliximab, which were not considered in the base case analysis of York's original model. Some of the trials included in the Woolacott model did not meet our inclusion criteria and were thus excluded from our evidence synthesis. Reasons for exclusion were: not having FDA or EMEA approval[115], not having a primary endpoint between 8 and 16 weeks[116], or equating a PGA of clear to PASI 75 response when no PASI response data was available[117]. This therefore changed the input parameters on response for each treatment.

- *Health utility values*. The utility values used in the York model were derived from a combination of sources and noted to be evidence of limited quality by the NICE committee.[6] A detailed analysis of the relationship between health utilities and PASI response was performed to enhance the evidence base. Further, it was possible to evaluate the improvement in the severe patient group recommended for treatment in the BAD guidelines. The impact of using the different sources of values was examined in the sensitivity analysis.

- *Intermittent therapy*. It was previously assumed that patients on an intermittent therapy strategy incurred equal benefits to those on continuous therapy. Since intermittent therapy, by definition, means flares will occur, an adjustment has been made by incorporating a disutility during the time a patient experiences a flare. The frequency of dosing has also been updated from an analysis of administrative data. Again, the impact of these changes is examined in the sensitivity analysis.

- *Discount rates*. Originally costs and benefits were discounted at 6% and 1.5% respectively. In accordance with new guidelines, both have been discounted at 3.5% in the new analysis. Use of 3.5% discount rates inflates the ICERs compared to those presented in the York model.

6.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The base case model analysis uses utility data for patients with a DLQI score >10. Therefore, these results are applicable to the treatment of patients with severe psoriasis. A sensitivity analysis has been conducted using utility data from all patients, which corresponds to a moderate-severe patient population.

6.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strength of the evaluation is that it draws upon the analytical framework of the York model and considers the cost effectiveness of the main systemic therapies likely to be considered for the treatment of severe psoriasis. As outlined in section 6.3.4.1 a number of areas have been identified in the York model where further research was merited. In particular, the model uses EQ-5D utilities collected directly in the adalimumab trials, which it is argued are the best estimates of utility gain by levels of psoriasis improvement. One of the main potential limitations of the analysis is that treatment effect is only considered according to PASI response. It is argued that improvements in the PASI score are not an ideal proxy for treatment response. This may be particularly the case for patients with concomitant psoriatic arthritis where improvements in arthritis symptoms would be expected with anti-TNF agents such as adalimumab, but not necessarily with other psoriasis treatments. Similarly, the PASI score may not correlate with patient functioning as closely as other outcome measures such as the DLQI. However, the PASI score has the benefit that it has been reported for the majority of systemic therapies. Furthermore, establishing a closer relationship between utility gains and disease severity may only serve to improve the ICERs of those treatments considered the most effective in the evidence synthesis (adalimumab and infliximab). Therefore, this limitation is unlikely to affect the relative ordering of the cost effectiveness of therapies in this therapeutic area.

6.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

- *Head to head comparisons.* The comparative efficacy of treatments is estimated using statistical techniques to make indirect comparisons. However some treatments, such as PUVA, were not included in the analysis since they had not been compared to a treatment that is linked to the chain of evidence. A randomised controlled trial of all potential treatment options would form a better source of evidence. However, the value of information analysis suggests that the additional costs of this trial are not necessarily warranted given current decision uncertainty. Observational studies would be a more prudent course for future research in this topic.

- *Hospitalisations*. As recommended in the NICE Guidance for etanercept and efalizumab, research on the rate of inpatient hospitalisation in people with moderate-to-severe psoriasis is warranted. While average length-of-stay in hospital for non-responders is informed from real-life data from hospitals in the UK, there is still limited evidence in the literature for validation of this number.

- *Other resource utilisation*. It has been found that the costs of treating psoriasis increase with disease severity[109]. However, our model only incorporates hospitalisation costs due to the limited detailed evidence that links disease severity with additional resource costs, such as dermatologist or GP consultations, out-of-pocket expenses, over-the-counter medicines or prescription medicines and psychological services.

- *Long-term outcomes in clinical practice*. Much of the analysis is based on results from clinical trials. A number of data gaps could be filled with longitudinal cohorts and registries. Firstly, patients recruited into clinical trials typically differ from patients in clinical practice due to the specific inclusion/exclusion criteria. Consequently, the efficacy,

safety and frequency of administration for individual treatments need to be verified in clinical practice. Secondly, since it is unlikely that head to head comparisons of biologic treatments will be undertaken in the near future, the relative efficacy between different treatments could be compared in clinical practice. Lastly, longitudinal data would enable the investigation of resistance patterns between moving between different treatments.

7 Assessment of factors relevant to the NHS and other parties

7.1 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact has been calculated assuming a number of different scenarios with regard to market share of adalimumab for patients eligible for an anti-TNF agent. Patients receiving adalimumab would be assessed for treatment response after 16 weeks. This budget impact analysis has been calculated assuming that patients not achieving a PASI 75 response would discontinue treatment. The PASI 75 response rate has been taken from the evidence synthesis presented in section 5.

Assuming all patients eligible for an anti-TNF agent according to the current NICE guidance for etanercept receive adalimumab, the estimated annual budget impact is shown on table 7.1.1:

Table 7.1.1: Annual budget impact assuming 100% of eligible psoriasis patients receive adalimumab (eligible for an anti-TNF agent as per current NICE guidance for etanercept)

	Year 1	Year 2	Year 3	Year 4	Year 5
All England	£66,126,110	£52,344,700	£52,344,700	£52,344,700	£52,344,700
All Wales	£3,967,521	£3,140,646	£3,140,646	£3,140,646	£3,140,646
TOTAL	**£70,093,631**	**£55,485,346**	**£55,485,346**	**£55,485,346**	**£55,485,346**

7.2 What number of patients were assumed to be eligible? How was this figure derived?

The estimated prevalence of psoriasis in England and Wales is 1-2%. Using an estimate of 1.5% for the prevalence and national population statistics[118], Table 7.2.1 gives details of the estimated prevalence of psoriasis. NICE guidance TA103 estimates that 1.1% of patients with severe psoriasis would be eligible for treatment with etanercept. Current prevalence data and the 1.1% eligibility rate were combined to present the number of patients eligible for adalimumab

Table 7.2.1: Estimated number of people with psoriasis eligible for treatment with adalimumab in England and Wales

	Population	Prevalence	Eligible for adalimumab
All England	49,632,436	744,487	8,189
All Wales	2,977,912	44,669	491
TOTAL	**52,610,348**	**789,155**	**8,681**

There are limited published data available on the incidence of psoriasis in the UK. This budget impact analysis uses only a prevalence-based approach to estimating the numbers of patients eligible for adalimumab. This analysis assumes the numbers of patients eligible over time remains constant as per the budget impact analysis presented by NICE for TA 103 (costing template).

7.3 What assumption(s) were made about current treatment options and uptake of technologies?

Table 7.1.1 presented above, assumes that 100% of eligible psoriasis patients would receive adalimumab. Table 7.3.1 and Table 7.3.2 present estimates using scenarios where 33% and 66% of eligible patients receive adalimumab respectively.

Table 7.3.1: Annual budget impact assuming 33% of eligible PsA patients receive adalimumab

	Year 1	Year 2	Year 3	Year 4	Year 5
All England	£21,821,616	£17,273,751	£17,273,751	£17,273,751	£17,273,751
All Wales	£1,309,282	£1,036,413	£1,036,413	£1,036,413	£1,036,413
TOTAL	**£23,130,898**	**£18,310,164**	**£18,310,164**	**£18,310,164**	**£18,310,164**

Table 7.3.2: Annual budget impact assuming 66% of eligible PsA patients receive adalimumab

	Year 1	Year 2	Year 3	Year 4	Year 5
All England	£43,643,232	£34,547,502	£34,547,502	£34,547,502	£34,547,502
All Wales	£2,618,564	£2,072,826	£2,072,826	£2,072,826	£2,072,826
TOTAL	**£46,261,796**	**£36,620,328**	**£36,620,328**	**£36,620,328**	**£36,620,328**

The net resource implications depend on which treatments are displaced by the introduction of adalimumab. Assuming that all patients are currently receiving conventional systemic therapy rather than a biologic agent, the net resource implications of introducing adalimumab would be as estimated above in Table 7.1.1. The net budget impact of giving adalimumab to patients who would previously have been prescribed etanercept (50mg weekly dose) would be negligible due to the equivalent maintenance annual treatment cost of etanercept (50mg weekly dose) and adalimumab. The prescription of adalimumab rather than infliximab would result in a net budget saving due to the lower annual treatment cost of adalimumab compared to infliximab. It is considered that adalimumab would be unlikely to displace the use of efalizumab because the proposed position of adalimumab is earlier in the treatment sequence. Efalizumab is currently only recommended as an option by NICE for etanercept failures or for those in whom etanercept is not suitable due to intolerance or contraindications.

7.4 What assumption(s) were made about market share (where relevant)?

See section 7.3 above.

7.5 What unit costs were assumed? How were these calculated?

Unit costs applied in the budget impact analysis were the same as those outlined in section 6 for use in the cost-effectiveness model.

7.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

The use of adalimumab has been demonstrated to reduce the symptoms of severe psoriasis and improve patient quality of life. As indicated in the economic modelling, a successful PASI response would be expected to result in fewer hospital admissions with prolonged stays, thus reducing pressures on the need to admit patients to hospital. It is also anticipated that outpatient visits and treatment of psychological comorbidities could be reduced by successful treatment, however limited data are available to quantify costs associated with these resources according to the levels of disease severity.

Adalimumab is supplied in a ready-to-use prefilled syringe or as a single-use automatic injection device with needleguard that delivers 40mg adalimumab by pushbutton, as a single subcutaneous injection once every two weeks. Patients can be trained to self-administer the injections at home. Additionally, adalimumab can be delivered to the patient's home as a free of charge service paid for by Abbott. Therefore, infrastructure support costs in providing a day-case service for the administration of treatment are not required for adalimumab. However, infliximab is administered intravenously. This places demand on day-case services and waiting list targets may be impacted. As adalimumab is available in-prefilled form, no reconstitution of the product is required, which is the case for efalizumab.

7.7 Were there any estimates of resource savings? If so, what were they?

The budget impact estimates presented above do not incorporate the resource savings for reduced hospital admissions for patients responding to adalimumab therapy. As outlined in section 6 these costs are substantial for patients with severe psoriasis. Assuming a 21-inpatient stay for a non-responder the cost is £5,376 per patient. Assuming 67% of patients respond to adalimumab (PASI 75 response from evidence syntheses), there will be 5,816 responders to adalimumab. The resultant resource savings from reduced inpatient stays is £31,267,214 per year.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Savings in other direct medical costs associated with psoriasis are likely through the use of adalimumab, principally outpatient consultations and GP consultations. No data are available for the impact of adalimumab on use of concomitant psoriasis medications, either prescription or over the counter treatments. Furthermore, a proportion of costs of the disease are borne by patients and society. These costs mainly take the form of lost productivity due to absenteeism or presenteeism as a result of severe psoriasis. Treatments that are able to reduce hospital admissions, and improve work productivity should be able to offset the sizeable non-medical costs of psoriasis. There are reduced patient costs associated with adalimumab treatment compared to infliximab, for patients who self-injecting adalimumab. These costs are principally travel costs, and lost work or leisure time taken up by receiving infliximab infusions in an inpatient setting.

8 References

Full references are provided at the end of this document

9 Appendices

9.1 Appendix 1

Summary of Product Characteristics or Technical Manual or drafts

9.2 Appendix 2: search strategy for section 5

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

1) Databases

The following databases searched and the span dates for these databases are given below. Unless otherwise specified the server provider used was Dialog DataStar:

Database	**Date Span**	**Search Strategy**
MedLine	1996-to date	Table 9.2.1
MedLine (R) In Process	1996-to date	Table 9.2.1
EMBASE	1996-to date	Table 9.2.2
BIOSIS	1996-to date	Table 9.2.3
Cochrane Library*	-to date	Table 9.2.4

*Cochrane Central Library of Controlled Trials CENTRAL – direct subscription access

CENTRAL includes details of published articles taken from bibliographic databases (notably MEDLINE and EMBASE), and other published and unpublished sources.

2) Conference Abstracts

The following conference abstracts were searched;

Abstracts	**Date Span**	**Search Strategy**
American Academy of Dermatology AAD (www.aad.org)	-to date	Manual Search
European Academy of Dermatology and Venerology EADV (www.**eadv**.org)	-to date	Manual Search
British Association of Dermatology BAD (abstract discs)	-to date	Manual Search

3) Other

An in-house database was searched.

9.2.2 The date on which the search was conducted.

The most recent literature search was undertaken on 8th August 2007.

9.2.3 The date span of the search.

Sub-section 9.2.1 provides details of the date spans of the searches. As previously mentioned, it was not deemed necessary to search older databases as the clinical phase of adalimumab began in 1997.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Tables 9.2.1 – 9.2.4 provide details of the search strategies used, which include free text words, key words and details of the search terms *e.g.* Boolean:

Table 9.2.1: Medline (PubMed)

No.	Database	Search term	Info added since	Results
CP		[Clipboard]		0
1	MEDLINE - 1996 to date	PT=RANDOMIZED-CONTROLLED-TRIAL	unrestricted	149571
2	MEDLINE - 1996 to date	PT=CONTROLLED-CLINICAL-TRIAL	unrestricted	31647
3	MEDLINE - 1996 to date	RANDOMIZED-CONTROLLED-TRIALS.DE.	unrestricted	42912
4	MEDLINE - 1996 to date	RANDOM-ALLOCATION.DE.	unrestricted	24652
5	MEDLINE - 1996 to date	DOUBLE-BLIND-METHOD.DE.	unrestricted	49937
6	MEDLINE - 1996 to date	SINGLE-BLIND-METHOD.DE.	unrestricted	8902
7	MEDLINE - 1996 to date	PT=CLINICAL-TRIAL$ OR PT=MULTICENTER-STUDY	unrestricted	290523
8	MEDLINE - 1996 to date	CLINICAL-TRIALS.DE.	unrestricted	53502
9	MEDLINE - 1996 to date	CLINICAL NEAR TRIAL	unrestricted	373461
10	MEDLINE - 1996 to date	(SINGL$ OR DOUBL$ OR TREBL$ OR TRIPL$).TI,AB. AND (MASK$ OR BLIND$).TI,AB.	unrestricted	53407
11	MEDLINE - 1996 to date	(LATIN ADJ SQUARE).TI,AB.	unrestricted	1433
12	MEDLINE - 1996 to date	PLACEBOS.W..DE.	unrestricted	8903
13	MEDLINE - 1996 to date	PLACEBO$	unrestricted	68579
14	MEDLINE - 1996 to date	RANDOM$.TI,AB.	unrestricted	292028
15	MEDLINE - 1996 to date	RESEARCH-DESIGN.DE.	unrestricted	28374
16	MEDLINE - 1996 to date	COMPARATIVE-STUDY.DE.	unrestricted	1195
17	MEDLINE - 1996 to date	EVALUATION-STUDIES.DE.	unrestricted	26312
18	MEDLINE - 1996 to date	FOLLOW-UP-STUDIES.DE.	unrestricted	184168
19	MEDLINE - 1996 to date	PROSPECTIVE-STUDIES.DE.	unrestricted	154470
20	MEDLINE - 1996 to date	CROSS-OVER-STUDIES.DE.	unrestricted	18828

21	MEDLINE - 1996 to date	CONTROL$.TI,AB.	unrestricted	872094
22	MEDLINE - 1996 to date	PROSPECTIV$.TI,AB.	unrestricted	182857
23	MEDLINE - 1996 to date	VOLUNTEER$.TI,AB.	unrestricted	59000
24	MEDLINE - 1996 to date	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23	unrestricted	1619951
25	MEDLINE - 1996 to date	ANIMALS.W..DE.	unrestricted	1719233
26	MEDLINE - 1996 to date	HUMAN.DE.	unrestricted	4400888
27	MEDLINE - 1996 to date	25 NOT 26	unrestricted	1163597
28	MEDLINE - 1996 to date	24 NOT 27	unrestricted	1369498
29	MEDLINE - 1996 to date	ADALIMUMAB OR HUMIRA OR D2E7 OR TRUDEXA OR D2 ADJ E7	unrestricted	738
30	MEDLINE - 1996 to date	ADALIMUMAB.RN.	unrestricted	443
31	MEDLINE - 1996 to date	29 OR 30	unrestricted	738
32	MEDLINE - 1996 to date	PSORIASIS	unrestricted	8970
33	MEDLINE - 1996 to date	PSORIASIS.W..DE.	unrestricted	6295
34	MEDLINE - 1996 to date	PUSTULOSIS	unrestricted	548
35	MEDLINE - 1996 to date	32 OR 33 OR 34	unrestricted	9303
36	MEDLINE - 1996 to date	35 AND 31 AND 28	unrestricted	40
37	MEDLINE In-Process - latest eight weeks	PT=CLINICAL-TRIAL-PHASE-II OR PT=CLINICAL-TRIAL-PHASE-III OR PT=CLINICAL-TRIAL-PHASE-IV OR PT=CONTROLLED-CLINICAL-TRIAL OR PT=RANDOMIZED-CONTROLLED-TRIAL	unrestricted	28
38	MEDLINE In-Process - latest eight weeks	PT=RANDOMIZED-CONTROLLED-TRIAL	unrestricted	26
39	MEDLINE In-Process - latest eight weeks	PT=CONTROLLED-CLINICAL-TRIAL	unrestricted	1
40	MEDLINE In-Process - latest eight weeks	PT=CLINICAL-TRIAL$ OR PT=MULTICENTER-STUDY	unrestricted	23
41	MEDLINE In-Process - latest eight weeks	CLINICAL NEAR TRIAL	unrestricted	3826
42	MEDLINE In-Process - latest eight weeks	(SINGL$ OR DOUBL$ OR TREBL$ OR TRIPL$).TI,AB. AND (MASK$ OR BLIND$).TI,AB.	unrestricted	1945
43	MEDLINE In-Process - latest eight weeks	(LATIN ADJ SQUARE).TI,AB.	unrestricted	43
44	MEDLINE In-Process - latest eight weeks	RANDOM$.TI,AB.	unrestricted	11645
45	MEDLINE In-Process - latest eight weeks	PLACEBO$	unrestricted	2352
46	MEDLINE In-Process - latest eight weeks	CONTROL$.TI,AB.	unrestricted	37776

47	MEDLINE In-Process - latest eight weeks	**PROSPECTIV$.TI,AB.**	**unrestricted**	**7512**
48	MEDLINE In-Process - latest eight weeks	**VOLUNTEER$.TI,AB.**	**unrestricted**	**1917**
49	MEDLINE In-Process - latest eight weeks	**37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48**	**unrestricted**	**52343**
50	MEDLINE In-Process - latest eight weeks	**ADALIMUMAB OR HUMIRA OR D2E7 OR D2 ADJ E7 OR TRUDEXA**	**unrestricted**	**66**
51	MEDLINE In-Process - latest eight weeks	**ADALIMUMAB.RN.**	**unrestricted**	**0**
52	MEDLINE In-Process - latest eight weeks	**50 OR 51**	**unrestricted**	**66**
53	MEDLINE In-Process - latest eight weeks	**PSORIASIS**	**unrestricted**	**333**
54	MEDLINE In-Process - latest eight weeks	**PSORIASES**	**unrestricted**	**0**
55	MEDLINE In-Process - latest eight weeks	**PUSTULOSIS**	**unrestricted**	**17**
56	MEDLINE In-Process - latest eight weeks	**53 OR 54 OR 55**	**unrestricted**	**344**
57	MEDLINE In-Process - latest eight weeks	**56 AND 52 AND 49**	**unrestricted**	**5**

After duplicate removal no unique citation was found in Medline in Process. The number of results includes reviews that were removed from the above list of citations. Of the 40 hits from Medline, 8 were considered relevant and included patients with psoriatic arthritis as well those with psoriasis.

Table 9.2.2: EMBASE

58	EMBASE - 1996 to date	**CLINICAL-TRIAL#.DE.**	**unrestricted**	**378609**
59	EMBASE - 1996 to date	**CONTROLLED-CLINICAL-TRIAL.MJ. OR MULTICENTER-STUDY.MJ. OR PHASE-1-CLINICAL-TRIAL.MJ. OR PHASE-2-CLINICAL-TRIAL.MJ. OR PHASE-3-CLINICAL-TRIAL.MJ. OR PHASE-4-CLINICAL-TRIAL.MJ.**	**unrestricted**	**183**
60	EMBASE - 1996 to date	**RANDOMIZED-CONTROLLED-TRIAL.MJ.**	**unrestricted**	**618**
61	EMBASE - 1996 to date	**CLINICAL NEAR TRIAL$**	**unrestricted**	**413157**
62	EMBASE - 1996 to date	**(SINGL$ OR DOUBL$ OR TREBL$ OR TRIPL$).TI,AB. AND (MASK$ OR BLIND$).TI,AB.**	**unrestricted**	**51423**
63	EMBASE - 1996 to date	**(LATIN ADJ SQUARE).TI,AB.**	**unrestricted**	**505**
64	EMBASE - 1996 to date	**PLACEBOS.W..DE.**	**unrestricted**	**64814**
65	EMBASE - 1996 to date	**PLACEBO$**	**unrestricted**	**92824**
66	EMBASE - 1996 to date	**RANDOM$.TI,AB.**	**unrestricted**	**245787**
67	EMBASE - 1996 to date	**COMPARATIVE-STUDY.MJ.**	**unrestricted**	**242**

68	EMBASE - 1996 to date	PROSPECTIVE-STUDIES.MJ.	unrestricted	65
69	EMBASE - 1996 to date	CONTROL$.TI,AB.	unrestricted	559314
70	EMBASE - 1996 to date	PROSPECTIV$.TI,AB.	unrestricted	164121
71	EMBASE - 1996 to date	VOLUNTEER$.TI,AB.	unrestricted	52280
72	EMBASE - 1996 to date	EVALUATION.W..MJ.	unrestricted	380
73	EMBASE - 1996 to date	FOLLOW-UP.MJ.	unrestricted	475
74	EMBASE - 1996 to date	CROSSOVER-PROCEDURE.MJ.	unrestricted	59
75	EMBASE - 1996 to date	RANDOMIZATION.W..MJ.	unrestricted	248
76	EMBASE - 1996 to date	DOUBLE-BLIND-PROCEDURE.MJ.	unrestricted	25
77	EMBASE - 1996 to date	SINGLE-BLIND-PROCEDURE.MJ.	unrestricted	3
78	EMBASE - 1996 to date	58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77	unrestricted	1154841
79	EMBASE - 1996 to date	ADALIMUMAB.W..DE.	unrestricted	2232
80	EMBASE - 1996 to date	331731-18-1.RN.	unrestricted	2208
81	EMBASE - 1996 to date	ADALIMUMAB OR HUMIRA OR D2E7 OR D2 ADJ E7	unrestricted	2303
82	EMBASE - 1996 to date	TRUDEXA	unrestricted	7
83	EMBASE - 1996 to date	79 OR 80 OR 81 OR 82	unrestricted	2303
84	EMBASE - 1996 to date	PSORIASIS-DT.MJ. OR PARAPSORIASIS-DT.MJ. OR PSORIASIS-VULGARIS-DT.MJ. OR PUSTULAR-PSORIASIS-DT.MJ. OR PUSTULOSIS-PALMOPLANTARIS-DT.MJ.	unrestricted	3584
85	EMBASE - 1996 to date	PSORIASIS-DT#.MJ.	unrestricted	3584
86	EMBASE - 1996 to date	84 OR 85	unrestricted	3584
87	EMBASE - 1996 to date	78 AND 83 AND 86	unrestricted	99

After duplicate removal 84 hits were available from Embase. After removal of reviews and other non-relevant citations 20 hits were considered potentially relevant.

Table 9.2.3: BIOSIS

88	BIOSIS Previews (R) - 1996 to date	PSORIASIS.TI.	unrestricted	3227
89	BIOSIS Previews (R) - 1996 to date	HUMANS#.DE.	unrestricted	2908363
90	BIOSIS Previews (R) - 1996 to date	PSORIASIS.DE.	unrestricted	6244
91	BIOSIS Previews (R) - 1996 to date	PSORIASES.TI,AB.	unrestricted	4
92	BIOSIS Previews (R) -	PUSTULOSIS.TI.	unrestricted	187

	1996 to date			
93	BIOSIS Previews (R) - 1996 to date	**PUSTULOSIS.DE.**	**unrestricted**	**280**
94	BIOSIS Previews (R) - 1996 to date	**88 OR 90 OR 91 OR 92 OR 93**	**unrestricted**	**6712**
95	BIOSIS Previews (R) - 1996 to date	**ADALIMUMAB OR HUMIRA OR D2E7 OR D2 ADJ E7**	**unrestricted**	**661**
96	BIOSIS Previews (R) - 1996 to date	**ADALIMUMAB.TI.**	**unrestricted**	**256**
97	BIOSIS Previews (R) - 1996 to date	**331731-18-1.DE.**	**unrestricted**	**600**
98	BIOSIS Previews (R) - 1996 to date	**ADALIMUMAB.DE.**	**unrestricted**	**605**
99	BIOSIS Previews (R) - 1996 to date	**TRUDEXA.TI,AB,DE.**	**unrestricted**	**0**
100	BIOSIS Previews (R) - 1996 to date	**95 OR 96 OR 97 OR 98**	**unrestricted**	**661**
101	BIOSIS Previews (R) - 1996 to date	**(CLINICAL ADJ TRIAL).TI.**	**unrestricted**	**9590**
102	BIOSIS Previews (R) - 1996 to date	**RANDOMIZED-CLINICAL-TRIAL.DE.**	**unrestricted**	**811**
103	BIOSIS Previews (R) - 1996 to date	**(CLINICAL ADJ TRIAL).DE.**	**unrestricted**	**40365**
104	BIOSIS Previews (R) - 1996 to date	**CLINICAL NEAR TRIAL$**	**unrestricted**	**51270**
105	BIOSIS Previews (R) - 1996 to date	**101 OR 102 OR 103 OR 104**	**unrestricted**	**55850**
106	BIOSIS Previews (R) - 1996 to date	**105 AND 100 AND 94**	**unrestricted**	**9**

After duplicate removal 5 citations were left in Biosis of which 2 were considered relevant and included one study in patients with PsA.

Table 9.2.4: Cochrane

Search String	Description	Hits
1	adalimumab or humira or trudexa or d2e7 or d2 e7	
2	Psoriasis or Pustulosis	
3	Controlled Clinical Trials Database	
4	1 and 2 and 3 and 4	7

All the hits from Cochrane were already retrieved in the Medline search.

Conference Abstracts

Abstracts from the American Academy of Dermatology (AAD), the European Academy of Dermatology and Venerology (EADV) and the British Association of Dermatology (BAD) were manually searched for data relating to randomised controlled trials or open-label trials of adalimumab for psoriasis. The following hits were identified and considered relevant to this submission.

AAD: 2004 – 1 hit

2005 – 7 hits
2006 – 4 hits
2007 – 4 hits

EADV: 2005 – 5 hits
2006 – 2 hits
2007 – 4 hits

BAD: 2006 – 1 hit
2007 – 2 hits

Table 9.2.5 – Duplicate Removal Strategy

107	BIOSIS Previews (R) - 1996 to date EMBASE - 1996 to date MEDLINE - 1996 to date MEDLINE In-Process - latest eight weeks [all]	**combined sets 36, 57, 87, 106**	**unrestricted**	**153**
108	BIOSIS Previews (R) - 1996 to date EMBASE - 1996 to date MEDLINE - 1996 to date MEDLINE In-Process - latest eight weeks [all]	**dropped duplicates from 107**	**unrestricted**	**26**
109	BIOSIS Previews (R) - 1996 to date EMBASE - 1996 to date MEDLINE - 1996 to date MEDLINE In-Process - latest eight weeks [all]	**unique records from 107**	**unrestricted**	**127**
110	MEDLINE - 1996 to date	**split set 109**		**38**
111	MEDLINE In-Process - latest eight weeks	**split set 109**		**0**
112	EMBASE - 1996 to date	**split set 109**		**84**
113	BIOSIS Previews (R) - 1996 to date	**split set 109**		**5**

9.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

The company database, Abbott Product Literature (PRLIT), was also searched for relevant information.

Table 9.2.6 - PRLIT

Search String	Description	Hits
1	Adalimumab (Keyword)	2449

2	Psoriasis	312
3	Comparative Study OR Controlled Study OR Placebo Controlled Study OR Single Blind Study OR Double Blind Study	65

Manual review of the hits revealed that of the 65 hits, 6 were considered relevant.

The database complies relevant and substantial information relating solely to Abbott products and was devised in Abbott Park, Chicago, Illinois, USA.

In addition to information retrieved from PRLIT, the Clinical Overview, the Safety Overview, and all the Clinical Study Reports (CSRs) supplied to the FDA and the EMEA for the marketing authorisation application were included in the review of the literature.

9.2.6 The search inclusion and exclusion criteria.

Inclusion criteria

Although in the search strings listed above all types of trials were included in the strategy, the inclusion criteria for the literature search was as follows: all randomised controlled trials (RCTs) comparing adalimumab to an alternative treatment (including placebo) when used for the treatment of psoriasis. Trials of patients with psoriatic arthritis were also identified and considered important, but have not been included in Section 5.2.1 because the list of RCTs is specifically for trials evaluating adalimumab for psoriasis. Open-labelled controlled trials were also included. All types of trial were included in the search string to capture all the studies pertaining to adalimumab for Ps, the RCTs were then extracted manually after a thorough inspection of the citations.

Exclusion criteria

Reviews and studies that did not fit the inclusion criteria or studies based on juvenile data (0-17 years old) were excluded.

9.2.7 The data abstraction strategy.

The relevant search terms were entered into the database being searched and the terms were then combined to form search strings as detailed in section 9.2.4. The titles and abstracts (if available) of all papers revealed at this stage were then reviewed and eliminated manually if they were not relevant to the search – as per the inclusion and exclusion criteria.

9.3 Appendix 3: search strategy for section 6

9.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

The search criteria were set deliberately wide as preliminary reviews indicated little available literature, given the limited number of systemic treatments available for psoriasis.

The search terms used were "cost AND effectiveness AND psoriasis" (AND being the Boolean term). After removing duplications, the titles and abstracts (if available) of all papers revealed at this stage were then reviewed and eliminated manually if they were not relevant to the search. Only six published studies met the inclusion criteria of being full economic evaluations of systemic treatments, as the other identified studies were either reviews or cost comparison studies or were dealing with topical treatments only.

The following databases searched are given below. Unless otherwise specified the server provider used was Dialog DataStar:

Database	Date Span	Search Strategy
MedLine (PubMed)	1996-to date	Table 9.3.1
MedLine (R) In Process	1996-to date	Table 9.3.2
EMBASE	1996-to date	Table 9.3.3
HEED	-to date	N/A
NHS EED	-to date	N/A

9.3.2 The date on which the search was conducted.

The latest literature search was undertaken on 4th September 2007.

9.3.3 The date span of the search.

Sub-section 9.3.1 provides details of the date spans of the searches.

9.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 9.3.1; MedLine (PubMed) Search Strategy

No	Database	Search term	Info added since	Results
1	MEDLINE − 1996 to date	psoriasis	unrestricted	9083
2	MEDLINE − 1996 to date	PSORIASIS.W..DE.	unrestricted	6389
3	MEDLINE − 1996 to date	cost ADJ effectiveness	unrestricted	15593
4	MEDLINE − 1996 to date	COST−BENEFIT−ANALYSIS.DE.	unrestricted	26931
5	MEDLINE − 1996 to date	cost	unrestricted	127383
6	MEDLINE − 1996 to date	effectiveness	unrestricted	101989
7	MEDLINE − 1996 to date	5 AND 6	unrestricted	20289
8	MEDLINE − 1996 to date	3 OR 4 OR 7	unrestricted	37205
9	MEDLINE − 1996 to date	1 OR 2	unrestricted	9083
10	MEDLINE − 1996 to date	8 AND 9	unrestricted	56

Table 9.3.2: MedLine In Process Search Strategy

11	MEDLINE In−Process − latest eight weeks	psoriasis	unrestricted	357
12	MEDLINE In−Process − latest eight weeks	cost ADJ effectiveness	unrestricted	551
13	MEDLINE In−Process − latest eight weeks	cost	unrestricted	3538
14	MEDLINE In−Process − latest eight weeks	effectiveness	unrestricted	3902
15	MEDLINE In−Process − latest eight weeks	13 AND 14	unrestricted	700

16	MEDLINE In−Process − latest eight weeks	12 OR 15	unrestricted	700
17	MEDLINE In−Process − latest eight weeks	11 AND 16	unrestricted	4

Table 9.3.3: EMBASE Search Strategy

18	EMBASE − 1996 to date	psoriasis	unrestricted	12244
19	EMBASE − 1996 to date	PSORIASIS.W..DE.	unrestricted	9798
20	EMBASE − 1996 to date	18 OR 19	unrestricted	12244
21	EMBASE − 1996 to date	cost ADJ effectiveness	unrestricted	45429
22	EMBASE − 1996 to date	COST−EFFECTIVENESS−ANALYSIS.DE.	unrestricted	43079
23	EMBASE − 1996 to date	cost	unrestricted	157939
24	EMBASE − 1996 to date	effectiveness	unrestricted	114111
25	EMBASE − 1996 to date	23 AND 24	unrestricted	49204
26	EMBASE − 1996 to date	21 OR 22 OR 25	unrestricted	49204
27	EMBASE − 1996 to date	20 AND 26	unrestricted	131

28	EMBASE − 1996 to date MEDLINE − 1996 to date MEDLINE In−Process − latest eight weeks	combined sets 10, 17, 27	unrestricted	191
29	EMBASE − 1996 to date MEDLINE − 1996 to date MEDLINE In−Process − latest eight weeks	dropped duplicates from 28	unrestricted	45
30	EMBASE − 1996 to date MEDLINE − 1996 to date MEDLINE In−Process − latest eight weeks	unique records from 28	unrestricted	146

Table 9.3.3: HEED Search Strategy

The search identified 25 references, 2 of which were considered relevant.

Table 9.3.3: NHS EED Search Strategy

The search identified 62 hits, among which 5 articles were deemed relevant.

Combining the hits from all these databases resulted in 10 relevant articles being ordered, from which 4 were withdrawn because they were not economic evaluations. Therefore there were 6 articles in the critical review that contain economic evaluations of systemic treatments for psoriasis.

9.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

No additional searches were conducted.

9.4 Appendix 4: IHCIS analysis

OBJECTIVE

Etanercept in patients with psoriasis can be administered via either a continuous or intermittent dosing strategy, where in the latter, a treatment is recommenced only when the disease flares. The frequency of disease flares have important implications on the number of doses administered, and therefore, cost of therapy. Since the only currently available evidence on this frequency comes from a clinical study in a non-typical setting, we sought an alternative source of data. With little long-term use of etanercept in the UK and the rest of Europe for psoriasis, the best source of evidence was found in the US where it has been in use since April 2004.

METHODS

Data

Medical, pharmacy and inpatient confinement administrative claims data on patients ever diagnosed with psoriasis (identified by ICD 9-CM code: 696.1x) between January 1, 1999 to June 30, 2006 were abstracted from the Integrated Healthcare Information Services (IHCIS) National Managed Care Benchmark database. Coverage and benefit data on medical and pharmacy services were also obtained. The database is nationally representative and includes data from 30 health plans covering more than 25 million lives.

Sample Selection

Patients with a pharmacy claim of etanercept between April 30, 2004 (FDA approval date of etanercept for psoriasis) and June 30, 2006 were identified in the database. The index date for patients was the date of their first etanercept prescription. To ensure that etanercept was prescribed for patients' psoriasis condition, patients were required to have a diagnosis of psoriasis within 30 days of their index date and be without any diagnosis of psoriasis arthritis since January 1, 1999. Patients were also required to have continuous coverage for medical and pharmacy services for 12 months after their index date. Patients meeting all selection criteria were included in the analysis.

Status of psoriasis following the Use of Etanercept

A patient is considered "cleared" of psoriasis if, following an etanercept prescription, there were no medical visits coded as a psoriasis visit and there were no prescriptions of systemic therapies within 6 months. A patient is considered a "non-responder" if, following an etanercept prescription, there were no prescriptions of etanercept and at least one prescription of other systemic therapies within 6 months. "Non-responders" were not included in the analysis. We assumed that patients classified as "cleared" had no subsequent use of etanercept.

Outcome of Analysis

The analysis outcome is the average weekly dose of etanercept. We determine the duration of treatment from the first and last dates of prescription fills. All doses received were calculated as the sum of all doses from the first date through to the last date excluding the last dose. Average weekly dose was calculated as the total amount received divided by the total duration. Patients with records showing days of supply of etanercept < 7 were excluded. Patients with less than 90 days of etanercept use or with average weekly dose greater than 200mg were also excluded. To avoid double counting, we selected the record with the maximum quantity/amount when two pharmacy claims had the same values for fields such as date of service, NDC, days supplied, quantity dispensed and/or standard cost amount.

Results

A total of 525 patients met all study inclusion criteria. Table 9.4.1 presents the patient characteristics. The population was predominantly women (63%) with a mean age of 44.3 years. Among the 497 (95%) patients who responded to the treatment of etanercept, 54% started at 50mg BIW while 35% started at 25mg BIW and 11% started at <25mg BIW during their first 90 days of treatment Table 9.4.2 presents the average weekly dose by time periods for all users and for users who started at 25mg BIW. We found that beyond the first 90 days of treatment, the average weekly dose of patients started on a regimen of 50 mg per week (25 mg twice weekly), was 43.9 mg per week. This translates to an intermittent use rate of 88% of the continuous dose.

Table 9.4.1. Patient Characteristics (at index date)

N	525
% Male	62.7%
Age: mean (SD)	44.3 (12.8)
Insurance type[vii]	
HMO	177 (33.7%)
POP	64 (12.2%)
PPO	267 (50.9%)
IND	15 (2.9%)
OTH	2 (0.4%)
Census region	
New England	217 (41.3%)
Middle Atlantic	151 (28.8%)
South Atlantic	36 (6.9%)
ES Central	11 (2.1%)
WS Central	41 (7.8%)
EN Central	30 (5.7%)
WN Central	20 (3.8%)
Mountain	10 (1.9%)
Pacific	9 (1.7%)
Prior use of other systemic therapy	
Alefacept	9 (1.7%)
Ciclosporin	35 (6.7%)
Adalimumab	0
Infliximab	0
Methotrexate	105 (20%)
Efalizumab	19 (3.6%)

Table 9.4.2. Average weekly dosage (mg/week) by treatment periods

	All Users (n=497)			starting dose=25mg BIW (N=173)		
Period	**N**	**mean (SD)**	**median (Q1-Q3)**	**n**	**mean (SD)**	**median (Q1-Q3)**
0-90	**497**	**73.8 (26.2)**	**80.5 (52.4-95.9)**	**173**	**56.1 (10.4)**	**54.4 (48.5-65.4)**
91-180	**496**	**54.7 (25.5)**	**51.5 (38.8-66.8)**	**173**	**49.2 (23.0)**	**46.6 (36.2-56.7)**
181-270	**476**	**45.7 (23.5)**	**45.8 (30.9-56.1)**	**166**	**45.2 (22.3)**	**44.8 (31.1-54.0)**
271-360	**455**	**44.2 (25.6)**	**44.7 (27.6-56.3)**	**161**	**42.0 (25.5)**	**41.1 (25.9-54.5)**
91-360	*497*	*46.3 (22.1)*	*46.6 (30.7-57.6)*	*173*	*43.9 (20.6)*	*44.0 (29.7-55.1)*

Table 9.4.3 gives more detail on the transitions between doses in subsequent 3 monthly periods which make up the averages. In this it can be observed that 24% of patients remain on treatment continuously. Some 15% of patients immediately use a reduced dosage (<50mg per week) in subsequent 3 months. However, 14% of patients use a higher dose (100mg or higher per week) in the 2nd 3 monthly period.

[vii] HMO: Health Maintenance Organization, POS: Point of Service, PPO: Preferred Provider Organization, OTH: Other, IND:

Table 9.4.3. Transitions between doses in subsequent quarters in patients beginning on 50mg per week in first 3 months.

91-180 Days	181-270 Days	271-360 Days	N (%)
>100mg	100mg	100mg	1 (0.6%)
100mg	100mg	100mg	7 (4%)
100mg	100mg	UNKNOWN	2 (1.2%)
100mg	50mg	50mg	6 (3.5%)
100mg	50mg	<50mg	4 (2.3%)
100mg	50mg	5:0mg	0 (0%)
100mg	<50mg	5:0mg	0 (0%)
100mg	5:0mg	5:0mg	0 (0%)
100mg	UNKNOWN	UNKNOWN	4 (2.3%)
50mg	100mg	100mg	5 (2.9%)
50mg	100mg	50mg	7 (4%)
50mg	100mg	UNKNOWN	1 (0.6%)
50mg	50mg	100mg	7 (4%)
50mg	50mg	50mg	41 (23.7%)
50mg	50mg	<50mg	13 (7.5%)
50mg	50mg	5:0mg	2 (1.2%)
50mg	50mg	UNKNOWN	2 (1.2%)
50mg	<50mg	50mg	5 (2.9%)
50mg	<50mg	<50mg	14 (8.1%)
50mg	<50mg	5:0mg	1 (0.6%)
50mg	5:0mg	5:0mg	1 (0.6%)
50mg	UNKNOWN	UNKNOWN	3 (1.7%)
<50mg	50mg	100mg	1 (0.6%)
<50mg	50mg	50mg	6 (3.5%)
<50mg	50mg	<50mg	8 (4.6%)
<50mg	<50mg	50mg	3 (1.7%)
<50mg	<50mg	<50mg	26 (15%)
<50mg	<50mg	5:0mg	1 (0.6%)
<50mg	<50mg	UNKNOWN	0 (0%)
<50mg	5:0mg	5:0mg	2 (1.2%)

9.5 Appendix 5: Replication of York Results

This replication of the model produced very similar results to those found in the York Assessment report as shown in the tables below. While costs and QALYs are slightly larger in this replication, order of magnitude is identical in all of the scenarios. These slight differences can be attributed to the different random numbers generated in the model. The ICERs generated in the replication were within 1-2% of the original York results.

Scenario I Replication:

Table 9.5.1. 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 Intermittent	0.118	0.06	0.177	7,775	7,498	8,328	65,841	65,841
Efalizumab	0.114	0.059	0.169	9,439	9,311	9,634	Dominated	82,996
Etanercept 25 mg Continuous	0.118	0.08	0.177	9,738	9,658	9,899	Dominated	82,465
Etanercept 50 mg	0.125	0.067	0.184	14,883	14,623	15,364	1,096,969	119,474

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

Table 9.5.2. 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	
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 Intermittent	Supportive care
75,000	Etanercept 25 mg Intermittent	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.

Table 9.5.3. 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 intermittent	Etanercept 50 mg	Efalizumab	Etanercept 25 mg continuous	Supportive care
20,000	Probability 1st in sequence	0.00	0.00	0.00	0.00	1.00
30,000	Probability 1st in sequence	0.00	0.00	0.00	0.00	1.00
50,000	Probability 1st in sequence	0.1157	0.00	0.0002	0.00	0.8841
20,000	Probability included	0.00	0.00	0.00	0.00	1.00
30,000	Probability included	0.00	0.00	0.00	0.00	1.00

50,000	Probability included	0.1158	0.00	0.0051	0.0069	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.

Scenario II Replication:

Table 9.5.4. 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 intermittent	0.22	0.104	0.338	7,775	7,498	8,328	35,389	35,389
Efalizumab	0.211	0.102	0.326	9,439	9,311	9,634	Dominated	44,636
Etanercept 25 mg Continuous	0.22	0.104	0.338	9,738	9,658	9,899	Dominated	44,324
Etanercept 50 mg	0.232	0.116	0.351	14,883	14,623	15,364	599,035	64,267

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

Table 9.5.6. Most cost-effective ordering of therapies for Alternative Scenario I 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	Supportive care				
40,000	Etanercept 25 mg intermittent	Supportive care			
45,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care	
50,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care	
55,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care	
60,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care	
65,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
70,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
75,000	Etanercept 25 mg intermittent	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.

Table 9.5.7. 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 intermittent	Etanercept 50 mg	Efalizumab	Etanercept 25 mg continuous	Supportive care
20,000	Probability 1st in sequence	0.0041	0.00	0.00	0.00	0.9959
30,000	Probability 1st in sequence	0.2623	0.00	0.0027	0.00	0.7350
50,000	Probability 1st in sequence	0.8210	0.0002	0.0376	0.00	0.1412
20,000	Probability included	0.0041	0.00	0.00	0.00	1.00
30,000	Probability included	0.2633	0.00	0.0401	0.0414	1.00
50,000	Probability included	0.8517	0.1385	0.6506	0.6605	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.

Scenario III Replication:

Table 9.5.8. 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 intermittent	0.118	0.06	0.177	3,378	2,646	4,820	28,668	28668
Efalizumab	0.113	0.058	0.168	5,216	4,678	6,031	Dominated	46,015
Etanercept 25 mg Continuous	0.118	0.06	0.177	5,342	4,806	6,398	Dominated	45,326
Etanercept 50 mg	0.124	0.066	0.183	10,239	9,731	11,181	1,089,497	82,468

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

Table 9.5.9. 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 intermittent	Supportive care		
35,000	Etanercept 25 mg intermittent	Supportive care		
40,000	Etanercept 25 mg intermittent	Supportive care		
45,000	Etanercept 25 mg intermittent	Supportive care		
50,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care
55,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care
60,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care

65,000	Etanercept intermittent	25	mg	Etanercept continuous	25	mg	Efalizumab	Supportive care
70,000	Etanercept intermittent	25	mg	Etanercept continuous	25	mg	Efalizumab	Supportive care
75,000	Etanercept intermittent	25	mg	Etanercept continuous	25	mg	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 9.5.10. 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 intermittent	Etanercept 50 mg	Efalizumab	Etanercept 25 mg continuous	Supportive care
20,000	Probability 1st in sequence	0.1117	0.00	0.00	0.00	0.8883
30,000	Probability 1st in sequence	0.5782	0.00	0.0030	0.00	0.4188
50,000	Probability 1st in sequence	0.9040	0.00	0.0362	0.00	0.0598
20,000	Probability included	0.1117	0.00	0.00	0.00	1.00
30,000	Probability included	0.5787	0.00	0.0311	0.0412	1.00
50,000	Probability included	0.9282	0.0052	0.6189	0.6418	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.

Scenario IV Replication

Table 9.5.11. 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 Intermittent	0.221	0.104	0.342	3,378	2,646	4,820	15,314	15,314
Efalizumab	0.212	0.1	0.327	5,216	4,678	6,031	Dominated	24,565
Etanercept 25 mg Continuous	0.221	0.104	0.342	5,342	4,806	6,398	Dominated	24,213
Etanercept 50 mg	0.233	0.114	0.351	10,239	9,731	11,181	574,256	44,025

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

Table 9.5.12. 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 intermittent	Supportive care			
25,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care	
30,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care	
35,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care	
40,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Supportive care	
45,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
50,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
55,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
60,000	Etanercept 25	Etanercept 25	Efalizumab	Etanercept 50	Supportive

	mg intermittent	mg continuous		mg	care
65,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
70,000	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Etanercept 50 mg	Supportive care
75,000	Etanercept 25 mg intermittent	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.

Table 9.5.13. 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 intermittent	Etanercept 50 mg	Efalizumab	Etanercept 25 mg continuous	Supportive care
20,000	Probability 1st in sequence	0.7710	0.00	0.0153	0.00	0.2137
30,000	Probability 1st in sequence	0.9142	0.0001	0.0444	0.00	0.0413
50,000	Probability 1st in sequence	0.9212	0.0005	0.0724	0.00	0.0059
20,000	Probability included	0.7776	0.00	0.2231	0.2440	1.00
30,000	Probability included	0.9479	0.0444	0.7367	0.7480	1.00
50,000	Probability included	0.9900	0.6759	0.9661	0.9652	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.

Scenario V Replication

Table 9.5.14. 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	0.128	0.064	0.193	–4,192	–4,521	–3,345	–	Dominates
Ciclosporin	0.124	0.067	0.183	–387	–733	100	Dominated	Dominates
Fumaderm	0.104	0.034	0.168	–221	–2,153	2,132	Dominated	Dominates
Supportive care	0	0	0	0	0	0	Dominated	–
Etanercept 25 mg intermittent	0.118	0.06	0.176	3,378	2,646	4,820	Dominated	28,657
Efalizumab	0.114	0.059	0.169	5,216	4,678	6,031	Dominated	45,941
Etanercept 25 mg continuous	0.118	0.06	0.176	5,342	4,806	6,398	Dominated	45,307
Infliximab	0.134	0.064	0.204	6,672	4,143	9,581	1,613,031	49,654
Etanercept 50 mg	0.124	0.065	0.183	10,239	9,731	11,181	Dominated	82,322

[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 9.5.15 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 intermittent	Supportive care			
35,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg intermittent	Supportive care			
40,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg intermittent	Supportive care			
45,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg intermittent	Supportive care			
50,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Infliximab	Supportive care
55,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Infliximab	Supportive care
60,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Infliximab	Supportive care
65,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Efalizumab	Infliximab	Supportive care
70,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Infliximab	Efalizumab	Supportive care
75,000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25 mg intermittent	Etanercept 25 mg continuous	Infliximab	Efalizumab	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 9.5.16. 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	0.0020	0.9965	0.0015	0	0
30,000	Probability first in sequence	0	0	0	0	0. 0026	0.9950	0.0024	0	0
50,000	Probability first in sequence	0	0	0	0	0.0049	0.9912	0.0039	0	0
20,000	Probability included in sequence	0.1118	0	0	1.00	1.00	0.9999	0.9264	0.0027	0
30,000	Probability included in sequence	0.5806	0	0.0313	1.00	1.00	0.9999	0.9552	0.0640	0.0398
50,000	Probability included in sequence	0.9316	0.0068	0.6210	1.00	1.00	0.9999	0.9767	0.5095	0.6398

[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

9.6 Appendix 6: Quality Assessment Tool

Scoring instructions for the Jadad scale:

Please read the article and try to answer the following questions (see attached instructions):

1. Was the study described as randomised (this includes the use of words such as randomly, random, and randomisation)?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring the items:

Either give a score of 1 point for each "yes" or 0 points for each "no." There are no in-between marks.

Give 1 additional point if:	For question 1, the method to generate the sequence of randomisation was described **and** it was **appropriate** (table of random numbers, computer generated, etc.)
and/or:	If for question 2 the method of double blinding was described **and** it was **appropriate** (identical placebo, active placebo, dummy, etc.)
Deduct 1 point if:	For question 1, the method to generate the sequence of randomisation was described **and** it was **inappropriate** (patients were allocated alternately, or according to date of birth, hospital number, etc.)
And/or:	For question 2, the study was described as double blind but the method of blinding was **inappropriate** (e.g. comparison of tablet vs. injection with no double dummy)

Guidelines for Assessment

1. Randomisation
A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should be not regarded as appropriate.

2. Double blinding
A study must be regarded as double blind if the word "double blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and dropouts
Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

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