REMICADE®
(*infliximab*)

Remicade® in the treatment of psoriasis in England and Wales

A Submission to the National Institute for Health and Clinical Excellence

Schering-Plough Ltd

Date of Report: 8 may 2007

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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.

The brand name is Remicade® (infliximab). Therapeutic class: immunologic, 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).

September 29th 2005

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:
Remicade, in combination with methotrexate, is indicated for: the reduction of signs and symptoms as well as the improvement in physical function in:

- patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate.
- patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.
- In these patient populations, a reduction in the rate of the progression of joint damage, as measured by x-ray, has been demonstrated.

Crohn's disease:
Remicade is indicated for:

- treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Ulcerative colitis:
Remicade is indicated for: Treatment of moderately to severely active ulcerative colitis in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis:
Remicade is indicated for: Treatment of ankylosing spondylitis, in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy.

Psoriatic arthritis:
Remicade is indicated for: Treatment of active and progressive psoriatic arthritis in patients who have responded inadequately to disease-modifying anti-rheumatic drugs. Remicade should be administered

- in combination with methotrexate, or:
- alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated

Psoriasis:

Remicade is indicated for: Treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

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.

4% of psoriasis patients are eligible for treatment with anti-TNFs. Of that 4%, 50% is currently being treated with inflixmab (market research).

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

Infliximab has regulatory approval following a positive opinion granted on July 28th 2006, by the European Union's (EU) Committee for Medicinal Products for Human Use (CHMP), for the European Agency for the Evaluation of Medicines Agency (EMEA). The Commission approval results in Marketing Authorization with unified labeling valid in all EU-member states (current 25 members), as well as Iceland and Norway.

The FDA also approved infliximab, in the USA, for the treatment of chronic severe plaque psoriasis on September 27th 2006.

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?

Infliximab for the treatment of psoriasis is also being assessed by the Scottish Medicines Consortium (SMC). The submission is due November 6th 2006. A final recommendation is expected to be made public May 7th 2007.

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

Infliximab is available in 100 mg powder, in vials, for concentrate for solution for infusion.

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 proposed course of treatment is 5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given.

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.

£419.62 per 100mg vial;

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

Infliximab is to be administered under the supervision of a healthcare professional.

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?

Tests to screen patients for eligibility for treatment, such as chest x-rays and Heaf tests for tuberculosis.

Treatment of adverse events.

2 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with moderate to severe plaque psoriasis who have not responded to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA or whom these treatments are contraindicated.	-PASI: measure of the average redness, thickness and scaling of the lesions, weighted by the area of involvement. Score ranges from 0-72, with higher scores indicating more severe disease. -DLQI: patient reported outcome on QoL. Assesses the limitations due to the impact of skin disease. Score ranges from 0-30, with 30 representing the worst QoL; Patients who have a PASI score >10, DLQI>10 and a body surface area>10 are considered to have severe psoriasis.
Intervention	Infliximab for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.	Infliximab 5mg/kg IV
Comparator(s)	-Etanercept -Efalizumab -Standard treatment without a TNF-inhibitor or efalizumab	-etanercept 25-50 mg administered twice weekly until remission (then 25mg administered twice weekly for continuous treatment); -efalizumab: initial single dose of 0.7 mg/kg, Weekly injections of 1.0 mg/kg body Supportive care includes inpatients stay and clinic visits for symptom management.
Outcomes	The outcome measures to be considered include: • severity of psoriasis • Remission rate • Relapse rate • adverse effects of treatment • Health-related quality of life.	-Severity is defined by PASI and DLQI scores; -remission rates and relapse rates will be identified from the trials -HRQoL will be defined by a disease specific and generic QoL instrument;
Special considerations and other issues	Guidance will only be issued in accordance with the marketing authorisation. Where the evidence allows, sequencing of different drugs and the place of infliximab in such a sequence should be considered. If the evidence allows the appraisal will attempt to identify criteria for selecting people for whom this treatment would be particularly appropriate.	Analysis will investigate the place of infliximab in the sequence of biologic therapies for psoriasis. Criteria for patient selection will be identified using PASI and DLQI scores

3 Executive summary

Background

Psoriasis is a chronic, relapsing-remitting inflammatory disease of the skin that affects 1–3% of US and European populations. Approximately 25% of affected individuals have moderate-to-severe disease (Greaves and Weinstein, 1995). In the UK, this equates to approximately 305,000 people with moderate to severe psoriasis. Recently, biological therapies have been developed which target the T-cells involved in the underlying disorder. A TNF-α inhibitor, infliximab is a chimeric monoclonal antibody that binds with high affinity to TNF, thereby neutralising its activity (SPC March 2007).

Infliximab, marketed in the UK as Remicade®, is approved for use in patients with moderate-to-severe psoriasis. In addition, infliximab is approved for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis. Infliximab is available as a powder in 100-mg vials to be dissolved in solution. The proposed course of treatment is 5 mg/kg as an intravenous infusion over a two-hour period at weeks 0 (initation), 2, and 6, then every 8 weeks thereafter.

Besides supportive care, key comparators for infliximab include etanercept and efalizumab which were recently reviewed by NICE in TA #103. NICE recommended the use of both products for the treatment of patients with severe psoriasis who have failed to respond to other systemic agents. Infliximab did not have a license for moderate-to-severe psoriasis at the time and was therefore not included in the appraisal. The main comparator for the purposes of this appraisal is etanercept 25mg twice weekly continuous use, which reflects UK clinical practice in patients with severe plaque psoriasis who have previously failed systemic therapy.

The British Association of Dermatologists guidelines for the use of biological interventions in psoriasis (Smith et al, 2005) note that there are no head-to-head studies directly comparing the efficacy of infliximab with other biologic therapies that are licensed for the treatment of psoriasis - etanercept and efalizumab. However the guidelines also state that extrapolating data from short-term, placebo-controlled studies of each individual drug suggests a possible rank order of efficacy, with infliximab being the most effective and efalizumab the least effective at 12 weeks.

Clinical Effectiveness

The efficacy of infliximab in the treatment of psoriasis has been demonstrated in four placebo-controlled studies. All four studies investigated the efficacy of infliximab induction therapy; in one study, patients also received maintenance therapy at 8-week intervals for up to 1 year. In all four studies, infliximab induced a high rate of response with 76–88% of patients achieving an improvement in their Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) between baseline and week 10. More than half of patients (mean 53.87%) treated with infliximab achieved at least a 90% improvement in their PASI score (PASI 90) and this level of response corresponds to clearance of disease.

Infliximab therapy also produced a sustained improvement in health-related quality of life (HRQoL), as assessed using the Short-Form 36 (SF-36) and Dermatology Life Quality Index (DLQI). 66% of patients treated with infliximab achieved a DLQI score of 0-1 at 24 weeks, suggesting 'no effect' on quality of life from psoriasis compared to 2.7% of patients at baseline.

Treatment with infliximab was well tolerated with only small increases in serious adverse events observed relative to placebo. The most common adverse events were mild, and infusion reactions, occurring in 3-20% of study populations were reversible and generally mild.

In the absence of head-to-head clinical trials comparing the effectiveness of biologic therapies in patients with psoriasis, the relative effectiveness of these technologies has been evaluated using an indirect comparison method. The results of this analysis indicate that infliximab is significantly more effective than the other biologic treatments. Infliximab increased the likelihood of achieving PASI 75 at 10 to 12 weeks by 81% (95% CI 0.80-0.86) compared with placebo/supportive care; etanercept 25mg twice weekly increased the likelihood of achieving a PASI 75 by 36% (95% CI 0.56-0.70) and efalizumab 1mg/kg increased the likelihood of achieving a PASI 75 compared to

placebo by 29% (95% CI 0.25-0.34). Although a degree of heterogeneity between studies cannot be ruled out, this is unlikely to explain the large differences between response rates for infliximab and other treatments.

Cost-Effectiveness and NHS Impact

A cost-effectiveness analysis was conducted using an adaptation of the York Assessment Group modelling approach, as reported in NICE TA103. This analysis was designed to estimate the incremental cost-effectiveness of infliximab compared to current clinical practice in severe plaque psoriasis, defined as etanercept 25mg twice-weekly, continuous therapy. In the base case scenario, for a typical patient weighing between 61-80 kg with severe psoriasis (PASI of $\geq$10, DLQI of >10) and poor baseline quality of life (fourth quartile DLQI), infliximab generates an additional 0.116 QALYs at an additional cost of £3,031, compared to etanercept 25mg twice-weekly continuous. The incremental cost-effectiveness ratio for infliximab in the base case is estimated at £26,095.

This base case estimate of cost-effectiveness should be placed in the context of other important considerations relating to infliximab. Firstly, vial optimisation, which is increasingly recognised as best practice in UK centres, reduces the cost of infliximab thereby improving its cost-effectiveness. Secondly the cost of infliximab varies by patient weight. Lighter patients require fewer vials of infliximab and are associated with lower cost-effectiveness ratios.

Base case estimates of cost-effectiveness were found to be robust to extensive one-way sensitivity analyses. Results were most sensitive to assumptions regarding hospitalisation and length of inpatient stay for non-responding patients. Probabilistic sensitivity analyses indicate that, assuming a threshold value of £30,000 per QALY, the probability of infliximab being cost-effective is approximately 75 per cent. Overall, infliximab is a cost-effective treatment option for patients with severe psoriasis who have failed treatment with systemic therapy,

The average cost of infliximab per patient is estimated at £11,750, based on an average of 7 infusions per year for the expected duration of treatment. In the first year the estimated cost is £13,500 (8 infusions, 5mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter), decreasing to £10,910 in a maintenance year (6.5 infusions). Assuming eligible patients are offered infliximab as a treatment option following the failure of systemic therapy, the cost to the NHS is estimated to be approximately £5.2 million in year 1 rising to £11.7 million in year 5.

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.

The disease

Psoriasis is a chronic inflammatory skin disorder that is presently without a permanent cure. Its etiology seems to be multifactorial, with a strong genetic component. Twin studies show a 67% concordance for monozygotic twins versus 18% for dizygotic twins. This lack of complete concordance in monozygotic twins suggests multifactorial inheritance and interaction between genetic predisposition and the environment. At present, 8 different psoriasis susceptibility loci have been identified in genome-wide linkage scans, including locations on 15 different chromosomes. Genetic connections have been made between psoriasis and other diseases, including atopic dermatitis, rheumatoid arthritis, and Crohn's disease (Krueger et al., 2005).

Although strong hereditary factors govern the development of psoriasis, many environmental factors have been shown to play a role in the pathophysiology of psoriasis. External triggers such as physical trauma, psychological stress, sunburn, surgery, medications and infections can trigger an initial episode of psoriasis in those individuals who already have a genetic predisposition to develop it. The role of an infectious etiology in triggering psoriasis has been well documented in cases of bacterial, viral and fungal infections. Most noteworthy is the association between streptococci and various subtypes of psoriasis. Infection with HIV-1 may represent another important trigger factor of psoriasis although the incidence is quite variable (Kormeili et al., 2004).

Psoriasis is very common and affects 2–3% of the world's population. There is significant geographical variability with the lowest incidence of the disease seen at the equator and increasing frequency towards the poles. Psoriasis is more common among northern European caucasians, less common among Asian or African populations, and least common among natives to North and South America (Krueger et al., 1994; Swanbeck et al. Br J Derm V131;1994, p32). In England and Wales the prevalence is estimated at about 1,500 per 100,000 (NICE Psoriasis TAR). The Morbidity Statistics from General Practice dataset, based on a 1% random sample of the English and Wales population, estimated the prevalence of psoriasis and similar disorders at 24 per 10,000 persons, with an incidence density of 48 per 10,000 person-year.

Affecting men and women equally, psoriasis is a life-long disease that is often diagnosed at an early age in life, with an average diagnosis age of 27 years (National Psoriasis Foundation, 2002). It is estimated that between 6% and 42% of psoriasis patients develop PsA (Shbeeb et al, 2000, Green et al, 1981). In the majority of the cases, arthritis develops after the appearance of skin lesions, thus implying the importance of dermatologists in diagnosing early psoriatic arthritis. It is now accepted that psoriatic arthritis is more frequent and aggressive than previously thought.

Psoriasis may be typed as plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, pustular psoriasis, nail psoriasis, scalp psoriasis, and/or inverse psoriasis. These forms of psoriasis vary in severity and respond differently to treatment. The most common type of psoriasis is plaque psoriasis, accounting for approximately 80% of cases, and it is characterized by exacerbations and remissions of thickened, erythematous, scaly patches of skin that can occur anywhere on the body. The most common skin areas involved are the knees, elbows, scalp, and the trunk. Although not life threatening, the psoriatic lesions can cause pain and pruritus. Nail involvement is also very common, affecting up to 78% of patients (de Jong et al, 1996). The majority of patients have mild disease, however, approximately 30% of psoriasis patients will progress to moderate to-severe disease at some point in their disease history.

Individuals with psoriasis report distress with their appearance, physical symptoms, functional abilities and physical pain associated with psoriasis and co-morbidities, in particular psoriatic arthritis. Patients with moderate-severe psoriasis report major decreases in their quality of life (QoL), leading in some cases to suicidal wishes, depression, increased depression rates/sleeping disorders, difficulties with job/careers, much increased time for activities of daily living, and increased alcohol and cigarette consumption (Rapp et al, 2004). Many psoriasis patients with moderate-severe disease take more time off work, and experience decreased productivity, or the

necessity to leave the workforce altogether (Feldman et al.,2005; Stein et al., 2005; Dubertret et al. 2006).

In a recent European survey (EUROPSO), over 77% of 18,386 individuals with psoriasis reported that psoriasis was a problem or significant problem. The authors of this survey concluded that psoriasis has a profound impact on QoL (Dubertret et al., 2006). Of note, the reduction in QoL in patients with psoriasis was described as being comparable to that seen in cancer, arthritis, hypertension, heart disease, diabetes, and depression (Rapp et al., 1999).

In addition to a reduced QoL, psoriasis is associated with an increased risk of comorbidity and mortality compared to the general population. It appears that patients with psoriasis have a higher prevalence of metabolic disorders such as diabetes, hypertension, obesity and hyperlipidemia (Naldi et al 2005, Sopasakis et al, Mallbris et al, JAAD 2006, 2005, Sommer et al 2006, Neimann et al, 2006, Gelfand et al 2006). Psoriasis has also been shown to confer an independent risk factor for a myocardial infarction, with the youngest patients having the highest risk (Gelfand et al., 2006; Ludwig et al., 2007; Mrowietz et al., 2007). This increased risk could be linked to the pathogenesis of the disease: inflammation, in particular the increase of Th1 cytokines, including TNF-α, are suggested to play important roles in cardiovascular and other comorbidities seen in psoriasis patients (Mrowietz et al., 2007). Even though the etiology of these associations is still elusive, physicians should be aware of them and take active steps to reduce the risk profiles of patients with psoriasis and psoriatic arthritis, in order to lessen mortality and comorbidity (Mallbris et al, Curr Rheumatol Rev 2006).

Summary of Standard Therapies

Recommendations for treatment of psoriatic patients are set out in the British Association of Dermatologists (BAD) guidelines (2005). The technologies and therapies mentioned therein are summarized below.

The standard of care for treating psoriasis includes a broad range of therapies depending on the severity of the disease. Mild forms of psoriasis are typically treated with topical therapy. Moderate psoriasis may be treated with a range of products including topical therapy, phototherapy (ultraviolet B [UVB]), or increasingly, some biologic therapies. For severe disease, PUVA, standard systemic therapies, or biologic therapy are used. Conventional treatment for moderate or severe psoriasis often includes a combination of therapies, since complete clearance is uncommon with monotherapy, or rotational therapy to prevent long-term organ damage specific to each individual therapy.

Topical therapies

Topical therapies are commonly used in the treatment of psoriasis, and include the following: corticosteroids, tazarotene, calcipotriene, anthralin, tar preparations, keratolytic agents (salicylic acid, lactic acid, urea), lubrication products, or combinations or sequential use of these agents (Callen et al, 2003; Lebwohl, 2005).

Phototherapies

In patients who do not respond to topical agents, typically those with moderate to severe psoriasis, phototherapy with narrowband or broadband UVB light or PUVA (combination of systemic psoralen plus ultraviolet A light) is commonly used. Treatments are frequent (2 to 3 treatments weekly), often inconvenient and sometimes unavailable. Toxicities include sunburn, photoaging, and increased risk of skin cancer, particularly with PUVA (Griffiths et al, 2000).

Conventional Systemic Therapies

Currently approved conventional systemic therapies for treatment of severe psoriasis include methotrexate, acitretin, and cyclosporin. Although effective, the potential benefit is weighed against possible risks as systemic therapies are often associated with significant toxicities, particularly organ damage with long-term administration. Rotational therapy is employed to avoid these significant side effects (Sterry et al, 2004). Thus, consistent or substantial improvement in symptoms is not always maintained.

Methotrexate (MTX)

MTX is effective and easy to use, administrated weekly; however, hepatic damage has been observed in psoriasis patients treated with MTX. Current guidelines suggest frequent liver function

tests (LFTs) and liver biopsies with the timing of the initial liver biopsy being dependent on individual risk factors such as history of excessive alcohol use or liver disease. The most common side effects with MTX are malaise, gastrointestinal tract effects, headache, and leukopenia (Roenigk et al, 1998).

Acitretin

Acitretin is difficult to tolerate at effective doses because of toxicities including hair loss,severe mucocutaneous side effects, visual disturbances, and lipid elevations. Skeletal abnormalities including hyperostosis have been identified with long-term therapy. It is a known human teratogen and can cause severe life-threatening birth defects. Additional toxicities include rare liver toxicity (Katz et al, 1999).

Cyclosporine

Cyclosporin is highly effective for psoriasis but has a limited, 1-year recommendation of use due to its toxicities. Chronic use has been associated with hypertension and structural changes in the kidney that result in irreversible renal disease. Cyclosporin may also increase the rate of development of squamous cell carcinoma in PUVA-treated patients. In addition, cyclosporin interacts with multiple medications that can result in significant adverse consequences (Lebwohl et al, 1998).

Biologic Therapies

Infliximab (REMICADE), an anti-TNF-α monoclonal antibody, was approved by the EMEA in October 2005 for the treatment of adult patients with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, MTX or PUVA. Two additional biologic agents were approved in September 2004 for the treatment of the same patient population (patients with moderate-to-severe psoriasis, refractory to systemic therapy): etanercept, another TNF inhibitor, and the T-cell modulator efalizumab.

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

Infliximab is an established technology whose efficacy and safety in other indications has already been evaluated in NICE technology appraisals. Infliximab was developed in response to findings about the immunopathogenesis of psoriasis, which is now recognized as the most common T-lymphocyte–mediated inflammatory disease in humans (Krueger, 2002).

Psoriasis is considered to be a disorder of keratinocyte hyperproliferation in the epidermis secondary to activated immune cells in the dermis. However, the precise mechanism and sequence of interactions between keratinocytes and immune cells is not yet fully understood (Kormeili et al., 2004). There is growing evidence that both the innate and the adaptive immune system are involved. Activated T lymphoytes (Type 1 T-cells) and their effector cytokines, in partiuclar TNF-α, appear to play a pivotal role (Vena et al., 2006).

Elevated TNF-α levels have been found in the skin lesions and sera of patients with psoriasis (Nickoloff et al, 1991; Kristensen et al, 1993; Bonifati et al, 1994) and increased serum levels have been shown to correlate with disease activity (Mussi et al, 1997). Increased TNF-α in skin lesions can mediate keratinocyte proliferation, the hallmark of psoriasis. Keratinocytes that are cultured in the presence of TNF-α produce transforming growth factor, which is a strong mitogen for keratinocytes (Kristensen et al, 1993).

Infliximab belongs to a novel class of parenteral therapies which target T-cell functions and/or molecular signaling pathways to mediate particular inflammation symptoms. Broadly these therapies are called biologics; in the UK infliximab, efalizumab and etanercept are licensed biologic treatments for psoriasis.

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

Infliximab is a chimeric murine-human immunoglobulin G_1 monoclonal antibody (Chaudhari et al., 2001; Weinberg and Saini, 2003). Both infliximab and etanercept are known as Tumour Necrosis Factor Alpha (TNF-α) inhibitors because they antagonize the vital inflammatory cytokine TNF-α.

The specific mode of action of infliximab differs substantially from etanercept, as is summarized in Table 1. While etanercept blocks the action of TNF-α by competitively occupying soluble TNF-α receptor sites, infliximab sequesters TNF-α and interacts with the T-cells which release it.

Table 1. Modes of Action of Infliximab and Licensed Competitor Products

Therapy	Drug Type	Targeted Inflammatory Agent	Mode of Action
Infliximab	Monoclonal Antibody	Tumour Necrosis Factor Alpha (TNF-α)	Affects T-cell functions that involve the release of TNF-α and binds to free TNF-α rendering it ineffective
Etanercept	Fusion Protein	Tumour Necrosis Factor Alpha (TNF-α)	Competitively occupies soluble TNF-α receptors on cell surfaces
Efalizumab	Monoclonal Antibody	Leukocyte function associated antigen 1 (LFA-1)	Interference with adhesion mediated by LFA-1; leukocyte recruitment to psoriatic skin is inhibited

Reference: Schön & Boehncke 2005

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

Infliximab is approved for treatment of adults with moderate-to-severe psoriasis who have not responded to (or are intolerant of) other systemic therapies. NICE published Guidance on the use of etanercept and efalizumab for the treatment of psoriasis in June 2006. Etanercept was recommended for patients that had failed treatment with systemic therapies and had a PASI score greater or equal to 10 and a DLQI>10. Efalizumab was recommended for patients not responding to etanercept or are shown to be intolerant of, or have contraindications to, treatment with etanercept.

Infliximab 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.

It should be noted that infliximab will be of particular benefit to patients with psoriatic arthritis, a disease that for which efalizumab is contraindicated.

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

Current clinical practice in the UK for the treatment of moderate to severe psoriasis consists of the use of infliximab, etanercept and efalizumab. Infliximab is administered according to its license. 5mg/kg are administered at weeks 0, 2, 6 and subsequently at 8-weekly intervals. In terms of etanercept, NICE has recommended intermittent use at 25mg twice weekly. However, clinical practice in the UK varies substantially. There is evidence from large centres in the UK, in addition to consensus being reached by key opinion leaders that the use of etanercept in the treatment of psoriasis is continuous.

Particularly in severe psoriasis, clinicians do not cease treatment with etanercept if a patient is responding, due to concerns regarding potential relapse. Additionally, there is evidence that etanercept is used at 50mg twice weekly in order to achieve the desired level of response on treatment, which is not always possible on a 25mg twice weekly dose. These significant variations in clinical practice have been taken into consideration in order to adequately reflect current clinical practice in the UK in the economic model.

Efalizumab was recommended by NICE in TA#103 but its use in the NHS remains sporadic. There is also limited use of adalimumab in the UK. Adalimumab is not currently licensed for the treatment of psoriasis and it does not form part of standard clinical practice in the UK. Therefore, it was not deemed to be a relevant comparator.

There is evidence from the NHS that infliximab wastage is minimized by implementing vial optimization. Increasingly this is regarded as best clinical practice.

4.6 Provide details of any relevant guidelines or protocols.

Technology appraisals have been carried out by NICE and SMC in dermatological indications including psoriasis, and the BAD has reviewed infliximab in its 2005 guidelines for psoriasis treatment. Infliximab is highlighted as the most effective biologic therapy for psoriasis in the BAD guidelines, which provides rapid and significant disease control (Smith et al 2005). Table 2 gives a summary.

Table 2. Relevant Guidelines for Infliximab in Psoriasis

Organisation	Disease Area	Relevant Recommendations
NICE	Psoriatic Arthritis	Infliximab, within its licensed indications, is recommended for the treatment of adults with severe active psoriatic arthritis if treatment with an anti-TNF (tumour necrosis factor) agent is considered appropriate and the person has been shown to be intolerant of, or have contraindications to, treatment with etanercept or has major difficulties with self administered injections.
SMC	Psoriasis	Infliximab 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).
BAD	Psoriasis	Infliximab is the most effective biologic agent at 12 weeks after treatment start. It also provides rapid disease control. Infliximab is recommended in circumstances requiring rapid disease control, due to its very rapid onset of action and high response rate.

5 Clinical evidence

5.1 Identification of studies

The major sources of information from published literature were searched through Medline, Embase, and Cochrane Clinical Trials Register (CCTR) databases using the Ovid software. Full details of the search strategy are given in the Appendix. All papers were analysed according to the CONSORT checklist; summary details are presented in this section.

The search strategy was made up of two sets of criteria: the first set identified psoriasis therapy, the second identified infliximab and competitor biologics etanercept and efalizumab. The main literature search was designed to retrieve infliximab and competitor anti-TNF-α trials simultaneously

5.2 Study selection

5.2.1 Complete list of RCTs

Lack of head-to-head data

The literature search did not identify any head-to-head studies where infliximab was directly compared to one or more of its competitors: etanercept and efalizumab. All relevant RCTs of infliximab efficacy were placebo-controlled. The same was true of the competitor biologics etanercept and efalizumab, whose related RCTs were placebo-controlled.

Infliximab trials identified

The search strategy identified 4 placebo-controlled RCTs involving infliximab in adult plaque psoriasis. The basic characteristics of these studies are given below in Table 3.

Table 3. Complete list of infliximab RCTs

Trial ID	Reference(s)	n	Intervention	Comparator	Primary Endpoints
<none>	(Chaudhari et al., 2001)	33	Infliximab	Placebo	– PASI
SPIRIT	(Gottlieb et al., 2004)	249	Infliximab	Placebo	– PASI – DLQI
EXPRESS	(Reich et al., 2005)	378	Infliximab	Placebo	– PASI – DLQI – SF-36
EXPRESS II	(Menter et al., 2006)	835	Infliximab	Placebo	– PASI – DLQI

Non-infliximab trials identified

A total of 8 placebo-controlled trials, 4 in etanercept and 4 in efalizumab, were also identified. These are listed in the Appendix and their primary efficacy results were used for an indirect comparison analysis in this submission.

5.2.2 Inclusion and exclusion criteria

RCTs of infliximab efficacy were selected as relevant if they were placebo-controlled, with randomized and double-blinded allocation to study arms. Baseline matching of key patient characteristics was also required: namely age, sex, as well as treatment and disease history. It was necessary that patients in all studies had active psoriasis at time of study entry, to be relevant to infliximab's licensed indication.

It was also required that the studies had as their primary, or co-primary, endpoint a relevant psoriasis severity score such as the Psoriasis Activity and Severity Index (PASI). Systematic review papers were scanned manually to identify any new RCTs referred therein.

The same criteria were applied in the selection of RCTs of competitor products etanercept and efalizumab.

5.2.3 List of relevant RCTs

The four infliximab RCTs were selected as relevant through the process given in Figure 1. It was possible to retrieve abstracts and usually papers for all studies identified in the first search pass. Accordingly it was possible to carry out the main study selection in one step, with papers retrieved electronically as needed to clarify each study's relevance.

The four relevant infliximab RCTs have all been written up in pivotal journal articles. Schering-Plough also holds the clinical study reports for two of these trials: EXPRESS and EXPRESS II. Where possible, published results have been used in this clinical section to prevent subsequent censorship, however some commercial-in-confidence information is included and is duly highlighted as per the example: commercial in confidence.

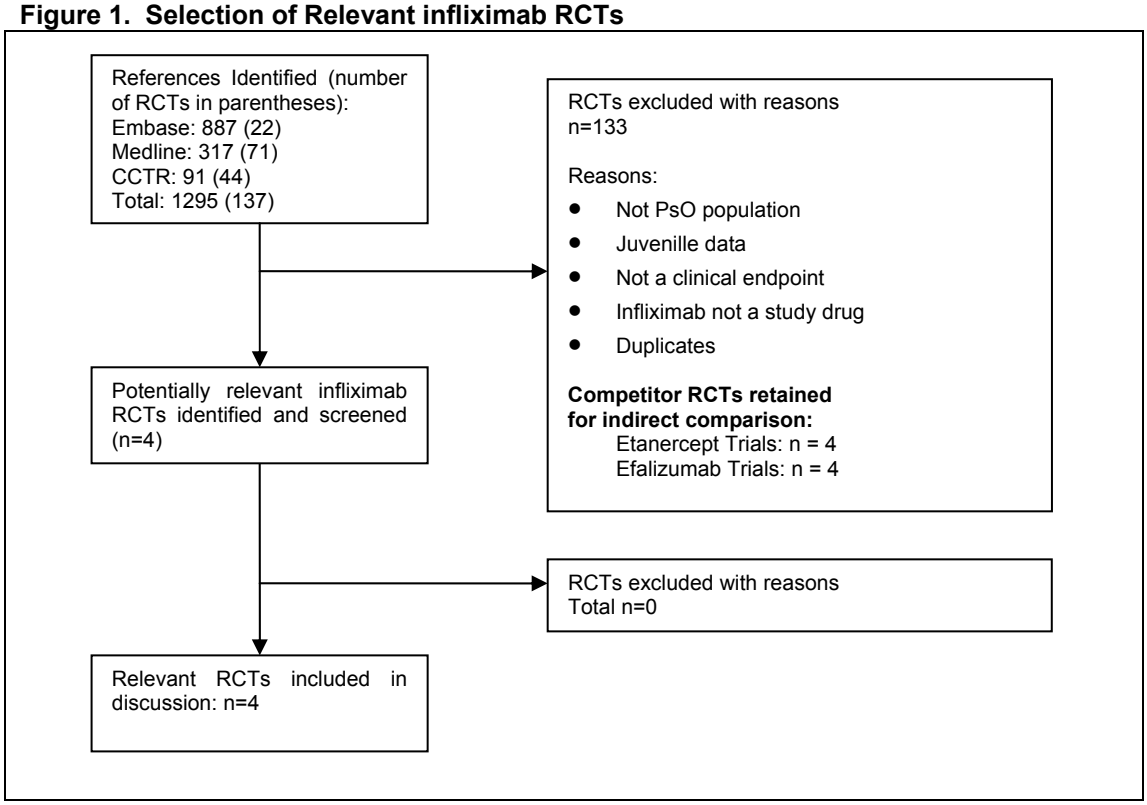
The listing of relevant RCTs is given in Table 4.

Table 4. List of Relevant Infliximab RCTs

Trial Name (ID number)	Reference and location	Design	Participants	Length	Intervention	Comparator	Endpoints (Primary endpoints in bold)
Chaudhari *et al*	**Chaudhari et al., 2001** *The Lancet* USA	Phase 3, randomized, double-blind, placebo controlled trial	n = 33 Adults with clinically stable plaque psoriasis; >5% BSA	10 Wks	Infliximab 5 mg/kg (n=11) 10 mg/kg (n=11)	Placebo (n = 11)	% patients achieving at week 10: – **PGA good/minimal/ clear** – PGA minimal/clear – PASI 75
SPIRIT (C0168T31)	**Gottlieb et al., 2004** *J Am Acad Dermatol* USA	Phase 2, induction safety and efficacy study	n = 249 Adults with clinically stable plaque psoriasis; >10% BSA; baseline PASI >10	10 Wks (50 wks follow-up)	Infliximab 5 mg/kg (n = 99) 3 mg/kg (n = 99)	Placebo (n = 51)	% patients achieving at week 10: – **PASI 75** – PASI 90 – PASI 50 – PGA minimal/cleared DLQI change fm baseline
EXPRESS (C0168T38)	**Reich et al., 2005** *The Lancet* Europe and Canada	Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel trial	n = 378 Adults with clinically stable plaque psoriasis; ≥ 10% BSA; baseline PASI ≥ 12	10 Wks (50 wks follow-up)	Infliximab 5 mg/kg (n = 301)	Placebo (n = 77)	% patients achieving at week 10: – **PASI 75** – PASI 90 – PASI 50 – PGA minimal/cleared DLQI change fm baseline Change in SF-36 scores NAPSI Nail Psoriasis Score
EXPRESS II (C0168T44)	**Menter et al., 2006** *J Am Acad Dermatol* USA, Canada, Europe	Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel trial	N = 835 Adults with moderate-to-severe plaque psoriasis; ≥ 10% BSA, baseline PASI ≥ 12	Induction: 14 Wks	Infliximab 3mg/kg (n=313) 5mg/kg (n=314)	Placebo (n=208)	% patients achieving at week 10: – **PASI 75** – PASI 90 – PGA minimal/cleared
				Follow-up: 36 Wks	Infliximab every 8 weeks 3mg/kg (n=148) 5mg/kg (n=150)	Infliximab "as needed" 3mg/kg (n=148) 5mg/kg (n=149)	DLQI change fm baseline PASI change fm baseline

BSA, Body Surface Area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; SF-36, Short Form-36.

Figure 1. Selection of Relevant infliximab RCTs



5.2.4 List of relevant non-randomised controlled trials

It was not necessary to seek further information from non-randomised trials in respect of the primary efficacy comparison.

5.2.5 Ongoing studies

There are no relevant ongoing RCTs. However The British Association of Dermatologists is planning a registry to track psoriasis patients receiving anti-TNF treatments. This registry is expected to start recruiting in the near future.

5.3 Summary of methodology of relevant RCTs

Please note: the tabulated detail of the EXPRESS and EXPRESS II trials includes information that is commercial in confidence. Such information is highlighted as per this example: Commercial in Confidence Information.

Detailed information about the trials' methodology follows in sections 5.3.1 onwards. A brief summary is given on this page.

Short Overview of Relevant RCTs

Patients – inclusion/exclusion criteria

All four studies involved adults with a diagnosis of moderate-to-severe plaque-type psoriasis. Patients enrolled in Chaudari et al had at least 5% of their total body surface area affected by psoriasis; in the other three studies at least 10% of total body surface area had to be affected. In Chaudari et al, patients also had to have a history of topical corticosteroid failure. Those enrolled into the SPIRIT study had to have been previously treated with psoralen/ultraviolet A treatment (PUVA) or other systemic antipsoriasis treatments, while those in the two EXPRESS studies had to be candidates for phototherapy or systemic therapy. In both SPIRIT and EXPRESS studies, patients had to have a baseline Psoriasis Area and Severity Index (PASI) score of at least 12.

Exclusion criteria were similar for all studies, comprising: use of topical therapy within 14 days of study entry; use of systemic therapy including infliximab within 28 days of study entry; and a history of tuberculosis or other serious infectious disease, lymphoproliferative disease or malignancy.

Treatments

In all four studies, initiation therapy involved administration of intravenous infusions of infliximab or placebo at weeks 0, 2 and 6. In Chaudari et al, infliximab was administered at a dose of 5 mg/kg or 10 mg/kg, in the SPIRIT study, infliximab was administered at a dose of 3 mg/kg or 5 mg/kg. In the EXPRESS trials (EXPRESS and EXPRESS II) patients were initially randomized to receive a set of three induction infusions with either placebo or infliximab. In EXPRESS only the 5mg/kg infliximab dose was assigned; in EXPRESS II, infliximab 3mg/kg or infliximab 5mg/kg were assigned.

In EXPRESS, patients received maintenance therapy for up to 1 year following their induction treatments. Infliximab 5mg/kg was administered at 8-week intervals from week 14 to week 46. Patients in the placebo group received placebo up to week 22 and then crossed over to receive a 3-injection infliximab induction (5mg/kg) followed by 8-weekly infliximab maintenance from week 38 onwards.

In EXPRESS II following induction, patients in infliximab 3mg/kg and 5mg/kg arms were randomized to continue receiving the same dose infusions, either at 8 week-intervals, or "as needed". This reassignment occurred at 14 weeks. Patients in the placebo arm were crossed over at 14 weeks to receive infliximab 5mg/kg every 8 weeks, following a 3-injection infliximab induction (5mg/kg).

Assessments of clinical efficacy

Two main measures were used to assess the impact of treatment on patients' symptoms: the PASI and the Physician Global Assessment (PGA). In addition, the EXPRESS trial assessed the effect of treatment on nail psoriasis using Nail Psoriasis Severity Index (NAPSI). Secondary measures also captured in some trials were the Dermatology Life Quality Index (DLQI) and Short Form 35 (SF-36) questionnaire. A description of these measures follows.

Description of Common Outcome Measures

The relevant infliximab RCTs share the same or overlapping endpoints, expressed by a variety of disease or quality-of-life scales. A brief explanation of these scales is found below:

PASI Score

The PASI is used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72, where higher scores

represent more severe disease. In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20% and 40% of the total BSA, respectively. Each of these areas was assessed separately for erythema, induration, and scaling, which were each rated on a scale of 0 to 4 (0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe).

PGA Score

The PGA is used to determine the subject's psoriasis lesions overall at a given timepoint. PGA scores range from 0 to 5 and a higher score represents more severe disease. Overall lesions were graded for induration (from 0 = no evidence of plaque elevation to 5 = severe plaque elevation of 1.25 mm or more), erythema (from 0 = no evidence of erythema, hyperpigmentation may be present to 5 = dusky to deep red coloration), and scaling (from 0 = no evidence of scaling to 5 = severe; very thick tenacious scale predominates). The sum of the 3 scales was divided by 3 to obtain a final PGA score.

NAPSI Score

The NAPSI score is determined for the target nail that represents the worst nail psoriasis at baseline. NAPSI scores range from 0 to 8, with a higher score representing more severe disease. Nails are divided into quadrants and graded for nail matrix psoriasis and nail bed psoriasis. Nail matrix psoriasis consists of any of the following: pitting, leukonychia, red spots in the lunula, and nail plate crumbling. Nail bed psoriasis is the presence of any of the following: onycholysis, splinter hemorrhages, oil drop discoloration, and nail bed hyperkeratosis. The sum of these 2 scores is the total NAPSI score.

DLQI Score

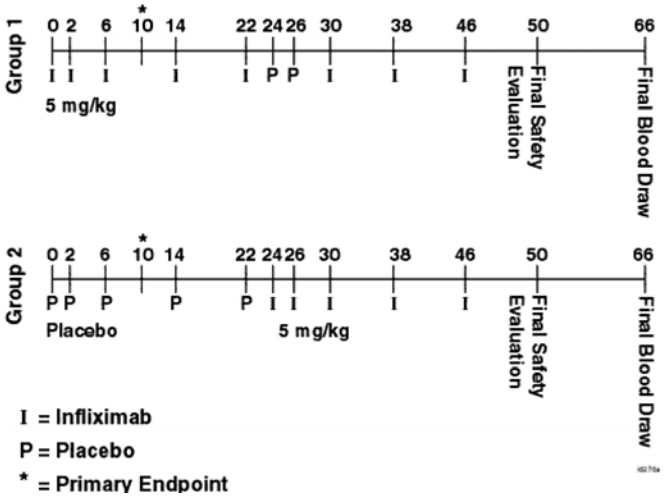
The DLQI is used to assess the impact of dermatological disease on a subject's quality of life (Finlay and Khan, 1994). It is a 10-item questionnaire and is calculated by summing the score of each question. Overall DLQI scores range from 0 to 30, with a lower score representing better quality of life.

SF-36 Questionnaire

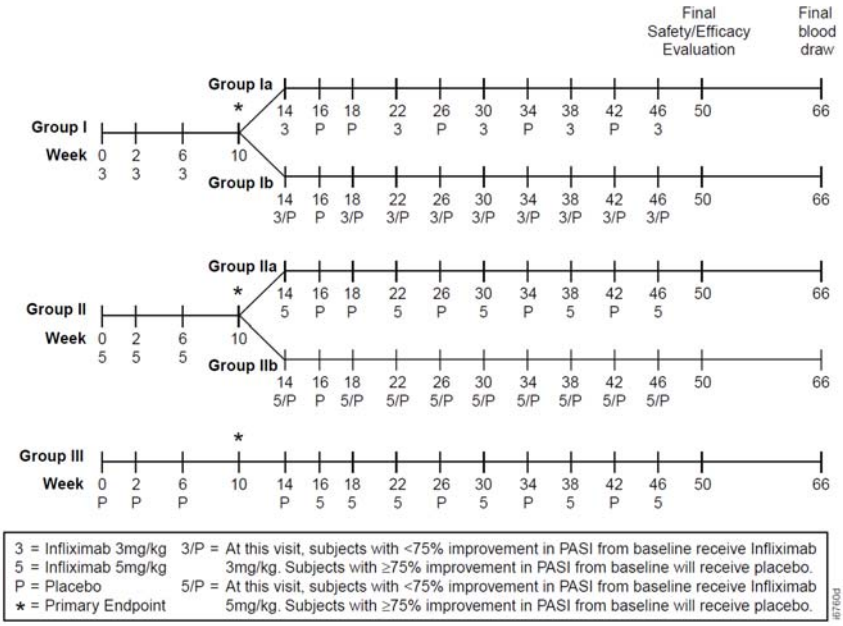
The SF-36 is used to evaluate subject well-being and quality of life. The SF-36 is a health survey questionnaire consisting of 8 multi-item scales: limitations in physical functioning due to health problems, limitations in usual role activities due to physical health problems, bodily pain, general mental health (psychological distress and well being), limitations in usual role activities due to personal or emotional problems, limitations in social functioning due to physical or mental health problems, vitality (energy and fatigue), and general health perception. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, thereby allowing comparison of relative burden of different diseases and the relative benefit of different treatments (Ware and Sherbourne, 1992). In the SF-36 and its subscales, higher scores represent a better quality of life.

5.3.1 Methods

Chaudhari et al	**Design** This was a double-blind, randomised, placebo-controlled trial to assess the clinical benefit and safety of infliximab, conducted at a single centre in the United states. **Dosage** The trial was designed to evaluate the efficacy of infliximab at 5mg/kg and 10mg/kg dosing. Initiation therapy involved administration of intravenous infusions of infliximab or placebo at weeks 0, 2 and 6. **Procedure** Clinical and laboratory assessments were done at screening, baseline, and every 2 weeks thereafter until 10 weeks after the start of therapy. Clinical assessments included physical examinations, vital signs, concomitant medications, monitoring for adverse events, and measures of psoriasis activity in the form of PASI and PGA, as well as photographs. At week 10, all patients were categorised as either nonresponders or responders and then the treatment assignment was revealed. Non-responders in the placebo group were subsequently randomised to receive open-label infliximab 5 or 10 mg/kg at weeks 10, 12, and 16. Responders in the placebo group were followed up for relapse and then offered infliximab in the same manner as the non-responders in the placebo group. Non-responders in the infliximab 5 mg/kg group were offered a single infusion of infliximab 10 mg/kg and followed up for response, whereas non-responders in the infliximab 10 mg/kg group were dropped from the study. Patients who responded to treatment with infliximab 5 or 10 mg/kg were followed up for relapse and offered single dose infusions of the drug upon relapse. The Chaudhari et al paper only reports results from the 10 week efficacy analysis. **Randomization and Blinding** Patients were randomly assigned to receive placebo or infliximab 5 or 10 mg/kg in a 1:1:1 fashion using block-of-six randomisation. The pharmacist who prepared placebo and infliximab infusions was not blinded to the treatment groups. **Safety** Patients were monitored for adverse events with assessors blinded to study group. Laboratory assessments were made several times during the 10-week study period including complete blood count, chemistry, anti-nuclear antibody concentration, urinalysis, and serum and urine β-human chorionic gonadotropin concentration. Clinically significant laboratory abnormalities that could not be attributed to other medical conditions were reported as adverse events.
SPIRIT	**Design** This was a randomized, double-blind, placebo-controlled trial conducted from 2001 to 2003 across 24 centres in the United States. **Dosage** The trial dosing was informed by the results of Chaudari et al, and was designed to evaluate the induction efficacy of infliximab at 3mg/kg and 5mg/kg dosing. Initiation therapy involved administration of intravenous infusions of infliximab or placebo at weeks 0, 2 and 6. **Randomization and Blinding** Eligible patients were randomly assigned in a 1:2:2 ratio to intravenous infusions of placebo, infliximab (3 mg/kg), or infliximab (5 mg/kg). Randomization was carried out using adaptive treatment allocation and stratified by investigational site. Patients and investigators were blinded as to treatment. To maintain the double blind independent pharmacists or staff members prepared all study infusions. **Procedure** Patients in each arm were treated with infliximab or placebo at weeks 0, 2, and 6. At week 26, patients with a static Physician Global Assessment (PGA) of moderate to severe disease activity were offered a single additional infusion of their assigned study treatment. Systemic or photo-therapies for psoriasis were stopped 1 month before and during the trial. No topical therapies for

	psoriasis were allowed 2 weeks before and during the trial except emollients and shampoos containing tar or salicylic acid. Screening medical history, physical examination, chest radiograph, and lab values were taken within 4 weeks of first study infusion. Clinical assessments of disease activity, haematology profiles, and chemistry profiles were conducted just before receiving the first study infusion (baseline), biweekly for the first 10 weeks, and then every 4 weeks through week 30. Disease activity was assessed using the PASI and a static PGA. **Safety** Safety assessments were based on observed and reported adverse events, lab tests, and discontinuations. The severity of each adverse event was classified as mild (easily tolerated), moderate (discomfort that interferes with usual activity), or severe (significant impairment of function or incapacitation). Serum samples collected at baseline and week 26 were assayed for antibodies, antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) if they were ANA-positive.
EXPRESS	**Design** This was a Phase 3, multicentre, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of infliximab induction and maintenance therapy in patients with moderate to severe plaque psoriasis. This 66-week study was conducted at 32 investigative centres (1 in Austria, 4 in Belgium, 9 in Canada, 3 in Denmark, 4 in France, 7 in Germany, 2 in Switzerland, and 2 in the United Kingdom). **Dosage** Patients were randomized to receive placebo or 5 mg/kg infliximab. The choice of dose was guided by previous experience with infliximab in other indications as well as observations in Chaudhari et al which suggested that infliximab 5mg/kg and 10mg/kg are equally efficacious. Initiation therapy involved administration of intravenous infusions of infliximab or placebo at weeks 0, 2 and 6. The study schema follows below. **Figure 2. EXPRESS Study Schema**  **Randomization and Blinding** Subjects were randomly assigned to treatment groups by the Interactive Voice Randomization System (IVRS) in a 4:1 ratio (active:placebo). Subject treatment allocation was stratified by investigational site. The treatment assignment for a given subject was determined by the IVRS during the randomization call. The assignment was stored electronically and distributed to the site pharmacist via fax or email. The pharmacist was not blinded to the treatment assignment. The clinical site monitors, study managers, clinical research associates, subjects, and site personnel were to be blinded to the subjects' treatment assignments until the Week-50 database was finalized. **Safety** Safety evaluations were conducted through Week 50 and included: 1) measurement of vital signs prior to, during, and for 1 hour after study agent infusions; 2) assessment at each visit of AEs and changes in concomitant medications; 3) routine laboratory analyses (hematology and chemistry), and 4) assessment of serum infliximab concentration (for subjects enrolled in a pharmacokinetic substudy), as well as the presence of antibodies to infliximab and autoantibodies in all subjects. In

	addition, blood specimens were collected at Week 66 (20 weeks after the last study agent infusion) for posttreatment assessments of serum infliximab concentration and antibodies to infliximab in all subjects. Serum infliximab levels were measured in all subjects at Week 66 because the presence of serum infliximab interferes with measuring antibodies to infliximab. Vital signs were measured for safety purposes; however, these data were not collected (ie, for inclusion in the database) for formal analyses unless entered as an AE on the eCRF. Any subject who discontinued from study agent infusions was to remain in the study and be assessed for safety and efficacy at all follow-up visits. For any subject who terminated the study, a full safety and efficacy evaluation was to be performed at the time the subject terminated completely from the study.
EXPRESS II	**Design** This was a Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel trial that evaluated the safety and efficacy of 2 dose regimens of infliximab induction therapy (3 mg/kg and 5 mg/kg administered by IV infusion) versus placebo followed by 2 regimens of maintenance infliximab therapy (either regularly scheduled every 8 weeks (q8wks) or "as-needed" (PRN) maintenance therapy for each infliximab dose) in subjects with moderate to severe plaque-type psoriasis. The study was conducted in 63 centres in the US, Canada, and Europe. The study consisted of 2 phases: the induction phase and the maintenance phase. The 3 treatment groups in the induction phase are presented below. INDUCTION PHASE (Weeks 0 to 10) • Group I: Infliximab 3 mg/kg infusions at Weeks 0, 2, and 6. • Group II: Infliximab 5 mg/kg infusions at Weeks 0, 2, and 6. • Group III: Placebo infusions at Weeks 0, 2, and 6. The second randomization of active treatment subjects (Groups I and II) to maintenance regimen treatment groups was stratified by PASI response status at Week 10 (either < 75% or ≥ 75% improvement from baseline) and investigational site. Infliximab administration during the maintenance phase for the 4 active treatment groups and 1 placebo group is presented below. Placebo was administered at visits when subjects did not receive infliximab in order to maintain the blind. MAINTENANCE PHASE (Weeks 14 to 46) • Group Ia (infliximab 3 mg/kg q8wks): Subjects received regularly scheduled maintenance therapy. • Group Ib (infliximab 3 mg/kg "as-needed"): Subjects returned every 4 weeks for PRN maintenance therapy through Week 46. At the visits when subjects did not achieve at least 75% improvement in PASI from baseline, they received infliximab 3 mg/kg. • Group IIa (infliximab 5 mg/kg q8wks): Subjects received regularly scheduled maintenance therapy. • Group IIb (infliximab 5 mg/kg "as-needed"): Subjects returned every 4 weeks for PRN maintenance therapy through Week 46. At the visits when subjects did not achieve at least 75% improvement in PASI from baseline, they received infliximab 5 mg/kg. • Group III (placebo → infliximab): At Weeks 16, 18, and 22, subjects received infliximab 5 mg/kg induction therapy in a double-blind fashion followed by regularly scheduled maintenance therapy. Subjects were treated through Week 46 and were followed for routine efficacy and safety assessments through Week 50, with 1 additional visit at Week 66 to measure antibodies to infliximab. An overview of the study schema through Week 66 is shown in Figure 3. **Figure 3. EXPRESS II Study Schema**



Dosage

The doses selected for this study (3 mg/kg and 5 mg/kg infliximab) were selected on the basis of findings in SPIRIT.

Initiation therapy involved administration of intravenous infusions of infliximab or placebo at weeks 0, 2 and 6.

Randomization and Blinding

Subjects were randomized using an adaptive treatment allocation with the investigational site as the stratum. Stratified by PASI response at Week 10 and by investigational site, subjects in the active treatment groups (3 mg/kg and 5 mg/kg infliximab) underwent a second randomization at Week 14 to either scheduled 8-weekly or PRN maintenance regimens at the same infliximab dose given during induction.

Both randomizations were performed by ClinPhone (Lawrenceville, NJ; US) using interactive voice response system (IVRS). Subjects randomized to placebo during the induction phase did not undergo another randomization at Week 14, but crossed over to active infliximab treatment (5 mg/kg) at Week 16 and continued treatment according to the figure under “Patient Disposition”.

Safety

Safety assessments included the following: 1) measurement of vital signs prior to, during, and for 1 hour after study agent infusions; 2) collection of AEs and serious AEs (SAEs); 3) changes in laboratory analyses (hematology and chemistry); 4) assessment of antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies; 5) assessment for the presence of antibodies to infliximab.

5.3.2 Participants

Chaudhari et al	**Population** Adult patients with moderate to severe plaque psoriasis involving at least 5% of body surface area and in good general health were included. All patients had clear chest radiographs within 1 month of study start. Patients were excluded if they had used topical therapy in the last 14 days or systemic therapy in the last 28 days, or if they had received treatment with any biologics or immunobiologics. Patients were also excluded if they had: positive HIV test, hepatitis B, hepatitis C; a history of current alcohol or drug abuse; history indicating serious infections such as hepatitis, pneumonia, or pyelonephritis in the last 3 months; history of active tuberculosis within the last 3 years; history of malignancy within the previous 5 years or suspicious lymphadenophathy or splenomegaly on physical examination; or a clinically significant abnormality in lab results. **Baseline Demographics** The three treatment groups were well-balanced on key demographics including sex, age, and

baseline disease severity, as is shown in Table 5. However, as only published data were available to Schering-Plough, the level of detail is lower than that can be presented for other trials.

Table 5. Chaudhari et al Baseline Demographics

		Infliximab		
Characteristic	Placebo	5 mg/kg	10 mg/kg	Total
No. of patients randomized	11	11	11	33
No. of women (%)	3 (27%)	4 (36%)	3 (27%)	10 (30%)
Age (y), mean (SD)	45 (12)	51 (14)	35 (11)	44 (12.6)
Psoriasis disease duration	Minimum 6 Months			
Body surface area (%)	Minimum 5%			
PASI score, mean (SD)	20.3 (5.5)	22.1 (11.5)	26.6 (10.3)	23 (9.1)

SD, Standard Deviation; PASI, Psoriasis Area and Severity Index.

Spirit

Population

The trial enrolled patients aged 18 years or older, with a diagnosis of plaque psoriasis for at least 6 months, and previously treatment history with PUVA or other systemic treatments. Patients had to have a baseline PASI score of 12 or more and psoriasis involving at least 10% of body surface area.

Key exclusion criteria included: nonplaque forms of psoriasis; a history of a chronic infectious disease or opportunistic infection; a serious infection within 2 months of enrolment; active or latent tuberculosis; pregnancy or planned pregnancy within 12 months of enrolment; a history of lymphoproliferative disease; active malignancy or history of malignancy within the previous 5 years, excepting successfully excised basal cell carcinoma.

Baseline Demographics

The treatment groups were well balanced with respect to demographics and baseline characteristics, as Table 6 illustrates. Only published data were available to Schering-Plough.

Table 6. SPIRIT Baseline Demographics

		Infliximab		
Characteristic	Placebo	3 mg/kg	5 mg/kg	Total
No. of patients randomized	51	99	99	249
No. of women (%)	20 (39.2%)	29 (29.3%)	26 (26.3%)	75 (30.1%)
Age (years), median (IQR)	45 (30, 52)	45 (37, 55)	44 (34, 53)	44 (35, 53)
Psoriasis disease duration (y), median (IQR)	16 (6, 22)	18 (12, 24)	16 (10, 25)	17 (11, 24)
Body surface area (%), median (IQR)	26 (19, 51)	29 (18, 45)	25 (20, 40)	27 (19, 45)
No. with psoriatic arthritis (%)	17 (33.3%)	32 (32.3%)	29 (29.3%)	78 (31.3%)
Prior antipsoriasis therapies				
Topical agents n (%)	50 (98.0%)	85 (85.9%)	91 (91.9%)	226 (90.8%)
Systemic agents n (%)	42 (82.4%)	86 (86.9%)	88 (88.9%)	216 (86.7%)
Phototherapies n(%)	34 (66.7%)	69 (69.7%)	68 (68.7%)	171 (68.7%)
Biologics n (%)	16 (31.4%)	32 (32.3%)	33 (33.3%)	81 (32.5%)
PASI score, median (IQR)	18 (15, 27)	20 (15, 26)	20 (14, 28)	19 (15, 27)
DLQI score, median (IQR)	14 (9, 18)	11 (6, 17)	12 (8, 17)	12 (8, 17)

DLQI, Dermatology Life Quality Index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index.

EXPRESS

Population

Subjects eligible to participate were men or women with plaque psoriasis who were at least 18 years of age and who were candidates for phototherapy or systemic therapy. In addition, subjects must have had a baseline PASI score of 12 or greater and at least 10% of their total BSA involved.

Subjects were excluded if they had nonplaque forms of psoriasis, had current drug-induced psoriasis, Were pregnant, nursing, or planning pregnancy (both men and women) within 18 months of enrolment, had any previous treatment with biologics, systemics, infliximab or any therapeutic agent targeted at reducing tumor necrosis factor (TNF) or psoriasis symptoms, used topical medications/treatments that could have affected psoriasis or PASI evaluation within 2 weeks of baseline visit, used any systemic immunosuppressants within 30 days of baseline visit, had received lithium within the previous 30 days, had received any live virus or bacterial vaccinations within 3 months or were scheduled to receive any up to 3 months after last study infusion, had a history of chronic or recurrent infectious disease, other serious infections, and other serious illnesses.

Baseline Demographics

All demographics characteristics were well balanced between treatment groups and are shown in Table 7.

Table 7. EXPRESS Baseline Demographics

Characteristic	Placebo	Infliximab 5 mg/kg	Total
No. of patients randomized	77	301	378
No. of women (%)	16 (21%)	94 (31%)	110 (29%)
Age (y), mean (SD)	43.8 (12.6)	42.6 (11.7)	42.8 (11.9)
Disease duration (y), mean (SD)	17.3 (11.1)	19.1 (11.0)	18.7 (11.1)
BSA (%), mean (SD)	33.5 (18)	34.1 (19)	34.0 (19)
No. with psoriatic arthritis (%)	22 (29%)	92 (31%)	114 (30%)
Prior antipsoriasis therapies			
UVB, n (%)	55 (71%)	196 (65%)	251 (66%)
PUVA, n (%)	35 (46%)	128 (43%)	163 (43%)
Methotrexate, n (%)	35 (46%)	126 (42%)	161 (43%)
Acitretin, n (%)	30 (39%)	80 (27%)	110 (29%)
Ciclosporin, n (%)	16 (21%)	99 (33%)	115 (30%)
PASI score, mean (SD)	22.8 (8.7)	22.9 (9.3)	22.9 (9.2)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
No. of pts with nail psoriasis (%)	65 (86%)	240 (81%)	302 (82%)
NAPSI score, mean (SD)	4.3 (1.9)	4.6 (2.0)	4.5 (2.0)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

SD, standard deviation
BSA, body surface area with psoriasis
UVB, ultraviolet light B
PUVA, Psoralen plus ultraviolet light A
PASI, Psoriasis Area & Severity Index
PGA, Physician's Global Assessment
NAPSI, Nail Psoriasis Score
DLQI, Dermatology Life Quality Index
SF-36, Short Form 36

EXPRESS II

Population

Subjects eligible to participate were men or women 18 years of age or older with a diagnosis of plaque-type psoriasis at least 6 months prior to screening and who were candidates for phototherapy or systemic therapy. Subjects must have had a baseline PASI score ≥ 12 and at least 10% of their total body surface area (BSA) involved. Results on tuberculosis (TB) testing at screening must have been negative and subjects must have passed the TB assessment.

Any subject who was pregnant, nursing, or planning pregnancy (both men and women) within 18 months of enrollment was excluded from study participation. Subjects with nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular) or current drug-induced psoriasis were also excluded. Any previous treatment with infliximab, the use of any biologic within the previous 3 months (regardless of the half-life), and the use of any investigational drug within the previous 4 weeks or 5 times the half-life of the investigational agent, whichever was longer, were reasons for exclusion. A subject who used any therapeutic agent targeted at reducing TNF within the previous 3 months, any systemic medications/treatments that could affect psoriasis or PASI evaluation within 4 weeks of baseline visit, or topical medications/treatments that could affect psoriasis or PASI evaluation within 2 weeks of baseline visit were excluded from the study. The trial also excluded subjects who had serious infections at or prior to study, including HIV and hepatitis.

Baseline Demographics

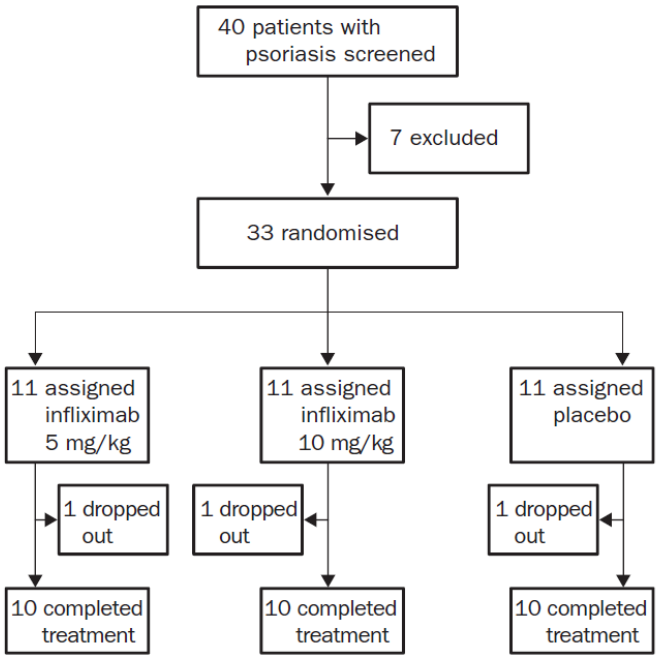
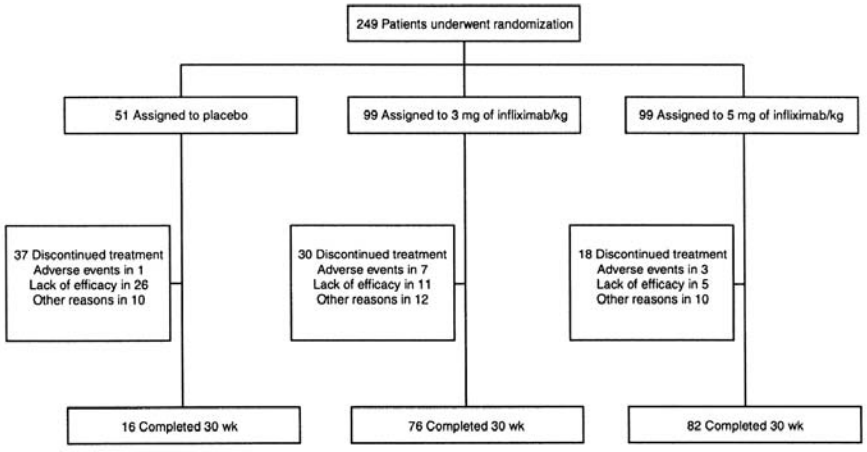
Demographic characteristics were generally well balanced among treatment groups as is shown in Table 8.

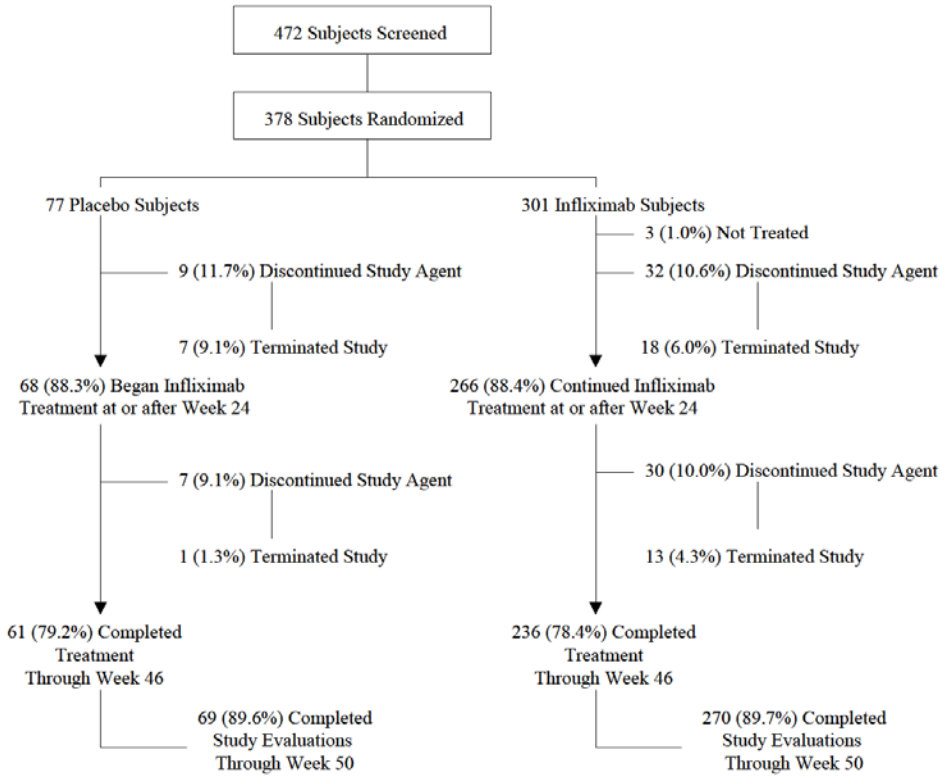
Table 8. EXPRESS II Baseline Demographics

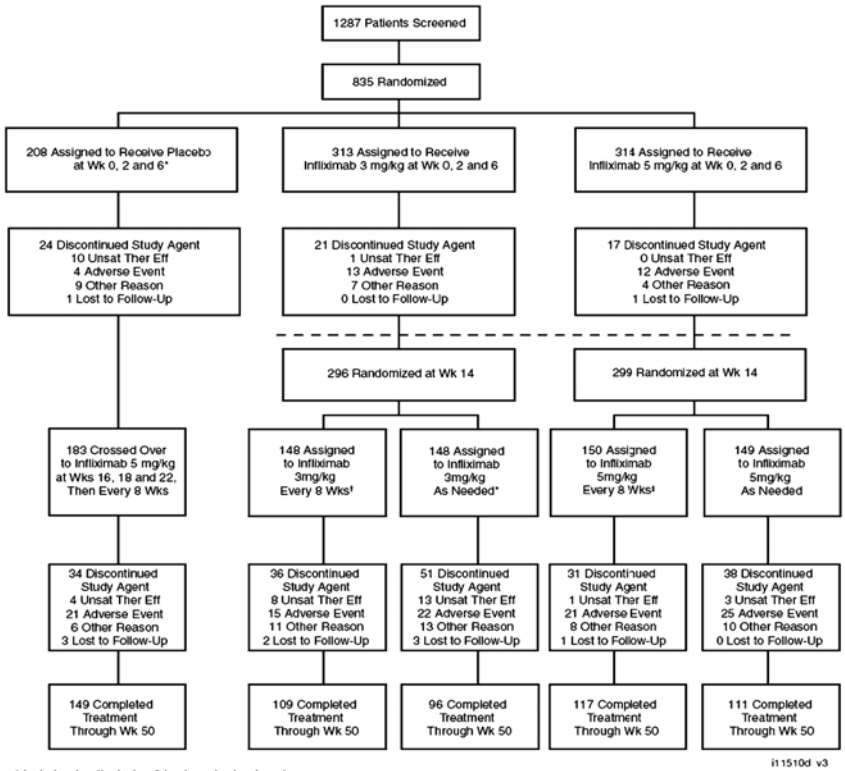
Characteristic	Placebo	Infliximab 3 mg/kg	Infliximab 5 mg/kg	Total
No. of patients randomized	208	313	314	835
No. of women (%)	64 (30.8%)	107 (34.2%)	110 (35.0%)	281 (33.7%)
Age (y), mean (SD)	44.4 (12.5)	43.4 (12.6)	44.5 (13.0)	44.0 (12.7)
Disease Dur (y), mean (SD)	17.8 (10.8)	18.1 (11.8)	19.1 (11.7)	18.4 (11.5)
BSA (%), mean (SD)	28.4 (17.6)	28.0 (16.3)	28.7 (16.4)	28.4 (16.7)
No. with psoriatic arthritis (%)	54 (26.0%)	87 (27.8%)	89 (28.3%)	230 (27.5%)
Prior antipsoriasis therapies				
Biologics, n(%)	27 (13.0%)	49 (15.7%)	45 (14.3%)	121 (14.5%)
Topical, n(%)	193 (92.8%)	297 (94.9%)	285 (90.8%)	775 (92.8%)
UVB, n (%)	103 (49.5%)	160 (54.3%)	173 (55.1%)	446 (53.4%)
PUVA, n (%)	62 (29.8%)	89 (28.4%)	86 (27.4%)	237 (28.4%)
Methotrexate, n (%)	70 (43.7%)	102 (32.6%)	109 (44.7%)	281 (43.7%)
Acitretin, n (%)	30 (14.4%)	47 (15.0%)	49 (15.6%)	126 (15.1%)
Ciclosporin, n (%)	28 (13.5%)	42 (13.4%)	35 (11.1%)	105 (12.6%)
PASI score, mean (SD)	19.8 ± 7.7	20.1 ± 7.9	20.4 ± 7.5	20.1 ± 7.7
PGA Scores	Not given at baseline			
DLQI score, mean (SD)	13.4 ± 7.3	12.8 ± 6.9	13.1 ± 7.0	13.1 ± 7.0
SF-36 score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

SD, standard deviation
BSA, body surface area
UVB, ultraviolet light B
PUVA, Psoralen plus ultraviolet light A
PASI, Psoriasis Area & Severity Index
PGA, Physician's Global Assessment
NAPSI, Nail Psoriasis Score
DLQI, Dermatology Life Quality Index
SF-36, Short Form 36

5.3.3 Patient numbers

Chaudhari et al	The basic assignment of patients in Chaudari et al was straightforward and is set out in Figure 4. **Figure 4. Chaudhari et al Patient Disposition** 
Spirit	The SPIRIT trial followed a similar set-up to Chaudari et al in terms of patient disposition, except that placebo and the two infliximab arms were assigned at a 1:2:2 ratio as described previously. Figure 5 summarizes. **Figure 5. Patient Disposition in SPIRIT trial**  **Fig 1.** Randomization, reasons for discontinuing treatment, and numbers of patients who completed study. Other reasons for discontinuing treatment were relocation, withdrawn consent, noncompliance, lost to follow-up, and violation of study entry criteria. Patients may have discontinued treatment and still completed 30-week study period.

EXPRESS	Patient disposition for the EXPRESS study is summarized in Figure 6. A total of 353 patients were included in the 24-week assessment of efficacy (infliximab, n = 276; placebo, n = 77) and 349 in the 50-week assessment (infliximab, n = 281; placebo, n = 68) (compared with 378 at week 10). **Figure 6. Patient Disposition in EXPRESS** 

EXPRESS II	In EXPRESS II induction treatments (placebo, infliximab 3mg/kg or 5mg/kg) were randomized evenly. At 14 weeks, patients assigned to every-8-week maintenance continued to receive their original infliximab dose, with infusions at weeks 14, 22, 30, 38 and 46. Placebo patients who crossed over to every-8-week maintenance received three induction infusions with infliximab 5mg/kg at weeks 16, 18, and 22, followed by 5mg/kg in weeks 40, 38, and 46. Patients assigned to "as needed" treatment received infusions at visits during which observed improvement in PASI from baseline fell below 75%. **Figure 7. Patient Disposition in EXPRESS II (subjects randomized week 0)**  * Includes 1 patient who did not receive treatment. † Includes 3 patients who did not receive treatment. ‡ Includes 2 patients who did not receive treatment. Unsat Ther Eff = Unsatisfactory Therapeutic Effect

5.3.4 Outcomes

Chaudhari et al	**The primary efficacy endpoint was:** . A positive response on PGA at week 10 given as a good (50–74% clearing with moderate improvement), excellent (75–99% clearing with striking improvement), or clear (100% clearing) rating. **The secondary endpoint was:** . The proportion of patients attaining at least 75% improvement in PASI from baseline at week 10.
SPIRIT	**The primary efficacy end point was:** . The proportion of patients attaining at least 75% improvement in PASI from baseline at week 10. **Major secondary endpoints included:** . Physician's Global Assessment (PGA) and Dermatology Life Quality Index (DLQI).
EXPRESS	**The primary efficacy endpoint was:** . The proportion of patients attaining at least 75% improvement in PASI from baseline at week 10. **Major secondary endpoints included:** . The proportion of subjects with a ≥ 75% improvement in PASI from baseline to Week 24. . The change in Dermatology Life Quality Index (DLQI) from baseline to Week 10 and Week 24. . The proportion of subjects achieving a PGA score of cleared (0) or minimal (1) at Week 10. . The NAPSI nail psoriasis score . The Short Form 36 (SF-36)
EXPRESS II	**The primary efficacy endpoint was:** . The proportion of patients attaining at least 75% improvement in PASI from baseline at week 10. **Major secondary endpoints included:** . The improvement from baseline in PASI response between Week 16 and Week 30. . The change in Dermatology Life Quality Index (DLQI) from baseline at Week 10. . The proportion of subjects with a Physician's Global Assessment of Disease (PGA) score of clear or excellent at Week 10.

5.3.5 Statistical analysis and definition of study groups

Chaudhari et al	**ARMS** The primary analysis compared the week 10 results of the study's three arms: placebo, infliximab 5mg/kg, and infliximab 10mg/kg. **ITT** The primary analysis was done according to intention to treat—ie, all randomised patients were included in the analysis. **POWER** The power for the study was adequate, and is described in detail in Table 9. **ANALYSIS** A Fisher's exact test was used to test the difference between the proportion of patients with a favourable response in each infliximab treatment group compared with the placebo group. No adjustments for multiple testing were made.
Spirit	**ARMS** The primary analysis compared the week 10 results of the study's three arms: placebo, infliximab 3mg/kg, and infliximab 5mg/kg. **ITT** Week 10 results were examined by intention-to-treat analysis. For patients who did not return for evaluation or had insufficient data to assess their score at week 10, the data from the closest visit before week 10 were used. **POWER** The power for the study was adequate, and is described in detail in Table 9. **ANALYSIS** Pearson chi-square tests were used to compare all dichotomous end points, and analysis of variance on the van der Waerden normal scores was used for continuous end points. In the results section, medians were presented for the continuous end points unless otherwise indicated. Analysis of safety included data from patients who received at least one dose of placebo or infliximab. No adjustment for multiple testing were made.

EXPRESS	**ARMS** The primary analysis compared the week 10 results of the study's two arms: placebo and infliximab 5mg/kg. **ITT** Week 10 PASI scores were examined by intention-to-treat analysis. Subjects who discontinued the study treatment due to lack of efficacy, loss of response, or were treated with protocol-prohibited medications/therapies from the baseline visit to Week 10 were considered treatment failures and who did not meet the primary endpoint. Subjects with missing or incomplete week 10 data were also considered treatment failures. Outcomes other than PASI response were analysed using available data to calculate means, rather than on an intention-to-treat basis. **POWER** The power for the study was adequate, and is described in detail in Table 9. **ANALYSIS** In order to address the primary objective, a 2-sided chi-square statistic was used to test for treatment group difference. To establish the efficacy of infliximab compared with placebo, the comparison must have been statistically significant at a significance level of 0.05 (2-sided). Extensive sensitivity analyses were carried out to assess the effect of missing data on inferences from the analysis. No adjustment for multiple testing were made.
EXPRESS II	**ARMS** The primary analysis compared the week 10 results of the study's three arms: placebo, infliximab 3mg/kg, and infliximab 5mg/kg. **ITT** Week 10 results were examined by intention-to-treat analysis. Subjects who discontinued the study treatment due to lack of efficacy, loss of response, or were treated with protocol-prohibited medications/therapies from the baseline visit to Week 10 were considered treatment failures and who did not meet the primary endpoint. Subjects with missing or incomplete week 10 data were also considered treatment failures. **POWER** The power for the study was adequate, and is described in detail in Table 9. **ANALYSIS** The CMH chi-square test stratified by site was used to compare the proportion of subjects who achieved a ≥ 75% improvement in PASI from baseline to Week 10 between the 3 mg/kg infliximab group and the placebo group, and between the 5 mg/kg infliximab group and placebo. Sites with the total number of subjects randomized less than 8 were aggregated by geographic region (ie, northeast, midwest, south, southeast, southwest, and west, for sites in the US and by country for sites outside the US) to allow contribution from each aggregate site for the computation of Mantel-Haenszel statistics. To establish the efficacy of infliximab compared with placebo, at least 1 of the comparisons must have been statistically significant at 0.025 (2-sided). Only when the infliximab dose group(s) was significantly different from placebo at a significance level of 0.025 (2-sided) was a claim made for infliximab being superior to placebo. Extensive sensitivity analyses were carried out to assess the effect of missing data on inferences from the analysis. No adjustments were made for multiple testing.

5.3.6 Critical appraisal of relevant RCTs

Randomization

The four pivotal trials all adapted rigorous double-blinding protocols to ensure that the patient and participating dispensing pharmacist were blinded as to treatment allocation. Clinicians carrying out the regular assessment of psoriasis outcomes were also blinded as to patient allocation. Randomization was carried for all four trials via a phone-based recruitment and allocation software solution. As has been shown in the results summary, the study groups were comparable.

Statistics

The size of difference each study was powered to detect varied by study as is shown in Table 9. All analyses were carried out on an intention-to-treat basis and were appropriately selected.

Table 9. Power Calculation for Infliximab Studies

Study	Primary Efficacy Endpoint	Minimum Difference to Detect			Total N	Significance Criterion (α) Power to Reject Type II Error (β)
		Arm	%	N		
SPIRIT	% patients attaining PASI 75	*Information not given*			249	α=0.05
Chaudhari et al	% patients attaining good, excellent or clear PGA score	Placebo: IFX:	10% 70%	(1/10) (7/10)	33	α=0.05 β=0.85
EXPRESS	% patients attaining PASI 75 at week 10	Placebo: IFX:	20% 40%	(15/75) (120/300)	378	α=0.05 β=0.93
EXPRESS II	% patients attaining PASI 75 at week 10	Placebo: IFX 3mg/kg: IFX 5mg/kg:	10% 50% 60%	(15/75) (120/300) (120/300)	835	α=0.0025 β>0.99

IFX, infliximab; PASI, Psoriasis Area & Severity Index

Follow-up

All trials assessed primary endpoints across short follow-up interval of ten weeks. Subsequent to this period, patients were followed up for a minimum of 50 weeks in all trials except Chaudhari et al, for which only 10 weeks' data are reported. The majority of follow-up was drug-free except in EXPRESS II where patients received maintenance or episodic treatment with infliximab or placebo. In the context of this technology appraisal, the short follow-up period offers limited information about the longer-term efficacy of infliximab in promoting remission in psoriasis.

Cross-over Effects and Dosing

The trials were all parallel group. However placebo subjects in EXPRESS and EXPRESS II trials were re-allocated after the primary efficacy assessment, to receive infliximab. This design is unlikely to cause the cross-over effects sometimes associated with studies where subjects swap treatments. The licensed dosage for infliximab infusion is 5mg of infliximab per kilogram of bodyweight, and was used in at least one study arm in each trial.

The clinical trials used a variety of dosing regimens in addition to the licensed dose of 5mg infliximab per kilogram of bodyweight. However each trial had one study group who received the licensed dose. To ensure that the results presented in this section and in Schering-Plough's economic model are applicable to licensed use of infliximab in the UK, this clinical summary has concentrated on efficacy results for subjects receiving licensed 5mg/kg infusions.

Centres and Geography

All trials except Chaudhari *et al* were multi-centre, with a wide distribution of locations. Predominantly, the data came from the United States as is shown in Table 10. The dominance of United States citizens in the efficacy population is unlikely to make the results less applicable in terms of disease aetiology, however in economic terms there is an effect since the American psoriasis population is heavier on average than the UK population.

Table 10. Distribution of Centres for Infliximab Trials

Study	Location	N. Centres
Chaudhari et al	United States	1
SPIRIT	United States	24
	Total	**24**
EXPRESS	Austria	1
	Belgium	4
	Canada	9
	Denmark	3
	France	4
	Germany	7
	Switzerland	2
	United Kingdom	2
	Total	**32**
EXPRESS II	United States	41
	Canada	15
	Austria	2
	Italy	2
	France	3
	Total	**63**

5.4 Results of the relevant comparative RCTs

The relevant RCT results are presented below aggregated by outcome type, all of which have been described at the introduction of the methodology section 5.3.

PASI 50 Response

Attainment of a 50 percent reduction in PASI was measured as a secondary endpoint in three trials at week 10, and in the EXPRESS and EXPRESS II trials at subsequent weeks. Across these trials patients on infliximab 5mg/kg had significantly higher likelihood of attaining PASI 50 than patients on placebo. Placebo patients in EXPRESS and EXPRESS II trials crossed over to receive infliximab after weeks 24 and 14 respectively hence the differences are no longer significant after crossover.

Study	Placebo*	Infliximab	RR (95% CI)
Proportion of Patients Achieving PASI 50			Week 10
SPIRIT	11/51 (21.6%)	96/99 (97.0%)	4.5 (3.9, 5.2)
EXPRESS	6/77 (8%)	274/301 (91%)	11.7 (8.6, 15.8)
EXPRESS II	[redacted]	[redacted]	11.3 (10.2, 12.6)
Proportion of Patients Achieving PASI 50			Week 24/26
EXPRESS	6/77 (6%)	248/276 (90%)	11.5 (8.5, 15.6)
EXPRESS II	126/141 (89.4)%	126/144 (87.5%)	1 (1, 1)
Proportion of Patients Achieving PASI 50			Week 50
EXPRESS	61/68 (90%)	193/281 (69%)	0.8 (0.8, 0.8)
EXPRESS II	97/134 (72.4%)	99/134 (73.9%)	1 (1, 1)

* Placebo patients crossed over to infliximab after week 24 in EXPRESS and week 14 in EXPRESS II

PASI 75 Response

Achieving a 75 percent reduction in PASI at week 10 was the primary endpoint of SPIRIT, EXPRESS and EXPRESS II trials, and was also measured in Chaudari et al as a secondary endpoint . In all trials patients on infliximab 5mg/kg had significantly higher likelihood of attaining PASI 75 at week 10 than patients on placebo. Placebo patients in EXPRESS and EXPRESS II trials crossed over to receive infliximab after weeks 24 and 14 respectively hence the differences are no longer significant after crossover.

Study	Placebo*	Infliximab	RR (95% CI)
Proportion of Patients Achieving PASI 75			Week 10
Chaudhari et al	2/11 (18.0%)	9/11 (82.0%)	4.5 (1.9, 10.4)
SPIRIT	3/51 (5.9%)	87/99 (87.9%)	14.9 (8.1, 27.7)
EXPRESS	2/77 (3%)	242/301 (80%)	31 (11.9, 80.5)
EXPRESS II	[redacted]	[redacted]	39.2 (24.2, 63.6)
Proportion of Patients Achieving PASI 75			Week 24/26
EXPRESS	3/77 (4%)	227/276 (82%)	21.1 (11.2, 39.6)
EXPRESS II	110/141 (78.0%)*	83/144 (57.6%)	0.7 (0.7, 0.7)
Proportion of Patients Achieving PASI 75			Week 50
EXPRESS	52/68 (77%)	170/281 (61%)	0.8 (0.8, 0.8)
EXPRESS II	73/134 (54.5%)*	51/134 (38.1%)	0.7 (0.7, 0.7)

* Placebo patients crossed over to infliximab after week 24 in EXPRESS and week 14 in EXPRESS II

PASI 90 Response

PASI 90, defined as a 90 percent reduction in PASI from baseline, was measured at week 10 in SPIRIT, EXPRESS and EXPRESS II trials. The EXPRESS and EXPRESS II trials also measured PASI 90 at weeks 24/26 and 50. Improvements in PASI 90 rates by infliximab compared with placebo were significant in all relevant comparisons before placebo patients crossed over.

Study	Placebo*	Infliximab	RR (95% CI)
Proportion of Patients Achieving PASI 90			Week 10
SPIRIT	1/51 (2.0%)	57/99 (57.6%)	29.4 (4.2, 203.6)
EXPRESS	1/77 (1%)	172/301 (57%)	44 (6.3, 306)
EXPRESS II	[redacted]	[redacted]	94.1 (13.3, 666.5)
Proportion of Patients Achieving PASI 90			Week 24/26
EXPRESS	1/77 (1%)	161/276 (58%)***	44.9 (6.5, 312.4)
EXPRESS II	79/141 (56.0%)*	34/144 (23.6%)	0.4 (0.4, 0.4)
Proportion of Patients Achieving PASI 90			Week 50
EXPRESS	34/68 (50%)	127/281 (45%)	0.9 (0.9, 0.9)
EXPRESS II	46/134 (34.3%)*	14/134 (10.4%)	0.3 (0.3, 0.4)

* Placebo patients crossed over to infliximab after week 24 in EXPRESS and week 14 in EXPRESS II

Relative Improvement in PASI score, and speed of improvement

Patients' absolute PASI score was measured at baseline in all studies, but its relative change was captured only in EXPRESS and Chaudari et al. EXPRESS recorded the improvement level as percentages at weeks 10, 24 and 50; Chaudari et al recorded the improvement in terms of average scores, without standard deviations, at week 10, and gave a graphical summary of percentage improvements in Figure 8.

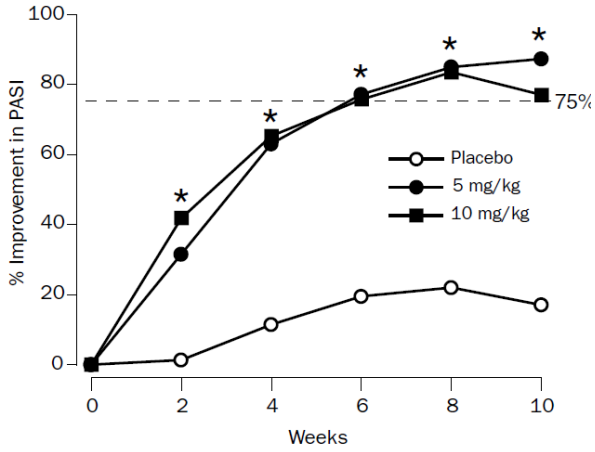
EXPRESS showed that infliximab was associated with approximately an 80 percent greater reduction in PASI compared with placebo.

Study	Placebo*	Infliximab	Mean difference (95% CI where possible)†
Improvement in PASI from Baseline, Mean (SD)			Week 10
Chaudhari et al Mean change in score units	-2.8	-18.3	-15.5 (no 95% CI)
EXPRESS (n) Mean % improvement (SD)	77 6.1 (29.9)	292 85.5 (21.4)	79.4 (75.5, 85.3)
Improvement in PASI from Baseline, Mean (SD)			Week 24/26
EXPRESS (n) Mean % improvement (SD)	77 4.4 (40.1)	276 83.9 (25.2)	79.5 (72.1, 86.9)
Improvement in PASI from Baseline, Mean (SD)			Week 50*
EXPRESS (n) Mean % improvement (SD)	68 80.7 (26.3)	281 64.3 (41.2)	-16.4 (-26.7, -6.1)

† Confidence interval calculated from two-tailed t-test where a measure of variance was supplied.
* Placebo patients crossed over to infliximab after week 24 in EXPRESS and week 14 in EXPRESS II

Several studies also gave results demonstrating the speed of onset of infliximab therapy in improving PASI-related symptoms, these are shown from Chaudhari et al, SPIRIT, EXPRESS and EXPRESS II trials in Figure 8, Figure 9, Figure 10, and Figure 11. As the figures illustrate, infliximab created clinically, and usually statistically significant improvements in PASI outcomes by as early as the second week following infusion.

Figure 8.Mean percentage improvement PASI by time in Chaudari et al



* - p<0.0003 in comparison with placebo

Figure 9. % of patients achieving PASI ≥ 75 by time in SPIRIT

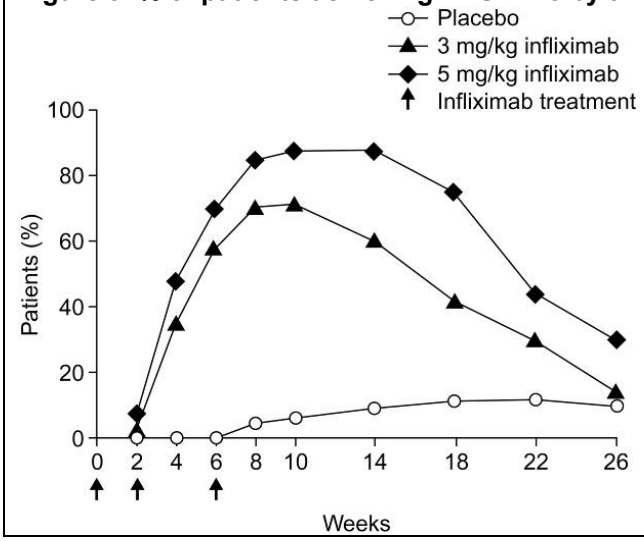
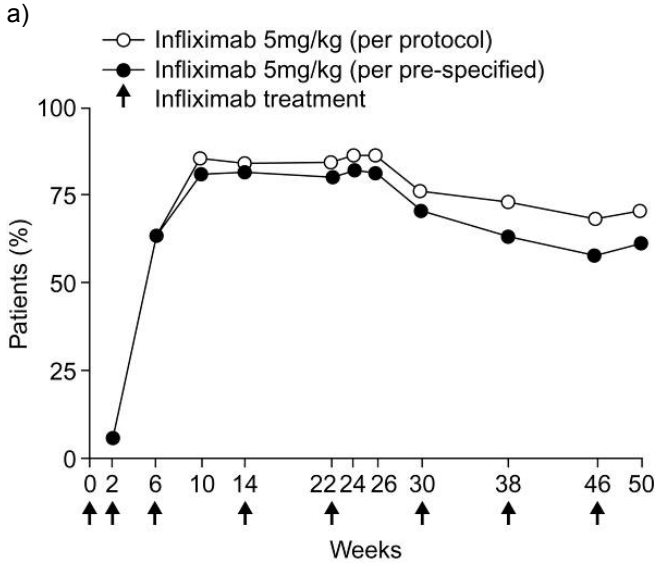


Figure 10. % of patients achieving PASI 75 by time in EXPRESS a) inflximab arm b) placebo-to-infliximab crossover arm [crossover at week 24]

a)



b)

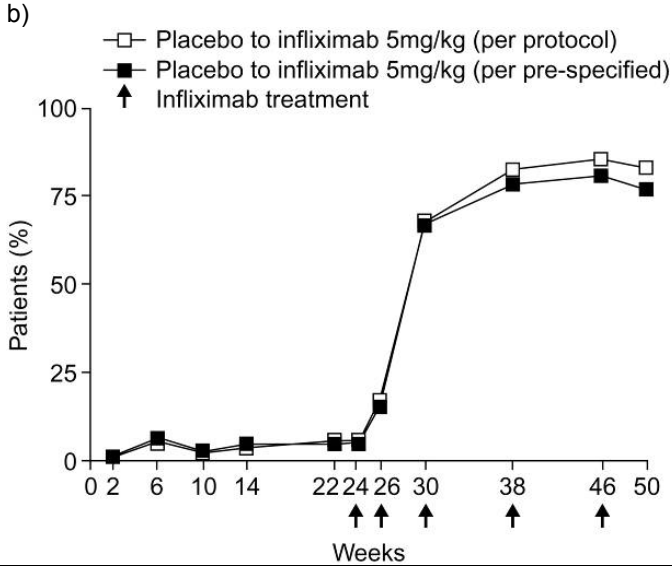
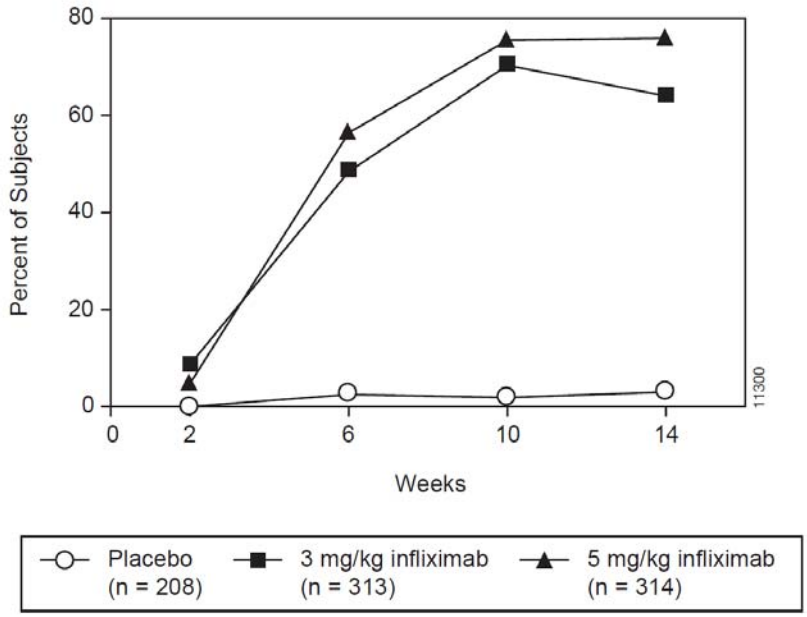


Figure 11. % of patients achieving PASI 75 by time before crossover in EXPRESS II



Patient outcomes measured on PGA

PGA status was the primary outcome in Chaudhari et al and a secondary outcome in SPIRIT, EXPRESS and EXPRESS II trials. In all relevant comparisons infliximab was associated with significantly higher rates of attainment of the "excellent" or "clear" ratings, as well as the less stringent "good", "excellent" or "clear" category in PGA. At week 10, infliximab patients were between 9 and [redacted] times more likely than placebo patients to attain "excellent" or "clear" PGA status, and between 2 and [redacted] times more likely to attain "good", "excellent" or "clear".

PGA "excellent" or "cleared"

Study	Placebo*	Infliximab	RR (95% CI)
Proportion of Patients Achieving PGA score of excellent/cleared			Week 10
Chaudhari et al	1/11 (9.0%)	9/11 (82.0%)	9 (1.5, 55.6)
SPIRIT	5/51 (9.8%)	89/99 (89.9%)	9.2 (6.4, 13.1)
EXPRESS	3/77 (4%)	242/301 (83%)	20.6 (11, 38.7)
EXPRESS II	[redacted]	[redacted]	79 (29.9, 209)
Proportion of Patients Achieving PGA score of excellent/cleared			Week 24/26
EXPRESS	2/77 (3%)	203/276 (74%)	28.3 (10.9, 73.7)
EXPRESS II	112/141 (79.4%)	82/144 (56.9%)	0.7 (0.7, 0.7)
Proportion of Patients Achieving PGA score of excellent/cleared			Week 50
EXPRESS	46/68 (68%)	149/281 (53%)	0.8 (0.8, 0.8)
EXPRESS II	78/134 (58.2%)	56/133 (42.1%)	0.7 (0.7, 0.7)

* Placebo patients crossed over to infliximab after week 24 in EXPRESS and week 14 in EXPRESS II

PGA "good", "excellent" or "cleared"

Study	Placebo	Infliximab	RR (95% CI)
Proportion of Patients Achieving PGA score of good/excellent/cleared			Week 10
Chaudhari et al	2/11 (18.0%)	9/11 (82.0%)	4.5 (1.9, 10.4)
SPIRIT	23/51 (45.1%)	97/99 (98.0%)	2.2 (2.1, 2.3)
EXPRESS II	[redacted]	[redacted]	12.9 (11.4, 14.6)

Patient outcomes measured on SF-36

The SF-36 quality of life score was only captured comprehensively in the EXPRESS trial. This is a general life quality score rather than a disease-specific score, and is broken broadly into physical and mental components. These component scores can be further broken down into sub-scales. The EXPRESS study write-up included the physical and mental scores in its summary. In all relevant comparisons of infliximab and placebo prior to crossover, infliximab patients experienced a significantly greater mean improvement in SF-36 score than placebo patients.

Study	Placebo*	Infliximab	Mean difference (95% CI)†
Mean improvement from Baseline on SF-36			Week 10
EXPRESS (n)	77	290	
Physical Component	-0.4 (7.7)	5.0 (8.3)	5.4 (3.3, 7.5)
Mental Component	-0.8 (9.7)	6.3 (11.0)	7.1 (4.4, 9.8)
Mean improvement from Baseline on SF-36			Week 24/26
EXPRESS (n)	77	274	
Physical Component	-1.4 (9.2)	4.9 (9.5)	6.3 (3.9, 8.7)
Mental Component	-0.5 (10.1)	5.3 (10.3)	5.8 (3.2, 8.4)
Mean improvement from Baseline on SF-36			Week 50
EXPRESS (n)	68	276	
Physical Component	2.2 (8.8)	3.1 (9.4)	0.9 (-1.6, 3.4)
Mental Component	2.8 (10.9)	4.0 (9.7)	1.2 (-1.4, 3.8)

† Confidence interval calculated from two-tailed t-test
* Placebo patients crossed over to infliximab after week 24 in EXPRESS and week 14 in EXPRESS II

Patient outcomes measured on DLQI

The Dermatology life quality index (DLQI) was collected throughout the EXPRESS and EXPRESS II trials, with infliximab patients experiencing significantly greater reductions in the score's severity at all per-crossover timepoints compared with placebo. Differences post-crossover were statistically nonsignificant.

Note: DLQI score improvement statistics are given for competitor products in the Appendix.

Study	Placebo*	Infliximab	Mean difference (95% CI)†
Mean reduction from Baseline on DLQI			Week 10
EXPRESS (n) Mean change (SD)	[redacted]	[redacted]	[redacted]
EXPRESS II (n) Mean change (SD)	[redacted]	[redacted]	[redacted]
Mean reduction from Baseline on DLQI			Week 24/26‡
EXPRESS (n) Mean change (SD)	[redacted]	[redacted]	[redacted]
Mean reduction from Baseline on DLQI			Week 50
EXPRESS (n) Mean change (SD)	[redacted]	[redacted]	[redacted]
EXPRESS II (n) Mean change (SD)	134 8.3 (7.4)	134 7 (7.7)	-1.3 (-3.1, 0.5)

† Confidence interval calculated from two-tailed t-test
* Placebo patients crossed over to infliximab after week 24 in EXPRESS and week 14 in EXPRESS II
‡ DLQI not measured at week 26 in EXPRESS II

Patient outcomes measured on NAPSI

The NAPSI score was only collected in EXPRESS. It is an adjunct measure of psoriasis to PASI, but has important implications for life quality. Similar to PASI scores, infliximab patients experienced a significantly greater percentage improvement in their nail psoriasis relative to placebo.

Study	Placebo*	Infliximab	Mean difference (95% CI)†
Percent improvement from Baseline on NAPSI			Week 10
EXPRESS (n) Mean percent change (SD)	65 –5·9 (54·3)	235 26·0 (42·3)	 31.9 (19.4, 44.3)
Percent improvement from Baseline on NAPSI			Week 24/26
EXPRESS (n) Mean percent change (SD)	65 –3·2 (62·3)	223 56·3 (43·4)	 59.5 (46.1, 72.9)
Percent improvement from Baseline on NAPSI			Week 50
EXPRESS (n) Mean percent change (SD)	58 72·5 (38·9)	226 56·3 (52·0)	 -16.2 (-30.6, -1.8)

† Confidence interval calculated from two-tailed t-test

* Placebo patients crossed over to infliximab after week 24 in EXPRESS and week 14 in EXPRESS II

Subgroup analysis: Primary Efficacy Parameter (PASI 75 Response Rate at Week 10) by Baseline History of Disease Treatment

The EXPRESS and EXPRESS II trials included analyses of their primary endpoint, PASI 75 by the most common patient disease history characteristics as well as prior treatment history. The trials supply this information in graphical format shown in Figure 12 and Figure 13.

The studies included these analyses to confirm the independence of PASI response to prior medication history. As the graphics clearly show, there is little clinical variation in patients' response on the PASI 75 goal across subgroups of past therapy, even if the therapy was systemic.

Figure 12. % of Patients achieving PASI 75 by Baseline Treatment History in EXPRESS

CiC-Table Removed

Figure 13. % Patients achieving PASI 75 by Baseline Treatment History in EXPRESS II

CiC-Table removed

Efficacy Conclusion

The results of the four placebo-controlled studies showed that infliximab produces clinically significant improvements in symptoms (i.e. improvement in PASI of at least 75%) in approximately 80% of patients following induction therapy (at week 10). This response was sustained at 24 weeks with maintenance therapy given at 8-week intervals and only declined slightly at 50 weeks (70% of patients having PASI ≥ 75).

In the SPIRIT and EXPRESS/EXPRESS II studies, 76–88% of patients treated with infliximab achieved a ≥ 75% improvement in PASI from baseline at week 10 compared with an average response rate of approximately 5% for placebo-treated patients ($p < 0.001$). Infliximab also improved nail psoriasis.

Improvements in symptoms were achieved rapidly with infliximab, with significant differences compared with placebo being observed within 2 weeks of starting treatment. These results suggest that infliximab is a highly effective systemic treatment for moderate-to-severe psoriasis, and is an appropriate choice for patients who fail to respond to or are intolerant of systemic therapies.

The improvement in signs and symptoms of disease was also mirrored in the life quality scores DLQI and SF-36, which were consistently higher in infliximab groups.

These data therefore demonstrate the efficacy of the licensed initiation dose of 5 mg/kg for the treatment of moderate-to-severe psoriasis.

Analyses by prior systemic therapy from the EXPRESS I and EXPRESS II trials 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. These results suggest that the benefits for infliximab are likely to be representative of those expected in patients meeting the licensed indication, namely failing or intolerant of systemic therapies.

This finding introduces a critical issue which was raised in a previous NICE MTA in psoriasis (TA#103), namely that infliximab therapy is likely to be equally as efficacious in patients who are treatment naïve as in patients who have had previous systemic therapy.

Data from the new EXPRESS II trial further showed that significant benefits on the main efficacy parameters could be observed if a consistent maintenance regimen of one infliximab infusion every 8 weeks was applied, rather than “as needed” episodic infusion. This was true regardless of the dosage per kilo of bodyweight patients received.

Long term efficacy

Clinical efficacy data beyond week 10 from the EXPRESS/EXPRESS II trials indicate that the response to infliximab was sustained, with the difference between infliximab and placebo remaining highly statistically significant out to week 24 in EXPRESS. At week 50 there was a slight decline in response in the infliximab group compared with week 24, but 61% of EXPRESS patients retained a clinically significant improvement in symptoms, and the response rate increased to 70% when patients who had missed two infusions were excluded from the analysis. In the EXPRESS trial nail psoriasis response continued to improve between week 10 and week 24 and hence was delayed compared to the skin response. The nail response achieved at 24 weeks was maintained at week 50. EXPRESS showed a similar maintenance of PASI 75 response beyond the induction phase, although a decline was evident in both studies. Data beyond one year are currently not available, so it is difficult to draw robust conclusions about the longer-term efficacy of infliximab.

5.5 Meta-analysis

PASI outcomes

Pooled relative risks have been computed in Table 11 using a Mantel-Haenszel method under a fixed-effects model. PASI response at week 10 is the common outcome measure and only the infliximab 5mg/kg arm from each trial is used.

The results from the Mantel-Haenszel analyses suggest significant heterogeneity between infliximab trials, meaning that an indirect comparison with other trials using a fixed-effects model would be inappropriate. Therefore, the comparison with competitor products was carried out using a random effects model as described in section 5.6.

Table 11. Pooled PASI Score Analysis from Four Infliximab Trials

Study	Infliximab 5mg/kg	Placebo	RR (95% CI)
Proportion of Patients Achieving PASI 50			
Chaudhari et al	96/99 (97.0%)	11/51 (21.6%)	4.50 (2.66, 7.60)
EXPRESS	274/301 (91.0%)	6/77 (6.9%)	11.68 (5.41, 25.21)
Pooled OR Test for heterogeneity			7.35 (4.65, 11.61) Q=4.77 (df=1), *P*=0.029
Proportion of Patients Achieving PASI 75			
Chaudhari et al	9/11 (81.8%)	2/11 (18.2%)	4.50 (1.25, 16.25)
SPIRIT	87/99 (87.9%)	3/51 (5.9%)	14.94 (4.97, 44.89)
EXPRESS	242/301 (80.4%)	2/77 (2.6%)	30.95 (7.87, 121.68)
EXPRESS II	237/314 (75.5%)	4/208 (1.9%)	39.25 (14.84, 103.80)
Pooled OR Test for heterogeneity			25.48 (14.04, 46.23) Q=8.742 (df=3), P=0.033
Proportion of Patients Achieving PASI 90			
SPIRIT	57/99 (57.6%)	1/51 (2.0%)	29.36 (4.19, 205.98)
EXPRESS	172/301 (57.1%)	1/77 (1.3%)	44.00 (6.26, 309.16)
EXPRESS II	142/314 (45.2%)	1/208 (0.5%)	94.054 (13.26, 667.143)
Pooled OR Test for heterogeneity			53.94 (17.65, 164.89) Q=0.351 (df=2), P=0.839

DLQI outcomes

It was not possible formally meta-analyse health-related quality of life data because of insufficient consistency in data collection and reporting methods across RCTs, however the pooled DLQI scores for competitor products have been given in the Appendix for reference and comparison with those in the Results section 5.4.

Informal comparison of infliximab DLQI scores and competitor DLQI scores suggests that infliximab is associated with the greatest reduction in DLQI score 10 or 12 weeks after initiation.

5.6 Indirect/mixed treatment comparisons

Data extracted from all RCTs were pooled by outcome and dose using a fixed effects Mantel-Haenszel model. This analysis suggested that the degree of variability is such that a random effects model would be more appropriate. A random effects model was therefore used for the evidence synthesis Bayesian hierarchical model.

An evidence synthesis for efficacy data of efalizumab, etanercept and infliximab was conducted. To enable an indirect comparison between these treatments a meta-analysis of PASI 50, 75 and 90 response rates was performed. The endpoints were jointly modeled using an ordered probit model, details of which are given in the Appendix.

The evidence synthesis meta-analysis was conducted using WinBUGS version 1.4. A burn-in period of 100,000 simulations was used to allow convergence followed by 100,000 simulations for estimation. As a degree of autocorrelation was observed in some of the model parameters the model was 'thinned' so every 10th simulation was retained. Caterpillar plots of the estimated parameters were checked to ensure that the model converged satisfactorily. A comparison of predicted probabilities with the original data indicated a reasonable fit for the model.

The trials of comparator medications etanercept and efalizumab were identified using the search strategies set out in the Appendix. A combined literature search was conducted to identify the area of psoriasis therapy, and to this search were added search terms for infliximab, etanercept and efalizumab.

The competitor trials are listed in the Appendix, followed by a basic summary of their primary efficacy results. Detailed results for the trials are not supplied as the indirect comparison was only carried out for PASI score-related patient outcomes and DLQI. The data from etanercept RCTs were separated according to dose, with 25mg and 50mg doses analysed separately in the indirect comparison.

Comparison of PASI outcomes

The pooled trials could be used to compare PASI response relative to placebo/supportive care at 10 to 12 weeks. Additional analyses was undertaken for the available week 24 data.

Using the model, infliximab was shown to significantly increase the likelihood of achieving PASI 50, PASI 75, and PASI 90 compared with placebo plus supportive care at 10 to 12 weeks.

Bayesian 95% confidence intervals for comparisons between infliximab and other therapies in increasing the likelihood of different PASI responses typically did not overlap except slightly for PASI 50 responses to infliximab compared with etanercept 50 mg twice weekly. For instance, by indirect comparison, infliximab increased the likelihood of achieving PASI 75 at 10 to 12 weeks by 77.0% (95% CI=72.1%-81.7%) compared with placebo/supportive care, by 63.3% (95% CI=56.6%-69.6%) compared with efalizumab, by 45.1% (95% CI=36.8%-53.3%) compared with etanercept 25 mg, and by 31.0% (95% CI=23.1%-48.8%) compared with etanercept 50 mg (Table 12).

By indirect comparison, the relative risk of PASI 75 with each biologic therapy compared with placebo/supportive care (RR=1.0) was 7.41 (95% CI=5.96-9.09) for efalizumab, 9.06 (95% CI=7.03-11.53) for etanercept 25 mg, 12.36 (10.22-15.55) for etanercept 50 mg, and 20.49 (95% CI=16.28-25.37) for infliximab (Table 13). A forest plot summarizing data from the main PASI 75 efficacy analysis is shown in Figure 14.

Relative risks for achieving PASI 50 and PASI 90 at treatment week 10 to 12 were also significantly higher for infliximab. As with data from the indirect comparison, infliximab was also significantly more effective than other therapies in achieving PASI 50 and PASI 90 responses at 10 to 12 weeks according to direct comparisons under the random-effects model (Table 13). For instance, the relative risk for achieving PASI 90 compared with placebo/supportive care (RR=1.0) was 95.74 (95% CI=67.74-131.30) for infliximab compared with 16.50 (95% CI=12.08-21.93) for efalizumab, 22.58 (95% CI=15.58-31.87) for etanercept 25 mg, and 38.62 (95% CI=28.21-52.51) for etanercept 50 mg.

There were insufficient data to conduct a robust comparison of infliximab to competitor medicines at week 24, as is evidenced by the wide confidence intervals in Table 14. In addition, efalizumab trial data did not extend this far.

Table 12. Failure to attain PASI goals at 10 to 12 weeks: relative increase in risk with infliximab as reference; indirect comparisons according to a random-effects model

Treatment	Risk reduction		
		95% CI	
	Mean	Lower	Upper
Response = PASI 50			
Placebo/Supportive Care	0.7978	0.7679	0.8249
Etanercept 25 mg BIW	0.3152	0.2442	0.3884
Etanercept 50 mg BIW	0.1883	0.1341	0.2450
Efalizumab 1 mg/kg	0.3852	0.3285	0.4450
Infliximab 5 mg/kg	0 [reference]	0 [reference]	0 [reference]
Response = PASI 75			
Placebo/Supportive Care	0.7701	0.7208	0.8169
Etanercept 25 mg BIW	0.4512	0.3683	0.5333
Etanercept 50 mg BIW	0.3101	0.2306	0.4881
Efalizumab 1 mg/kg	0.5166	0.4508	0.5823
Infliximab 5 mg/kg	0 [reference]	0 [reference]	0 [reference]
Response = PASI 90			
Placebo/Supportive Care	0.5368	0.4674	0.6104
Etanercept 25 mg BIW	0.4139	0.3358	0.4931
Etanercept 50 mg BIW	0.3224	0.2400	0.4036
Efalizumab 1 mg/kg	0.4484	0.3784	0.5223
Infliximab 5 mg/kg	0 [reference]	0 [reference]	0 [reference]

BIW, twice weekly; CI=confidence interval.
Higher numbers signify a greater risk of failing a PASI goal, relative to infliximab.

Table 13. Likelihood of achieving PASI 50, 75, 90 goals at 10 to 12 weeks by indirect comparisons according to a random-effects model

Treatment	Probability of a Response			Relative risk		
		95% CI			95% CI	
	Mean	Lower	Upper	Mean	Lower	Upper
Response = PASI 50						
Placebo/Supportive Care	0.143	0.1219	0.1669	1.0	1.0	1.0
Etanercept 25 mg BIW	0.6258	0.5552	0.6958	4.34	3.74	5.19
Etanercept 50 mg BIW	0.7525	0.6986	0.8048	5.29	4.58	6.12
Efalizumab 1 mg/kg	0.556	0.498	0.6107	3.91	3.36	4.50
Infliximab 5 mg/kg	0.9406	0.9172	0.9604	6.62	5.65	7.69
Response = PASI 75						
Placebo/Supportive Care	0.04001	0.03189	0.05001	1.0	1.0	1.0
Etanercept 25 mg BIW	0.3592	0.2928	0.4317	9.06	7.03	11.53
Etanercept 50 mg BIW	0.5001	0.4348	0.5691	12.362	10.22	15.55
Efalizumab 1 mg/kg	0.2939	0.2452	0.3435	7.41	5.96	9.09
Infliximab 5 mg/kg	0.8102	0.7592	0.8567	20.49	16.28	25.37
Response = PASI 90						
Placebo/Supportive Care	0.005815	0.004139	0.008012	1.0	1.0	1.0
Etanercept 25 mg BIW	0.1289	0.09218	0.1732	22.58	15.58	31.87
Etanercept 50 mg BIW	0.2202	0.1729	0.2754	38.62	28.21	52.51
Efalizumab 1 mg/kg	0.09438	0.07069	0.1213	16.50	12.08	21.93
Infliximab 5 mg/kg	0.5427	0.4721	0.6164	95.74	67.74	131.30

BIW, twice weekly; CI, confidence interval.

Table 14. Likelihood of achieving different levels of reductions in the Psoriasis Area and Severity Index (PASI) at 24 weeks by indirect comparisons according to a random-effects model

Treatment	Probability of a Response at 24 weeks		
		95% CI	
	Mean	Lower	Upper
Response = PASI 50			
Supportive Care	0.1741	0.0355	0.4888
Etanercept 25 mg BIW	0.6744	0.0178	0.9996
Etanercept 50 mg BIW	0.7059	0.0003	1.0
Infliximab 5 mg/kg	0.8838	0.1119	1.0
Response = PASI 75			
Supportive Care	0.0760	0.0094	0.2864
Etanercept 25 mg BIW	0.5102	0.0043	0.9974
Etanercept 50 mg BIW	0.5644	0.0	1.0
Infliximab 5mg/kg	0.7920	0.0400	0.9999
Response = PASI 90			
Supportive Care	0.0198	0.0011	0.0982
Etanercept 25 mg BIW	0.2962	0.0004	0.9811
Etanercept 50 mg BIW	0.3611	0.0	0.9995
Infliximab 5 mg/kg	0.6028	0.0065	0.9990

BIW, twice weekly; CI, confidence interval.

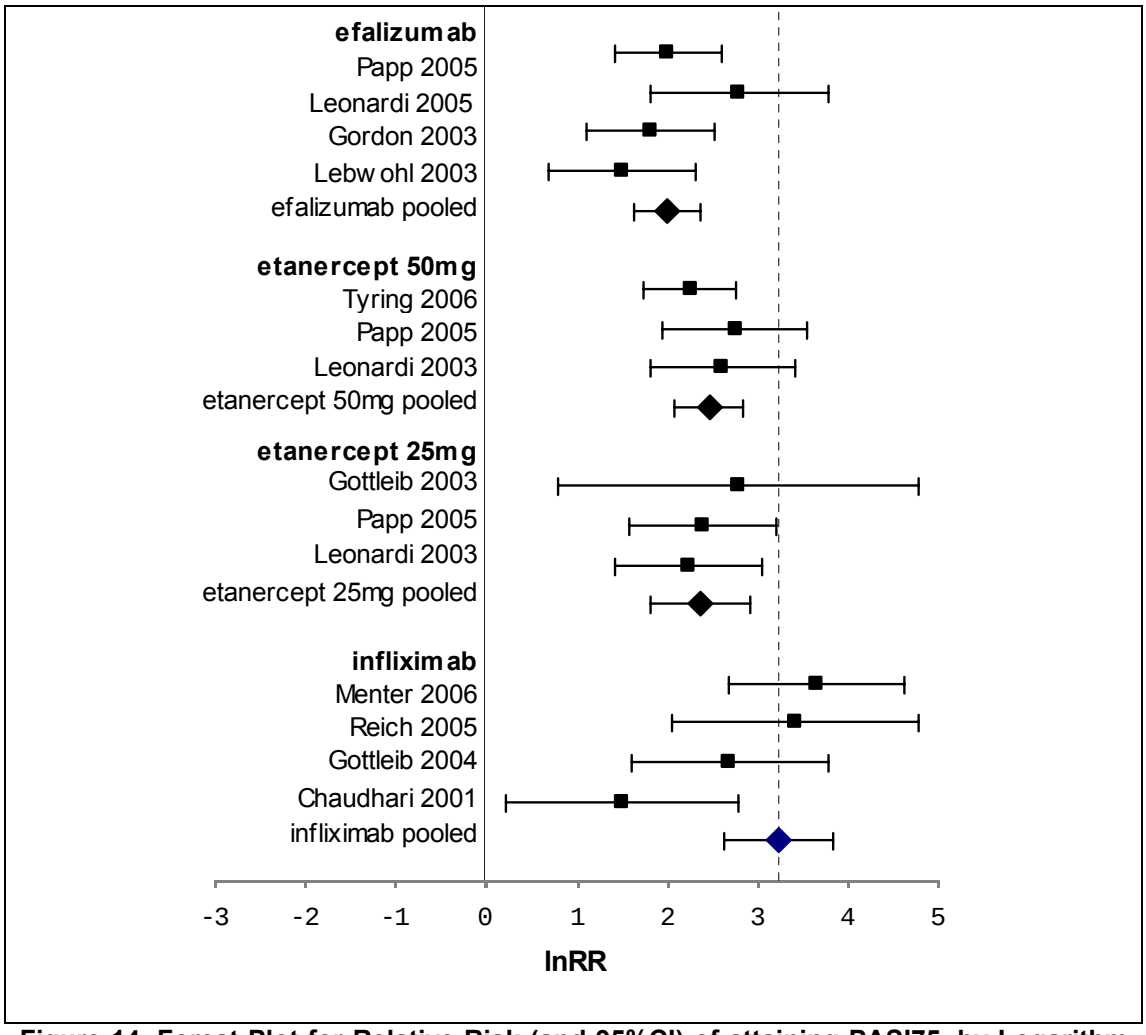


Figure 14. Forest Plot for Relative Risk (and 95%CI) of attaining PASI75, by Logarithm Scale

Indirect Comparison Conclusion

Infliximab was significantly more likely than other biologic treatments to reduce the severity of psoriasis, with the Bayesian 95% CI for infliximab overlapping only slightly with that for etanercept 50 mg twice weekly in terms of relative risk for achieving a 50% reduction in PASI (PASI 50). Although systematic differences between studies cannot be ruled out, these are unlikely to explain the large disparities in treatment responses between infliximab and other therapies.

The relative risks of patients' achieving PASI 75 under such models were 20.49 for infliximab, 12.36 for etanercept 50 mg twice weekly, 9.06 for etanercept 25 mg twice weekly and 7.41 for efalizumab. Between-treatment disparities in the probabilities of achieving more marked clearing (PASI 90) were even wider, ranging from 16.5 for efalizumab to 95.74 for infliximab.
All therapies improved quality of life as measured by the DLQI score, and although infliximab ranked highest among its competitors, the lack of information from the available evidence base about variability made it impossible to carry out a full meta-analysis.

5.7 Safety

Data relating to the safety profile of infliximab in the treatment of moderate-to-severe psoriasis is reported in infliximab's three key studies: SPIRIT and EXPRESS/EXPRESS II. In these studies, data was collected regarding: incidence of adverse events; changes in laboratory parameters; and the presence of anti-ds DNA antibodies and anti-infliximab antibodies. Data on the safety profile of infliximab has also been collected in clinical trials of in other indications including rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD), and psoriatic arthritis.

Clinical studies in patients with psoriasis

In the SPIRIT and EXPRESS/EXPRESS II studies, the incidence of any adverse event was slightly higher in patients receiving infliximab compared to placebo-treated patients (Table 15).

The most commonly reported adverse events (in ≥ 10% of patients in the infliximab group) in the EXPRESS study were upper respiratory tract infection and headache (Table 15). The incidence of both events was similar in the infliximab and placebo group. The incidence of other adverse events was also similar for the two treatment groups, with the exception of psoriasis, which was more prevalent in the placebo group. Results for the pilot study also reported headache and upper respiratory infection to be the most commonly reported adverse events, and headache was the only event that was more frequent in infliximab-treated patients compared with placebo. At the licensed dose, abdominal bloating/pain was the only adverse event reported more frequently compared with placebo.

Infusion reactions were reported in 20.3% of patients receiving infliximab in the SPIRIT study (18.4% of patients receiving the licensed dose) and 3% of those receiving infliximab in the EXPRESS study. This compared with 2% of placebo-treated patients in both studies.

Table 15. Incidence of adverse events in SPIRIT and EXPRESS I/II studies during placebo-controlled induction

	SPIRIT		EXPRESS		EXPRESS II	
	5 mg/kg	**placebo**	**5 mg/kg**	**placebo**	**5 mg/kg**	**placebo**
Patients with any AE, %	79	63	82	71	69	56

AE = adverse event

Table 16. Incidence of commonly reported adverse events (≥ 5% of patients) in EXPRESS study

Adverse event, %	EXPRESS		EXPRESS II	
	5 mg/kg	placebo	5 mg/kg	placebo
Upper respiratory infection	15	16	13	14
Headache	14	12	12	5
Nausea	.	.	4	4
Fatigue	8	4	.	
Pruritus	7	7	3	4
Arthralgia	7	4	.	.
Rhinitis	6	1	3	1
Pain	6	5	5	4
Pharyngitis	6	8	5	3
Herpes simplex	3	5	.	.
Psoriasis	3	13	2	5
Sinusitis	1	5	6	1
Coughing	.	.	2	1
Hypertension	.	.	2	4

Incidence of serious AEs (SAEs)

There were 12 SAE in the SPIRIT study, 4 of which were regarded as possibly being related to infliximab therapy. These were: squamous cell carcinoma, cholecystitis and cholelithiasis, diverticulitis, and sepsis and pyelonephritis. The incidence of SAE related to treatment was only slightly higher in patients receiving infliximab (infliximab, 2%; placebo, 0%). In the EXPRESS study, there were 17 SAE. These included three serious infections and delayed hypersensitivity reactions were developed in three patients. Serious adverse events previously observed during long-term infliximab therapy for other indications such as demyelinating events, tuberculosis, serious opportunistic infections, new onset congestive heart failure or haematological events were not observed in the EXPRESS study. The incidence of SAE was only slightly higher in the infliximab group compared with placebo (infliximab, 6%; placebo, 3%).

In the EXPRESS II study, two cases of tuberculosis were observed from weeks 0 through 50. No other serious opportunistic infections were observed. Between weeks 0 and 50 there were 12 malignancies among patients on infliximab including breast carcinoma, salpingeal adenocarcinoma, squamous cell skin carcinoma, and 9 basal cell carcinomas. All skin carcinomas occurred in patients with antecedent exposure to narrow-band ultraviolet B (8 patients), psoralen plus ultraviolet A (2 patients) or both (2 patients). No malignancies were observed in placebo patients during the placebo-controlled induction. Lupus-like syndrome was reported in two infliximab patients and one placebo patient, who improved when their placebo, hydralazine and/or infliximab regimen was stopped and their symptoms treated. There were no central nervous system demyelinating events, although one infliximab patient developed prolonged extremity muscle weakness which was diagnosed as peripheral neuropathy with possible relation to study agent. There were no patient deaths during the EXPRESS II study. One 41 male expired from fatal MI 9 months after discontinuing infliximab.

Changes in laboratory parameters

No clinically significant changes in laboratory parameters were observed during treatment with infliximab in the four studies with the exception of increases in alanine transaminase and aspartate transaminase.

Incidence of antibodies and infusion reactions

Antinuclear/ds DNA antibodies were detected in 8 patients (1.9%) receiving infliximab therapy at the licensed dose. Symptoms of drug-induced lupus or lupus-like symptoms were observed in 2 of these patients. Anti-infliximab antibodies were detected in approximately 25% of patients receiving infliximab at the licensed dose (SPIRIT study, 20%; EXPRESS study, 27% of patients analysed). It is unclear, however, whether the presence of anti-infliximab antibodies is likely to be clinically significant. There is some evidence to suggest that the presence of anti-infliximab antibodies may increase the risk of infusion reactions. Indeed, in the SPIRIT study, 23% of patients who were anti-infliximab antibody positive experience infusion reactions when retreated at week 26 (i.e. after 20 weeks without treatment) compared with 8% of patients who were antibody negative. However, the

incidence of infusion reactions during induction therapy was comparable for patients who were antibody negative and antibody positive (22% vs. 24%).

The same diagnostic tests for antibodies were carried out in the EXPRESS II study. The overall incidence of infusion reactions was low, with only infliximab 5 patients exhibiting symptoms through the study. There were 9 reports of possible delayed hypersensitivity reaction, of which 4 were considered serious. Antibody-positive patients in EXPRESS II generally did not experience infusion reactions, however their risk was slightly elevated over antibody-negative patients. This finding is inconclusive, however, because of incomplete data collection on antibodies.

Safety profile of infliximab's other indications

Safety data have been collected for infliximab in clinical studies in a range of indications including rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, and psoriatic arthritis (Johnson & Johnson, 2005). Results from these studies have shown a consistent safety profile for infliximab. The most frequently reported adverse events are infections and infusions.

Infections involving the upper respiratory tract are the most commonly reported, although serious infections including sepsis have also been reported. Patients receiving infliximab have an increased risk for tuberculosis, and other infections such as fungal and opportunistic infections and infections involving granuloma formation have been observed.

Some patients experience infusion reactions, commonly characterised by non-specific symptoms such as fever and chills, cardiopulmonary reactions, pruritus and/or urticaria. Most infusion reactions are mild but some can be severe and may be associated with an anaphylactic reaction.

Rare adverse events associated with infliximab include: delayed hypersensitivity reactions, lupus-like syndromes, optic neuritis, seizures, CNS demyelinating diseases, and CNS manifestations of systemic vasculitis. Infliximab has been associated with adverse outcomes in patients with heart failure. Infliximab therapy may also be associated with an increased risk of lymphoma and other malignancies.

Long-Term Safety Profile

The benefit-risk profile of TNF-α blocking agents continues to be positive and the safety findings to date are similar within the class (Desai and Furst, 2006). More than 5706 patients have received infliximab in the setting of company sponsored clinical trials (Centocor dossier, on file). An estimated 843,151 patients have been exposed to infliximab since launch of the drug in 1998 (Centocor, data on file). In comparison 400,000 patients have been exposed to etanercept (Enbrel web-page). Table 17 summarizes the side effect profile of infliximab and its comparators, based on the clinical summaries in Standard Product Characteristics forms.

Table 17. Side Effects Noted in SPCs of Infliximab and Comparators

Side Effect	Remicade	Etanercept	Adalimumab
Infusion / injection reactions	√ /	/ √	/ √
Hypersensitivity or allergy	√	√	√
Infections, TB, Sepsis	√ √ √	√ √	√ √ √
Malignancies/ Lymphoma	Caution	Caution	Caution
Congestive Heart failure	√	√	√
Autoimmune processes/ auto-antibodies	√	√	√
Neurological events	√	√	√
Haematologic disorders		√	√
Hepatobiliary event	√	√	
Renal event		√	

√ = in SPC

The most detailed long-term safety overview in infliximab was compiled for rheumatoid arthritis patients by the Health Technology Assessment NHS R&D HTA Programme (Chen et al 2006) in the form of a meta-analysis of trials for all anti-TNF products. In addition to short-term safety observations in relevant efficacy trials, Chen et al noted the following about long-term safety in anti-TNF treatments.

Malignancy and Lymphoma

Chen et al cite a number of sources which have concluded that the incidence of lymphoma in patients treated with anti-TNF products is significantly elevated relative to the general population. However the incidence of other malignancies in anti-TNF recipients was found to be similar to the background level.

Pulmonary Fibrosis

Chen et al cited data from the British Society of Rheumatologists Biologics Register (BSRBR) which suggested possible elevated mortality in the long term for TNF-treated patients who had pulmonary fibrosis at death, however they noted that pulmonary fibrosis patients were overrepresented in this group relative to the controls.

Non-RCT evidence

It was not necessary to consider non-RCT evidence in respect of infliximab's comparative efficacy.

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.

Relevance of Evidence Base to decision problem

The extent to which clinical trial evidence can be used to address the decision problem as set out in the final scope is related to two principal issues, which concern whether the clinical trial population correspond to the treatment population set out in infliximab's license.

Prior Treatment History

In NICE technology appraisal TA 103 the Appraisal Committee raised a concern that clinical trial populations may not have reflected the licensed populations for etanercept and efalizumab with respect to prior treatment using systemic therapies. This implies that the clinical trials may represent a population which is easier to treat than that which is set out in the license, namely patients who have previously failed on systemic therapies. However the available evidence suggested there was no difference in efficacy between patients who were systemic therapy-naive and patients who had previously failed systemic therapy. The relevant RCTs for infliximab have supported this finding: the primary outcomes in EXPRESS and EXPRESS II trials did not differ significantly according to prior systemic therapy, as was shown in Figure 12 and Figure 13.

Severity of Psoriasis

This submission relates principally to the population of patients with severe plaque psoriasis, reflecting the previously recommended population for biologic therapy as per NICE TA 103. However the license population for infliximab is broader covering moderate-to-severe plaque psoriasis. The clinical trials supporting this submission recruited patients with moderate-to-severe psoriasis and demonstrated efficacy in the entire license population. However baseline patient characteristics indicate that on average the patients studied had severe psoriasis as defined by PASI, BSA and DLQI assessments.

Therefore, in respect of these two issues, the decision problem can be addressed with the evidence in this submission.

Relevance of Outcomes in Clinical Trials to patient experience in practice

The outcomes assessed in clinical trials tend to separately measure physical symptoms and quality of life by way of PASI or PGA scores, and DLQI or SF-36 scores respectively. The PASI 75 goal was the primary endpoint of clinical trials of infliximab and also of its competitor products, and has been included in NICE recommendations (as per TA 103).

While the PASI scale does not fully capture the impact of psoriasis on a patient's health and quality of life, week 24 results of the EXPRESS trial, shown in Table 18, demonstrate that a higher PASI response is associated with a greater improvement on the Dermatology Life Quality Index (DLQI).

Table 18. Week 24 DLQI response from Baseline by Week 24 PASI response, infliximab arm, EXPRESS trial

CiC-Table removed;

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?

The trials studied followed up patients very closely to monitor their symptoms, which may be unrepresentative of clinical practice. However the choice of eligible patients in the studies was fair, especially in respect of prior treatment – which most patients had experienced in abundance. In conclusion, aside from the typical issues arising around clinical trials and their generalisability to clinical practice, these considerations have been addressed in 5.9.1.

Best practice patient selection would need to be guided primarily by infliximab's label.

The evidence base contains trials which all have at least one arm that administered the licensed infliximab dose of 5mg/kg, in the manner set out in SPC. As such, the trial findings are highly applicable to standard clinical practice, and can be used to support the implementation of any guidance which deals with infliximab and its cost-effectiveness.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

No full cost effectiveness studies of infliximab in psoriasis have yet been published. This literature review is intended as a supplement to the NICE HTA assessment report by the CHE/CRD Technology Assessment Group on 'Efalizumab and Etanercept for the treatment of psoriasis', which supplies a comprehensive literature review up until 2004. The time horizon for this literature search was limited from January 2004 to April 2007. Full details of the search strategies are provided in appendix 9.3.

The search strategy was developed to identify economic evaluations, data on costs and cost-effectiveness of biologics for the treatment of psoriasis from the following sources:

- Medline (OVID)
- EMBASE (OVID)
- BIOSIS (OVID)
- Derwent Drug file (OVID)
- Current content/clinical medicine (OVID)
- Pubmed
- Health Economic Evaluation Database
- NHS Economic Evaluation Database (NHS HEED)

Inclusion and exclusion criteria

The inclusion and exclusion criteria applied for the economic searches are shown in table 6.1.

Table 6.1: Inclusion criteria for cost-effectiveness review

Study Design	Cost-consequence analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis; cots-studies (UK only);
Population	People with moderate to severe psoriasis, severe plaque psoriasis;
Intervention	infliximab, etanercept , efalizumab
Comparator	systemic therapy (PUVA, ciclosporin, fumaderm), standard care, other biologics,
Outcome	Quality of life estimates, cost-estimates, cost-effectiveness;
Time Horizon	January 2004 to April 2007;

The characteristics and the main results of the included economic evaluations are included in the tables below.

6.1.2 Description of identified studies

One published study met the inclusion criteria. The key features are summarised in the table below.

Table 6.1.2.1: Summary of published economic analyses

Study	Biologics	Economic analysis	Model used	Time horizon
Woolacott et al (2006)	efalizumab and etanercept	Cost-effectiveness	Markov model	10 years

Table 6.1.2.2: Summary of published ICERs for biologics

Drug	Comparator	Study	Date	Time horizon	ICER
etanercept	supportive care	Woolacott	2006	10 years	all patients-no hospitalisations for non-responders • etanercept 25mg continuous £83,258 • etanercept 25mg intermittent £66,703 • etanercept 50mg £120,855 all patients-21 days hospitalisation for non-responders • etanercept 25mg continuous £45,975 • etanercept 25mg intermittent £29,420 • etanercept 50mg £83,378 4th Quartile DLQI at baseline-no hospitalisations for non-responders • etanercept 25mg continuous £43,473 • etanercept 25mg intermittent £34,834 • etanercept 50mg £63,103 4th Quartile DLQI at baseline-21 days hospitalisation for non-responders • etanercept 25mg continuous £23,905 • etanercept 25mg intermittent £15,297 • etanercept 50mg £43,395
efalizumab	supportive care	Woolacott	2006	10 years	all patients-no hospitalisations for non-responders • efalizumab 1mg/kg £84,018 all patients-21 days hospitalisation for non-responders • efalizumab 1mg/kg £46,866 4th Quartile DLQI at baseline-no hospitalisations for non-responders • efalizumab 1mg/kg £43,821 4th Quartile DLQI at baseline-21 days hospitalisation for non-responders • efalizumab 1mg/kg £24,346

The primary analysis in this economic evaluation considered etanercept and efalizumab compared to supportive care. The cost-effectiveness analysis presented results between £15,297 and £120,855 for the different scenarios and treatment dosing regimens of etanercept and between £24,346 and £84,018 for efalizumab in the different scenarios. The biologics were most cost-effective when patients with the worst quality of life at baseline were considered and non-responders were hospitalised.

For the primary analysis comparing etanercept, efalizumab and supportive care, the results suggest that the biologic therapies would only be cost-effective in a treatment sequence for all patients with moderate to severe psoriasis if the NHS is willing to pay over £60,000 per QALY gained.

Efalizumab is only a cost-effective option for patients with poor baseline DLQI (4th quartile) in a treatment sequence as long as the NHS is willing to pay up to £45,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment (21 in-patient days annually), efalizumab can be a cost-effective option as long as the NHS will pay up to £25,000 per QALY gained.

Continuous use of etanercept 25mg is only a cost-effective option in a treatment sequence for patients with poor baseline DLQI (4th quartile) as long as the NHS is willing to pay up to £45,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment, this therapy can be a cost-effective option as long as the NHS will pay up to £25,000 per QALY gained.

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

The analysis was carried out from the perspective of the NHS and therefore no indirect costs were taken into consideration. Each cycle of the model has an annual duration with those patients not responding switching to supportive care, responders continuing on therapy and a proportion of patients dropping out throughout the year. The time horizon of the model was 10 years.

6.2 De novo economic evaluation(s)

Attribute	Reference case	Section in 'Guide to the methods of technology appraisal'
Comparator(s)	The comparator that has been specified in the decision problem	6.2.3
Perspective costs	NHS and Personal Social Services	6.2.6
Perspective benefits	All health effects on individuals	6.2.8
Form of economic evaluation	Cost-effectiveness analysis	6.2
Time horizon	Sufficient to capture differences in costs and outcomes	6.2.5
Synthesis of evidence	Systematic review	5.6
Outcome measure	Quality-adjusted life years (QALYs)	6.2.8.2
Health states for QALY measurement	Described using a standardised and validated instrument	6.2.8.2
Benefit valuation	Time trade-off or standard gamble	N/A
Source of preference data	Sample of public	N/A
Discount rate	Health benefits and costs – both 3.5%	6.2.10
Equity	No additional weighting to QALYs	6.2.8.2
Sensitivity analysis	Probabilistic sensitivity analysis	6.3.3

6.2.1 Technology

Within the economic model infliximab is assumed to be used for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen/ultraviolet A treatment (PUVA).

Patients will receive the licensed dose, which is 5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion. If a patient shows no response after 10 weeks (i.e. after 3 doses), no additional treatment with infliximab should be given. For those patient who respond to treatment (i.e. achieve a PASI 75 or a PASI 50 and a five point reduction in DLQI) then infliximab is administered every 8 weeks thereafter. In the model, treatment with infliximab is assumed to continue for a maximum of ten years. This is mainly as a result of the 20% drop-out rate per annum assumed for biologics. At the end of ten years, the number of original patients remaining will be minimal.

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?

Patients with moderate to severe symptoms of psoriasis are defined in clinical studies as those with a psoriasis area and severity index (PASI) score of at least 12, having at least 10% of their total body surface area affected by psoriasis and a mean DLQI score of 12.5. The results of the economic evaluation focusing on patients with moderate to severe psoriasis are presented in Appendix D. The main focus of the economic evaluation will be around those patients with the worst baseline quality of life defined as fourth quartile DLQI; this analysis will constitute the base case.

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?

Yes. As noted in section 6.2.2.1, the main analysis was based around severity of disease and focused on those patients with the worst quality of life at baseline.

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

All obvious subgroups were considered and are described in section 6.2.2.2 above.

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 model and are allocated a treatment option for the duration of the 'trial' and treatment periods. The 'trial' period was estimated based on the period over which response was assessed in the efficacy trials for infliximab and published data for other comparators. A patient is considered to be a responder if they achieve a PASI 75 response. PASI 75 was the primary efficacy measure in infliximab clinical trials and is accepted as the desired patient outcome, corresponding to clear/almost clearing of symptoms. The mean 'treatment' duration for responding patients was estimated based on an assumed annual drop-out rate for responding patients receiving treatment. The mean treatment response period was then estimated from a 10-year Markov model with an annual cycle.

The estimated 'trial' and 'treatment' periods are shown in the table 6.2.6.2 in section 6.2.6 below. There is limited experimental or observational evidence to inform these parameters and consequently they are subject to uncertainty. To address this, these parameters are entered into the model as fixed values and sensitivity analysis of the annual withdrawal conducted. At the end of 10 years, assuming an annual drop out rate of 20%, less than 11% of patients will remain on treatment.

6.2.3 Comparator technology

When choosing the relevant comparators, it is important to understand the current method of treatment of moderate to severe psoriasis patients in the UK. This economic evaluation focuses on the comparison of the following treatment strategies in patients with severe psoriasis:

- Treatment by infusion with infliximab 5mg/kg at weeks 0, 2, and 6, then every 8 weeks
- Etanecept 25mg administered twice weekly as continuous treatment, as this reflects current use of etanercept in standard UK clinical practice, particularly in the most severe patients, according to UK clinical experts and audit data from psoriasis clinics in the UK;
- Etanercept 25-50 mg administered twice weekly until remission; a mean time to retreatment of 29 days equivalent to 3.2 cycles per year is used (TA103 Guidance 2006);
- Efalizumab initial single dose of 0.7 mg/kg, weekly injections of 1.0 mg/kg body (TA103 Guidance 2006)
- Supportive care includes inpatients stay and clinic visits for symptom management.

The economic evaluation has therefore not been restricted to a comparison with one treatment strategy. The base case results from the economic evaluation focus on a comparison with continuous etanercept 25mg administered twice weekly, as this reflects current practice in the relevant population. A number of different comparisons between infliximab and the alternative biologics are presented in Appendix D.

The scope for this appraisal included consideration of treatment sequences where the evidence allows. Currently there is a lack of clinical evidence to sufficiently inform an analysis of the sequential use of TNF-α inhibitors in psoriasis. This submission therefore excludes treatment sequences including more than one TNF-α inhibitor.

6.2.4 Study perspective

The perspective of the economic evaluation is to from that of the NHS in England and Wales. It captures direct costs and benefits to the NHS only.

6.2.5 Time horizon

To ensure that all future costs and outcomes were included in the analysis the evaluation was conducted over a 10 year time horizon. The mean ‘treatment’ duration for responding patients was estimated based on an assumed annual drop-out rate for responding patients receiving treatment and a maximum assumed treatment period based on published guidelines if appropriate. The cost-effectiveness analysis was conducted by comparing estimates of expected costs and health effects for each treatment, incorporating both patients who 'respond' and continue treatment with infliximab after a 'trial' period and those who do not 'respond' and are withdrawn from infliximab treatment.

6.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

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.
- A list of all variables that includes their value, range (distribution) and source.
- A separate list of all assumptions and a justification for each assumption.

Description of the model type

The cost-effectiveness analysis was conducted by comparing estimates of expected costs and health effects per unit time for each treatment, incorporating both patients who ‘respond’ and continue treatment after a ‘trial’ period and those who do not ‘respond’ and stop treatment.

To compute the expected costs and effects per unit time of interventions requires estimates of the proportion of patients responding and the costs, effects and total duration of treatment for responding and non-responding patients.

The model presented in this evidence submission is based on the York model, which was specified in the HTA report for etanercept and efalizumab. In adapting the model analysis of treatment sequences including multiple TNF-α inhibitors and non biologic therapies have been excluded, as they are not relevant to the context of this submission. However we have included the option of efalizumab as a second line treatment to reflect NICE guidance on its use (see Appendix). This differs from the York model where sequences are determined by individual net-benefit per unit time whereas the use of efalizumab 2nd line is explicitly defined in our model. Patients who do not respond to their first line treatment will then receive efalizumab. Costs and QALYs for 2nd line efalizumab are calculated following the same methods as first line use with a trial period followed by a treatment period. The proportion of patients who do not respond following efalizumab 2nd line are assumed to receive supportive care.

Furthermore it is possible to explore the effect of different stopping rules on cost-effectiveness estimates. That is whether a patient stops treatment when they achieve either PASI 75 or PASI 90 following the trial period.

To compute the expected costs and effects of interventions requires estimates of the proportion of patients responding and the costs, effects and total duration of treatment for responding and non-responding patients. It is assumed that non-responders to infliximab treatment will have the same utility as patients receiving supportive care. The model can be specified based on the following equations.

$$U^{sc} = u_{00} \times (1-p^{pasi50,sc}) + u_{50} \times (p^{pasi50,sc} - p^{pasi75,sc}) + u_{75} \times (p^{pasi75,sc} - p^{pasi90,sc}) + u_{90} \times (p^{pasi90,sc})$$

$$u^{trial,t} = u_{00} \times (1-p^{pasi50,t}) + u_{50} \times (p^{pasi50,t} - p^{pasi75,t}) + u_{75} \times (p^{pasi75,t} - p^{pasi90,t}) + u_{90} \times (p^{pasi90,t})$$

$$u^{responders,t} = u_{75} \times (p^{pasi75,t} - p^{pasi90,t}) + u_{90} \times (p^{pasi90,t})$$

$$Qalys_t = \frac{d^{trial} \times (u^{trial,t} - u^{trial,p}) + d^{treatment,effect} \times (u^{responders,t} - u^{sc} \times p^{pasi75,t})}{d^{trial} + d^{treatment,effect}}$$

$$c^{sc} = (c^{hospital} + c^{clinic}) \times (1 - p^{pasi75,p}) + p^{pasi75,p} \times c^{responder,p}$$

$$Cost_t = \frac{c^{trial} + p^{pasi75,t} \times d^{treatment,cost} \times c^{treatment} + (1 - p^{pasi75,t}) \times c^{hospital} \times (d^{trial} + d^{treatment,cost}) - (d^{trial} + d^{treatment,cost}) \times c^{sc}}{d^{trial} + d^{treatment,cost}}$$

Where the model outputs are:
$Cost_t$ = mean incremental cost per year for t^{th} treatment compared to supportive care.
$Qalys_t$ = mean incremental qalys per year for t^{th} treatment compared to supportive care.

The various parameters going into these equations are defined in Table 6.2.6.1.

Table 6.2.6.1 Definition of parameters used in the model, summary of sources and indication of how uncertainty assessed.

Parameter	Description	Source	Uncertainty
$c^{hospital}$	Yearly cost of hospitalisation for non-responding patient	Assumption based on survey data	Scenario analysis
c^{trial}	Cost of treatment with the infliximab for the 'trial' period	Various	Gamma or Beta distribution
$c^{treatment}$	Yearly cost of treatment with infliximab	Various	Gamma or Beta distribution
d^{trial}	Duration (in years) of the 'trial' period for infliximab	Assumption based on clinical trial designs	Scenario analysis
$d^{treatment,cost}$	Mean duration (in years) of the 'treatment' period for the calculation of costs	Assumption based on limited observational and trial data	Scenario analysis of patient attrition rate and cost discount rate
$d^{treatment,effect}$	Mean duration (in years) of the 'treatment' period for the calculation of effects	Assumption based on limited observational data	Scenario analysis of patient attrition rate and effect discount rate
u_{00}	Utility for a patient not achieving a PASI 50 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution
u_{50}	Utility for a patient achieving a PASI 50 response but not a PASI 75 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution
u_{75}	Utility for a patient achieving a PASI 75 response but not a PASI 90 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution
u_{90}	Utility for a patient achieving a PASI 90 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution
p^{pasi50}	Probability of a PASI 50 response	Bayesian hierarchical model of clinical trial data (see Section 6.2.1)	Simulated posterior distribution from MCMC analysis of trial data
p^{pasi75}	Probability of a PASI 75 response	Bayesian hierarchical model of clinical trial data (see Section 6.2.1)	Simulated posterior distribution from MCMC analysis
p^{pasi90}	Probability of a PASI 90 response	Bayesian hierarchical model of clinical trial data (see Section 6.2.1)	Simulated posterior distribution from MCMC analysis

MCMC: Markov Chain Monte Carlo

Schematic of the model

Decision rule

The health effects of the alternative treatments are expressed as quality-adjusted life years (QALYs). This is a generic measure of health effect and allows the decision to allocate resources to the treatments for psoriasis to be based on the opportunity cost of the treatments they displace, which could be based in other specialties. Cost-effective Acceptability Curves (CEACs) are calculated using expected net benefit (NBtx) per unit time, where:

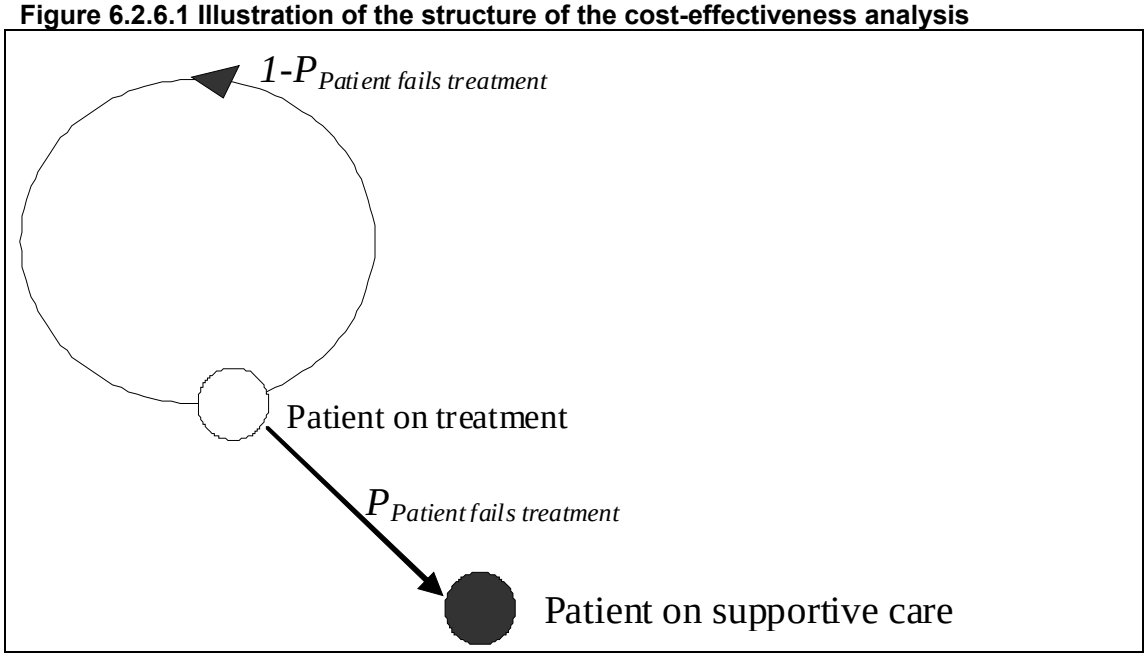
$$E[NBtx] = E[Qalystx] \times \lambda - E[Costtx]$$

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

'Trial' period and 'treatment' duration for responders

The 'trial' period was estimated based on the period over which response was assessed in the efficacy trials for each treatment option and 'expert' opinion. The mean 'treatment' duration for responding patients was estimated based on an assumed annual drop-out rate for responding patients receiving treatment and a maximum assumed treatment period based on published guidelines if appropriate. The mean treatment response period was then estimated from a 10-year Markov model with an annual cycle (figure 6.2.6.1).

Figure 6.2.6.1 Illustration of the structure of the cost-effectiveness analysis



The estimated 'trial' and 'treatment' periods are shown in Table 6.2.6.2. There is very little experimental or observational evidence to inform these parameters and they are consequently subject to a great deal of uncertainty. These parameters were entered into the model as fixed values and sensitivity analysis of the annual withdrawal conducted. Cost and effect discount rates were incorporated into the model by estimating separate 'treatment' durations for the estimation of cost and effects. Annual discount rates of 3.5% on costs and 3.5% on outcomes were applied.

Table 6.2.6.2: Estimated duration of 'trial' and 'treatment' periods.

Treatment	'Trial' period (Weeks)	Maximum 'treatment' period (Years)	Annual drop-out rate	Mean 'treatment' period for responders (Weeks)
Etanercept 25mg	12	10	0.2	186
Etanercept 50mg	12	10	0.2	186
Efalizumab	12	10	0.2	186
Infliximab	10	10	0.2	186

Table 6.2.6.3: Assumptions and justification for assumptions in model

Parameter	Description	Source	Uncertainty
$c^{hospital}$	Yearly cost of hospitalisation for non-responding patient	Assumption based on survey data	Scenario analysis
d^{trial}	Duration (in years) of the 'trial' period for infliximab	Assumption based on clinical trial designs	Scenario analysis
$d^{treatment,cost}$	Mean duration (in years) of the 'treatment' period for the calculation of costs	Assumption based on limited observational and trial data	Scenario analysis of patient attrition rate and cost discount rate
$d^{treatment,effect}$	Mean duration (in years) of the 'treatment' period for the calculation of effects	Assumption based on limited observational data	Scenario analysis of patient attrition rate and effect discount rate

Input parameter estimates

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

- Response rates
- Duration of the 'trial' and 'treatment' periods
- Costs
- The utility improvement associated with the various PASI response categories.

Response rates

The predicted response rates used in the model are taken directly from the evidence synthesis (section 5.5 and 5.6). If the trial only reported 'clear' or 'almost clear' as the endpoint, this was taken to be equivalent to a PASI 75 response. The increased decision uncertainty arising from

uncertainty in the predicted response rates was estimated by directly exporting the simulated posterior distribution from the Markov Chain Monte Carlo analysis in WinBUGS to the cost-effectiveness model.

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

Resource use

Estimates of resource use (quantities) were taken from the NICE HTA assessment report of etanercept and efalizumab in psoriasis. Direct costs incurred by the NHS in the UK were assessed. The analysis included the cost of drugs and of their administration and monitoring, the cost of outpatient visits and of inpatient stays.

The cost of tests undertaken solely to screen patients for eligibility for treatment was excluded from the analysis, no additional tests over an above what would occur in routine clinical practice would be conducted except possibly administration of the DLQI. The costs of adverse events have also been excluded due to lack of data on their treatment.

The main additional cost associated with 'supportive care' in the model resulted from the increased rate of hospitalisation due to the lower rate of PASI 75 response associated with supportive care. Length of stay for an inpatient admission was assumed to be 21 days. This is further supported by the Department of Health, Hospital Episode Statistics (2004/05) for psoriasis, which give a mean of 18.1 days. Dermatologists questioned across the UK supported that at least 21 days annually would be necessary to treat patients with severe psoriasis only being treated with supportive care. Hospitlisation ranged from 19 to 24 days in centres across the UK, depending on the severity of disease (Data on file). In addition physicians in the UK stated that non-responders would be expected to attend the clinic for management of their symptoms, including changing of dressings. This was estimated to be at least an average of 3 clinic visits per week for 6 weeks on an annual basis. Resource use is detailed in tables 6.2.6.4 and 6.2.6.5.

Table 6.2.6.4. Resource Use: Laboratory tests (source: NICE assessment report)

	Efalizumab	Etanercept Continuous	Etanercept Intermittent	Infliximab
FBC	4-8	2-4	2-4	4
LFT				4
Total Protein	4-8	2-4	2-4	
U&E	4-8	2-4	2-4	4

FBC: Full blood count with differential, LFT: liver function test, U&E: urea and electrolytes

Table 6.2.6.5. Resource use: number of outpatient visits (source: NICE assessment report and data on file)

	Number of visits (Trial Period)	Number of visits Annually (maintenance)
Infliximab	4-5	5-6
Efalizumab	3	4
Etanercept	3	4
Supportive care		18

The analysis adjusted the number of outpatient visits for infliximab by the number of infusion visits

Unit costs

Prices (unit costs) of drugs were taken, where available, from the BNF No. 53. Outpatient visits were based on NHS Reference Cost category 'Follow up attendance - Dermatology'. The cost of an inpatient day was based upon two NHS Reference Cost categories. An average of the categories 'Elective inpatient HRG data, major dermatological conditions J39 (>69 or w cc) (>69 or w cc: aged over 69 or with comorbidities or complications)' and 'Elective inpatient HRG data, major

dermatological conditions J40 (<70 or w/o cc)' was estimated, weighted by number of Finished Consultant Episodes. Prices relate to the year 2005/06.

The unit costs used in the model are given in Tables 6.2.6.6 to 6.2.6.7. Tables 6.2.6.9 and 6.2.6.10 show the total trial period and total annual per-patient costs for each drug respectively.

Table 6.2.6.6. Unit costs: drug costs, 2006

	Price per mg	Price per vial	Source
Efalizumab, 1mg/kg	£1.35	£169.20	BNF 53
Etanercept, 25 mg	£3.58	£89.38	BNF 53
Etanercept, 50 mg	£3.58	£178.75	BNF 53
Infliximab	£4.20	£419.62	BNF 53

Table 6.2.6.7. Unit costs: laboratory costs, 2004/05

	Cost per test	Source
Haematology	£2.80	NHS Reference Costs 2005-06
Biochemistry	£1.83	NHS Reference Costs 2005-06

Table 6.2.6.8. Unit costs: hospital visit costs

	Category	Cost	Source
Cost / inpatient day	Elective inpatient HRG data, major dermatological conditions. Weighted average of J39 (>69 or w cc) and J40 (<70 or w/o cc)	£294.86	NHS Reference Costs 2005-06
Cost / outpatient visit	Follow up attendance – Dermatology (specialty code 330)	£65.02	NHS Reference Costs 2005-06

Table 6.2.6.9: Total per-patient costs: Trial Period

	Drug cost	Administration cost	Monitoring cost	Outpatient visits	Total Cost
Supportive care	£0.00	£0.00	£0.00	£0.00	£0.00
Infliximab 5mg/kg	£5035.44**	£195.06	£22.72	£97.53*	£5,350.75
Efalizumab, 1mg/kg	£2,030.40	£0.00	£34.08	£195.06	£2,259.54
Etanercept, 25 mg, intermittent	£2,145.12	£0.00	£17.04	£195.06	£2,357.22
Etanercept, 25 mg, continuous	£2,145.12	£0.00	£17.04	£195.06	£2,357.22
Etanercept, 50 mg	£4,290.00	£0.00	£17.04	£195.06	£4,502.10

*The analysis adjusted the number of outpatient visits for infliximab by the number of infusion visits

**Infliximab is dosed according to weight. The estimate in this table is based on an average patients weight of 75kg.

Table 6.2.6.10. Total per-patient annual treatment period costs

	Drug cost	Administration cost	Monitoring cost	Inpatient cost	Outpatient cost	Total Cost
Supportive care	£0.00	£0.00	£0.00	£0.00	£130.04	£130.04
Non responders	£0.00	£0.00	£0.00	£7,364.52	£1,170.36	£8,534.88
Infliximab 5mg/kg	£10,910.12	£422.63	£22.72	£0.00	£0.00	£11,355.47
Efalizumab, 1mg/kg	£8,798.40	£0.00	£34.08	£0.00	£260.08	£9,092.56
Etanercept, 25 mg, intermittent	£6,864.38	£0.00	£17.04	£0.00	£260.08	£7,141.50
Etanercept, 25 mg, continuous	£9,295.52	£0.00	£17.04	£0.00	£260.08	£9,572.64
Etanercept, 50 mg	£13,728.77	£0.00	£17.04	£0.00	£260.08	£14,005.89

The analysis adjusted the number of outpatient visits for infliximab by the number of infusion visits

6.2.6.2 Why was this particular type of model used?

For this analysis we have adapted a model that has previously been validated and used to support a technology appraisal. The model used to conduct the economic evaluation has been adapted from the model developed by the Centre for Health Economics (CHE), University of York for the recent NICE HTA appraisal of etanercept and efalizumab in psoriasis. The same Bayesian hierarchical model of clinical trial data described in the appraisal document to synthesise response rates updated with recently published studies was used. Resources and costs appropriate to perform the analyses from the perspective of the NHS in England and Wales have been used. As previously mentioned, psoriasis has a significant impact on the health related quality of life and significant improvements in quality of life have been demonstrated with infliximab. A cost-utility analysis is therefore appropriate and has been conducted in this evaluation. The methodology and Monte-Carlo analysis is a valid approach for a chronic condition such as psoriasis.

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.

The structure of the model was influenced and is consistent with the model used by the York assessment group in the multiple technology appraisal for etanercept and efalizumab for the treatment of psoriasis. Change in PASI score and DLQI were used to evaluate disease progression. This is also in line with the values used by the York assessment report and is consistent with NICE's reference case.

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

The model inputs are a combination of the best available published data and expert opinion where it was necessary. The list of model inputs, both resource use and unit costs are listed in section 6.2.6.1.

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?

The model structure reflects the essential features of the condition that are relevant. It captures changes in disease status by modelling improvements in PASI and DLQI scores. The impact of responders and non-responders of the different treatments is included in the model structure. The time horizon of the model is also appropriate, reflecting the chronic nature of psoriasis.

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 cycle length (mean 'treatment' duration) for responding patients was estimated based on an assumed annual drop-out rate of 20% for responding patients receiving treatment and a maximum assumed treatment period based on published guidelines if appropriate (Sterry et al 2004 and Griffiths et al 2004). The mean treatment response period was then estimated from a 10-year Markov model with an annual cycle.

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

Half cycle correction was not used as the model does not have a cyclical Markov structure. Rather mean treatment response period is estimated from a Markov model and this estimated value is used in calculating costs and QALYs.

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?*

As per the York model in the Assessment report for etanercept and efalizumab for the treatment of psoriasis, costs and clinical outcomes are extrapolated beyond the trial follow-up periods. It is assumed that patients treated maintain their response to the respective treatments beyond the treatment periods. A linear extrapolation is assumed beyond the trial follow-up periods.

b) Non-model-based economic evaluations

6.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

Not Applicable-model based economic evaluation submitted.

6.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

Not Applicable-model based economic evaluation submitted.

6.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not Applicable-model based economic evaluation submitted.

6.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not Applicable-model based economic evaluation submitted.

6.2.6.13 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 any longer-term differences in effectiveness between the technology and its comparator?

Not Applicable-model based economic evaluation submitted.

6.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

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

Not Applicable

6.2.7.2 How were the relative risks of disease progression estimated?

Not Applicable

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?

The utility values used in the model were taken directly from the NICE HTA assessment report of etanercept and efalizumab in psoriasis. These were estimated from clinical trial data and the HODaR database. Data within the HODaR database included patients who had completed the DLQI and EQ-5D. This was used to map the change in DLQI associated with PASI response for clinical trial data to changes in utility. The mean gain in utility was estimated for each PASI response category for all patients and those with worst baseline quality of life (4th quartile DLQI).

6.2.7.4 Were the health effects or 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?

Adverse effects associated with the technology were not included in the economic evaluation. Disutility was gained by patients when they were put on standard care after being treated with one of the biologics.

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?

No. All the clinical parameters were derived from the clinical trials.

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

Table 6.2.7.6: Assumptions and justification for assumptions in model

Parameter	Description	Source	Uncertainty
$c^{hospital}$	Yearly cost of hospitalisation for non-responding patient	Assumption based on survey data	Scenario analysis
d^{trial}	Duration (in years) of the 'trial' period for infliximab	Assumption based on clinical trial designs	Scenario analysis
$d^{treatment,cost}$	Mean duration (in years) of the 'treatment' period for the calculation of costs	Assumption based on limited observational and trial data	Scenario analysis of patient attrition rate and cost discount rate
$d^{treatment,effect}$	Mean duration (in years) of the 'treatment' period for the calculation of effects	Assumption based on limited observational data	Scenario analysis of patient attrition rate and effect discount rate

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.

Patients' disease severity was measured by percentage change in PASI response at the relevant weeks, depending on the respective clinical trials for each drug. Total DLQI scores at baseline were also used, as psoriasis symptoms have a clinically significant impact on HRQoL. No adverse effects associated with drug treatments were included within the economic model.

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 utility values used in the model were taken directly from the NICE HTA assessment report of etanercept and efalizumab in psoriasis. These were estimated from clinical trial data and the HODaR database. Data within the HODaR database included patients who had completed the DLQI and EQ-5D. This was used to map the change in DLQI associated with PASI response for clinical trial data to changes in utility. The mean gain in utility was estimated for each PASI response category for all patients and those with worst baseline quality of life (4th quartile DLQI). The utility values for those with worst baseline quality of life were used in this evaluation and are shown in Table 6.2.8.2.

Table 6.2.8.2: Estimated gains in utility

	Gains in utility (mean (se))
PASI Response Category	**4th Quartile DLQI**
<50	0.12 (0.03)
>=50 and <75	0.29 (0.06)
>=75 and <90	0.38 (0.08)
>=90	0.41 (0.09)

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 measured and valued in a manner that is consistent with NICE's reference case.

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

The health effects associated with the treatment of adverse events were excluded from the economic analysis, as the incremental effects were not considered significant.

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?

Health effects were measured using QALYs.

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.)

Please refer to section 6.2.6 where there is a comprehensive description of the resources included in the evaluation.

6.2.9.2 How were the resources measured?

Resources were measured through a combination of published data sources and expert opinion where necessary. Detailed descriptions can be found in the previous sections.

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

Resources were not sourced from the respective clinical trials.

6.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)?

Yes, drug, administration and monitoring costs were included for all years of the economic model.

Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

No assumptions were made regarding subsequent treatments. If patients were not responding to one of the biologics or ceased treatment, they were assumed to receive standard care. An additional economic analysis is presented in Appendix D showing ICERs with the assumption that patients no longer responding to infliximab or etanercept would receive efalizumab, as per NICE Guidance TA #103.

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

NHS reference cost categories, Departement of Health hospital episode statistics, audit data from psoriasis clinics, drug costs from the British National Formulary (BNF). All the references are provided along with the respective tables of both the resources and unit costs;

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?

The unit costs are included in the table below. They do not differ from the costs reported in section 6.2.6.

Table 6.2.9.6. Unit costs: drug costs, 2006

	Price per mg	Price per vial	Source
Efalizumab, 1mg/kg	£1.35	£169.20	BNF 53
Etanercept, 25 mg	£3.58	£89.38	BNF 53
Etanercept, 50 mg	£3.58	£178.75	BNF 53
Infliximab	£4.20	£419.62	BNF 53

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?

Resources valuation was taken from the available published literature as well as from the Department of Health resources, as is recommended by the NICE Guide to Methods of Technology Appraisal (2004).

6.2.9.8 Were resource values indexed to the current price year?

The majority of resource values were taken from sources in the years 2004 to 2006.

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

The main comparator in the model is considered to be continuous use of etanercept 25mg administered twice weekly. This is assumed to be standard clinical practice across the UK. This assumption is based on data collected from a number of sources. Audit data from two of the leading dermatology clinics in the UK, where biologics are frequently used to treat severe psoriaisis patients, reveals that the majority of patients being receiving etanercept are treated continuously. Clinicians do not stop treatment with etanerept if patients are responding, as clinical practice demonstrates that they will relapse quickly after treatment stops. A number of patients are also treated with etanercept 50mg twice weekly, as a larger proportion of patients treated at this higher dose achieve a PASI 75 response (data on file).

An advisory panel ser convened in February 2007 with clinicians from across the UK attending. Clinicians were asked to define standard clinical practice with etanercept for severe psoriasis patients. The experts confirmed that standard practice is continuous use of etanercept 25mg twice weekly. In addition clinicians verified the assumption that patients are not taken off treatment once they have achieved a PASI 75 response. Taking them off treatment would lead to significant worsening of their symptoms and increase the risk of relapse (data on file).

Assumptions around inpatient hospitalisations and outpatient visits were also verified by clinical experts across the UK. 21 inpatient days per annum were assumed to be necessary to treat patients not responding to biologic therapies that would then receive supportive care only. Audit data revealed that inpatient days for these patients would range from 22 days to 24 for the most severe patients. Additionally, at least another 18 outpatient visits per annum were deemed necessary for the management of the symptoms of severe psoriasis for patients that have no other alternative treatment. It was noted that outside these visits the quality of life of these patients is very low (data on file).

6.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?
Costs and health benefits were both discounted at the 3.5% rate specified by NICE as the reference case.

6.2.11 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates.
For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

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

Utilities were varied within the range of +/- the standard error (se). The utility values used in this analysis have been mapped using the clinical trial DLQI and HODaR data. We are aware that higher utility valuations were additionally reported in the NICE HTA assessment report of etanercept and efalizumab in psoriasis, so there is some degree of uncertainty in these values.

The response rates were varied using the 2.5 and 97.5 centiles of the results from the Bayesian hierarchical model. Results are shown assuming best case response for supportive care and worst case for infliximab and comparator treatments, and also worst case response for supportive care with best case for infliximab and comparator treatments.

Because only limited data are available, a sensitivity analysis was carried out on annual drop out rate. For infliximab the baseline model gives has drop out of 18% in the first 10 weeks due to non-response and then an assumed rate of 20% per year thereafter, resulting in approximately 34% discontinuing treatment in the first 15 months. From Reich et al (2005) it can be seen that 22% of patients had discontinued treatment with infliximab by week 50. This is a little less than the baseline model. However, in the same study, of those patients who had a PASI75 response at week 10, 68% were still responders at week 50. It is reasonable to assume that some or all of those who become non-responders will stop treatment and therefore the annual drop out rate may be as high as 30%. We present sensitivity analysis results assuming annual drop out rates of 10% and 30%.

The length of the trial period has been dictated by the design of the clinical studies, which report results at 10 weeks. However it has been reported (Reich et al, 2005; Gottlieb et al, 2004) that onset of a therapeutic response occurs as early as 2 weeks with infliximab. It is therefore feasible that in clinical practice patients who are non-responders may be identified early and may not receive treatment at week 6. We have therefore included a sensitivity analysis assuming a 6 week trial period

We have varied the length of hospital admission for non-responders between 10 and 25 days. It is unlikely that patients with moderate to severe psoriasis who do not respond to treatment will not be hospitalised.

A sensitivity analysis on patient weight (vials of infliximab per treatment)-weight range of 40-60kg (3 vials) and 80-100kg (5 vials) was also performed.

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'.

A probabilistic analysis was undertaken. Distributions and sources are outlined below.

Parameter	Description	Source	Uncertainty
$c^{hospital}$	Yearly cost of hospitalisation for non-responding patient	Assumption based on survey data	Scenario analysis
c^{trial}	Cost of treatment with the infliximab for the 'trial' period	Various	Gamma or Beta distribution
$c^{treatment}$	Yearly cost of treatment with infliximab	Various	Gamma or Beta distribution
d^{trial}	Duration (in years) of the 'trial' period for infliximab	Assumption based on clinical trial designs	Scenario analysis
$d^{treatment,cost}$	Mean duration (in years) of the 'treatment' period for the calculation of costs	Assumption based on limited observational and trial data	Scenario analysis of patient attrition rate and cost discount rate
$d^{treatment,effect}$	Mean duration (in years) of the 'treatment' period for the calculation of effects	Assumption based on limited observational data	Scenario analysis of patient attrition rate and effect discount rate
u_{00}	Utility for a patient not achieving a PASI 50 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution
u_{50}	Utility for a patient achieving a PASI 50 response but not a PASI 75 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution
u_{75}	Utility for a patient achieving a PASI 75 response but not a PASI 90 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution
u_{90}	Utility for a patient achieving a PASI 90 response	Pooled clinical trial and HODaR data (NICE appraisal report)	Normal distribution
p^{pasi50}	Probability of a PASI 50 response	Bayesian hierarchical model of clinical trial data (see Section 6.2.1)	Simulated posterior distribution from MCMC analysis of trial data
p^{pasi75}	Probability of a PASI 75 response	Bayesian hierarchical model of clinical trial data (see Section 6.2.1)	Simulated posterior distribution from MCMC analysis
p^{pasi90}	Probability of a PASI 90 response	Bayesian hierarchical model of clinical trial data (see Section 6.2.1)	Simulated posterior distribution from MCMC analysis

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?

Structural uncertainty has not been directly investigated except for the inclusion of efalizumab as a 2nd line treatment (Appendix D)

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.

There is limited evidence on longer term outcomes with only a few trials reporting results to 52 weeks. However these are not generally placebo controlled beyond the initial "trial phase". Effectiveness may deteriorate over time and this is one of many reasons that a patient may stop treatment. The effect of this can be investigated by varying discontinuation rates.

6.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The primary validation of the model was by comparison with the results from the model used by the York assessment group in the multiple technology appraisal for etanercept and efalizumab for the treatment of psoriasis. The ICERs and ordering of treatments was checked for consistency. Allowing for the updated synthesised response rates and unit costs the ICERs versus supportive care were of a similar order for each treatment. The mean costs and QALYs in our model are calculated differently, with our results intuitively proportionate with the calculated and observed treatment response rates. This is a result of a different mathematical formula that was used to aid presentation, neither model being incorrect Appendix B).

The model was also checked for programming errors and tested for erroneous results by running varied analyses.

6.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves
- scatterplots on cost-effectiveness quadrants.

6.3.1 Base-case analysis

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

The baseline estimates of incremental cost effectiveness are shown in table 6.3.1 for patients with worst baseline quality of life (4th quartile DLQI). Infliximab is a cost-effective treatment for patients with severe psoriasis in whom other systemic agents have failed.

Infliximab is compared to treatment with continuous etanercept 25mg twice weekly use, as this is standard clinical practice in the UK, particularly for severe psoriasis patients. The ICER compared to intermittent treatment with etanercept is presented in Appendix D.

Table 6.3.1: Baseline results: Severe patients (4th Quartile DLQI): infliximab vs continuous treatment with etanercept 25mg twice weekly

	Mean Incremental QALYS*	Mean Incremental Costs*	ICER
continuous etanercept 25mg twice weekly	0.089	£1,531	-
infliximab 5mg/kg	0.205	£4,562	£26,095

*Results rounded for clarity

6.3.2 Subgroup analysis

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

The results presented as the base case are the results of the subgroup analysis focusing on patients with severe psoriasis as described on section 6.2.2.

6.3.3 Sensitivity analyses

6.3.3.1 What were the main findings of the sensitivity analyses?

The sensitivity analyses carried out are described in detail in this section and the results are presented in table 6.3.2. The model is most sensitive to the assumption regarding the length of inpatient stay for non-responders. However a number of different sources (HES data, physician opinion and observational data) do support a length of inpatient stay of around 3 weeks.

Sensitivity analysis on utilities

Utilities were varied within the range of +/- the standard error (se). The utility values used in this analysis have been mapped using the clinical trial DLQI and HODaR data. We are aware that higher utility valuations were additionally reported in the NICE HTA assessment report of etanercept and efalizumab in psoriasis, so there is some degree of uncertainty in these values. At the lower range of utility values the ICER for infliximab versus treatment with continuous etanercept 25mg twice weekly use is £32,970 and with the higher values £21,592.

Sensitivity analysis on response rates

The response rates were varied using the 2.5 and 97.5 centiles of the results from the Bayesian hierarchical model. Results are shown assuming best case response for supportive care and worst case for infliximab and comparator treatments, and also worst case response for supportive care

with best case for infliximab and comparator treatments. Using the worst case response for infliximab the ICER versus continuous etanercept 25mg twice weekly use is £67,413 and using the best case response for infliximab is £16,407.

Sensitivity analysis on annual withdrawal

Because only limited data are available, a sensitivity analysis was carried out on annual drop out rate. For infliximab the baseline model gives has drop out of 18% in the first 10 weeks due to non-response and then an assumed rate of 20% per year thereafter, resulting in approximately 34% discontinuing treatment in the first 15 months. From Reich et al (2005) it can be seen that 22% of patients had discontinued treatment with infliximab by week 50. This is a little less than the baseline model. However, in the same study, of those patients who had a PASI75 response at week 10, 68% were still responders at week 50. It is reasonable to assume that some or all of those who become non-responders will stop treatment and therefore the annual drop out rate may be as high as 30%. We present sensitivity analysis results assuming annual drop out rates of 10% and 30%. The ICER for infliximab versus continuous etanercept 25mg twice weekly treatment is £24,191 (10% drop out rate) and £28,725 (30% drop out rate).

Sensitivity analysis on length of trial period

The length of the trial period has been dictated by the design of the clinical studies, which report results at 10 weeks. However it has been reported (Reich et al, 2005; Gottlieb et al, 2004) that onset of a therapeutic response occurs as early as 2 weeks with infliximab. It is therefore feasible that in clinical practice patients who are non-responders may be identified early and may not receive treatment at week 6. We have therefore included a sensitivity analysis assuming a 6 week trial period and the ICER versus continuous etanercept 25mg twice weekly is £28,195.

Sensitivity analysis on cost of non-responders

We have varied the length of hospital admission for non-responders between 10 and 25 days. It is unlikely that patients with moderate to severe psoriasis who do not respond to treatment will not be hospitalised. The ICER for infliximab versus continuous etanercept 25mg twice weekly treatment ranges from £21,513 (25 days) to £38,694 (10 days).

Sensitivity analysis on patient weight (vials of infliximab per treatment)

In the base case analysis it is assumed that on average 4 vials of infliximab are required per treatment per patient. This equates to a range in patient weight of >60kg to ≤80kg. For a weight range of >40kg to ≤60kg (3 vials) the ICER is £4,984 compared to continuous etanercept 25mg twice weekly and for a weight range of >81kg to ≤100kg (5 vials) the ICER is £47,205.

Table 6.3.2. Sensitivity analysis results (ICERs vs etanercept 25mg continuous use)

		Infliximab
	Base Case	£26,095
	Patient weight >40kg to ≤60kg	£4,984
	Patient weight >80kg to ≤100kg	£47,205
A	Best case response for etanercept 25mg continuous (upper 95%CI), worst for infliximab (lower 95%CI)	£67,413
B	Worst case response for etanercept 25mg continuous (lower 95%CI), best for infliximab (upper 95%CI)	£16,407
C	Lower range of utility values (-se)	£32,970
D	Upper range of utility values (+se)	£21,592
E	10% annual drop out rate	£24,191
F	30% annual drop out rate	£28,725
G	6 week trial period for infliximab	£28,195
H	10 day inpatient stay for non-responders	£38,694
I	25 day inpatient stay for non-responders	£21,513
J	No additional clinic visits for non-responders*	£30,640
	A + C	£124,640
	A + D	£47,631
	A + E	£62,217
	A + F	£73,000
	A + G	£77,488
	A + H	£99,043
	A + I	£55,543
	A + J	£80,333
	B + C	£19,974
	B + D	£14,672
	B + E	£15,223
	B + F	£18,446
	B + G	£18,109
	B + H	£24,627
	B + I	£15,590
	B + J	£19,541
	A + C + F + G + H +J (worst case for infliximab)	£251,565
	B + D + E + I (best case for infliximab)	£11,657

*Comparable to resources used in NICE Assessment Report on Etanercept and Efalizumab

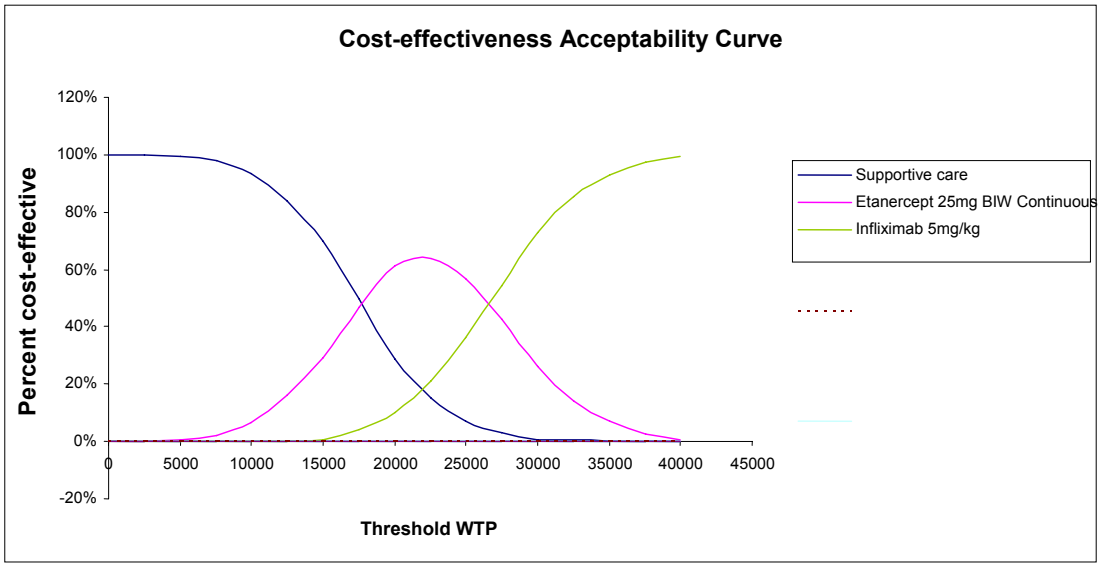
6.3.2.6 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was conducted using response rates from the WinBUGS evidence synthesis sampled using a normal distribution. Costs, resources and utilities were sampled as described earlier in Table 6.1.2.

Results of the probabilistic sensitivity analysis are presented in table 6.3.4.

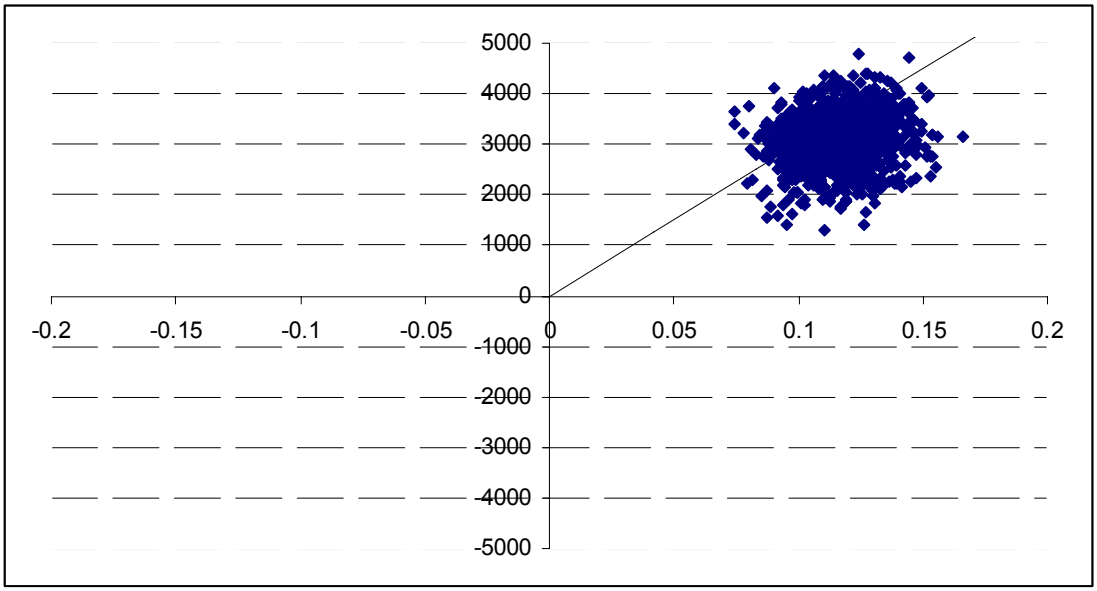
Table 6.3.2.6 Probabilistic Sensitivity analysis

	Incremental QALYs			Incremental Costs			
	mean	**2.5% CI**	**97.5% CI**	**mean**	**2.5% CI**	**97.5% CI**	**ICER**
continuous etanercept 25mg twice weekly	0.089	0.064	0.117	£ 1525	£ 750	£ 2190	
infliximab 5mg/kg	0.205	0.164	0.251	£ 4609	£ 2696	£ 6190	£ 26,589



Proportion Cost-effective				
Threshold Value of cost-effectiveness	**Supportive care**	**Etanercept 25mg BIW Continuous**	**Infliximab 5mg/kg**	
0	100%	0%	0%	
2500	100%	0%	0%	
5000	99%	1%	0%	
7500	98%	2%	0%	
10000	94%	7%	0%	
12500	84%	16%	0%	
15000	70%	29%	1%	
17500	50%	47%	4%	
20000	29%	61%	10%	
22500	15%	64%	21%	
25000	7%	57%	36%	
27500	3%	43%	54%	
30000	1%	26%	73%	
32500	0%	14%	85%	
35000	0%	7%	93%	
37500	0%	3%	97%	
40000	0%	1%	99%	

Satter plot-ICER infliximab vs continuous etanpercept 25mg twice weekly



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?

There are no published economic evaluations of infliximab in psoriasis. The only published economic evaluation of efalizumab and etanercept in psoriasis by Woolacott et al (2006) presents results that do not include infliximab.

The results in this economic evaluation are consistent with those from Woolacott et al (2006). However, the values of the ICERs presented here are lower than the ones in the published economic evaluaton. This is mainly due to the additional costs that have been included for those patients not responding and then being treated with supportive care. The addional costs that have been attributed to these patients have been verified by UK clinical experts.

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

The results of the economic evaluation are relevant to all patients who could potentially use the technology. The base case results focus on patients with severe psoriasis, who are more likely to use infliximab. However, patients with moderate to severe psoriasis are also eligible for treatment with infliximab. The results of this analysis are presented in Appendix C.

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 the model design and structure are based on an accepted model structure that was used in the previous appraisal of efalizumab and etanercept in the treatment of psoriasis. Furthermore, the main comparator in the model, continuous treatment with etanercept 25mg twice weekly, represents actual clinical practice in the UK and therefore the model gives a realistic representation of treatment of severe psoriasis patients in the UK.

The main potential weaknesses of the model are around parameter uncertainty. Parameters, other than those relating to efficacy, have been used in the cost-effectiveness model and are characterised by significant uncertainty. The most fundamental of these relates to long-term experience with biologic therapies, in particular the annual drop-out rate from therapy.

The cost of adverse events also constitutes an area of uncertainty. The assumption is that the most common adverse events will generally resolve once therapy is discontinue. Rates of discontinuation are part of the model. The cost implications of more serious adverse events are unclear given the uncertainty about the incidence of such events.

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

The robustness and completeness of the results could be enhanced by data from head-to-head trials and long-term follow-up trials.

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

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

The figures used in Table 7.1, in this funding model are based on the following:

- 0.45% of the population are likely to receive biologics. It is estimated that 3% of patients with psoriasis will be eligible for treatment with biologics and that 8% of these have been treated rising to 15% in 2007; thus, 0.45% anti-TNF treated prevalence;
- 88% of patients responding after four infusions
- 20% of patients drop out of therapy every year, based on 50-week data for infliximab (Feldman *et al*., 2005).
- The cost of drug is £419.62 for a 100 mg vial. Costs of treatment are based on the average weight between 61-80kg (average weight was estimated from the mean weights of men, 80.8 kg, and women, 68.3 kg, from 1998 Health Survey of England (Office for National Statistics, 1999), giving a cost per infusion of £1,678.46
- Infusions are given at 0, 2 and 6 weeks, then every 8 weeks, making a total of eight infusions in year 1, and an average of 6.5 in all subsequent years for a 8-week post-induction infusion cycle.

Table 7.1 shows the funding required for the provision of infliximab to patients with moderate-to-severe psoriasis over the full financial year based on an 8-week infusion regimen.

This figure represents the maximum likely financial impact in the first full year based on an 8-week post induction infusion cycle, with estimated patient numbers in England and Wales. If infusions are given 8-weekly, costs would be approximately £8,642,786 for year 1.

Table 7.1. Funding required for the provision of infliximab to patients with severe psoriasis over the full financial year based on an 8-week infusion regimen.

	Figure	Numbers in England and Wales
Population		53,390,300
Anti-TNF treated prevalence of Psoriasis	0.45%	1,369
Patients responding	88%	482
Patients not responding	12%	82
Cost per responder (8 infusions in year 1) 8 week	£13,427.84	£8,091,1189
Cost per non responder (2 infusions)	£6,713.92	£551,667
Total Cost for year 1 – 8 week Infusion regime		£8,642,786

TNF = tumour necrosis factor

It is assumed that infliximab will have 50% market share, given positive NICE Guidance at the end of 2007 (market research data). Infliximab patients are infused every 8 weeks after induction and 20% are assumed to drop out of therapy at the end of every year, thus the five year treatment costs would be as per Table 7.1.1.

The cost of psoriasis is currently driven by the cost of the disease and its consequences on work capacity. However, the costs of supportive care (in the absence of infliximab) are substantial and therefore lead to certain cost offsets. Additionally, productivity gains are also likely to contribute to offsetting the cost of therapy.

Table 7.1.1. Net resource implications for England and Wales over the first 5 years after introduction

Annual cost of infliximab treatment					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Number of infliximab treated patients	482	1,061	1,487	1,887	2,262
Cost of responders 8-week infusions (year 1)	£8,091,119	£9,064,891.77	£10,019,189.53	£10,954,401.32	£11,870,908.88
Cost of non-responders (year 1)	£551,667.17	£618,060.80	£683,126.56	£746,891.00	£809,380.15
Cost of responders subsequent years		£4,207,381.65	£8,079,649.04	£11,673,697.79	£15,035,246.92
Total cost of infliximab per year	£8,642,786	£13,890,334	£18,781,965.13	£23,374,990.11	£27,715,535.95
Direct savings per patient (if not treated with infliximab)	£7,099.93				
Direct savings	£3,422,166	£7,533,025	£10,557,595	£13,397,567	£16,060,041
Net costs per annum	£5,220,620	£6,357,309	£8,224,370	£9,977,423	£11,655,494

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

Prevalence of psoriasis of 2%, a prevalence of moderate-to-severe psoriasis of 25% in the UK population, a constant annual incidence of moderate-to-severe psoriasis of 0.08% and a standardised annual mortality rate of 2% for this patient population.

Currently, approximately 3% of patients with severe psoriasis are eligible for treatment with biologics and an estimated 15% (market research) of these psoriasis patients are treated with biologics. Based on the population of England and Wales in 2006, which was estimated at 53,390,300, and the above assumptions, the number of patients with moderate to severe psoriasis assumed to be eligible for treatment with biologics is 266,952 in year 1.

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

According to current NICE Guidance, patients that have failed to respond to standard systemic therapies and have a PASI≥10 and DLQI>10 should be treated with etanercept. Consideration of the response rates for etanercept has also been taken into account. Based on the response rates and the Guidance, it is assumed that 30% of all eligible moderate to severe psoriasis patients will be treated with etanercept. Efalizumab is recommended as a second-line treatment option to etanercept. Similarly, based on response rates for efalizumab, he rates for etanercept non-responders and current Guidance, 20% of moderate to severe psoriasis patients are assume to be treated with efalizumab. Current market research indicates that infliximab will be used for approximately 50% of moderate to severe psoriasis patients eligible for biologic treatment, given positive NICE Guidance at the end of 2007, due to its superior efficacy.

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

It is assumed that patients will be offered infliximab as a first-line treatment following the failure of systemic therapy. Patients with severe psoriasis are treated with infliximb due to its superior efficacy and its speed of response. As mentioned above, market share is assumed to be approximately 50%-based on market research-to be updated with current data;

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

The table below presents the assumed drug costs that were incorporated into the economic model.

Drug	Unit cost	Dose and dosing schedule	Cost
infliximab	£419.62	1 vial 100mg Dose: 5mg/kg 61-80 kg patient assumed 4 vials=£1,678.48 per infusion Week 0,2,6 and subsequently every 8 weeks	Annual cost, average over 5 years =£11,749.36 8 infusions in year 1= £13,500 6.5 infusions in subsequent years=£10,910
etanercept 25mg biweekly continuous	£89.38	25mg vial Dose: 25mg*2 weekly for 52 weeks 104 vials per annum	Annual cost, average over 5 years =£9,295.52
etanercept 25mg biweekly intermittent	£89.38	25mg vial Dose: 25mg*2 weekly for 39 weeks 78 vials per annum	Annual cost, average over 5 years =£6,971.64
etanercept 50mg biweekly intermittent	£178.75	50mg vial Dose: 50mg*2 weekly for 39 weeks 78 vials per annum	Annual cost, average over 5 years =£13,942.50
efalizumab 1mg/kg	£169.20	125mg vial Dose: 1mg/kg 70 kg patient assumed 1 vial=£169.20 Weekly injection	Annual cost, average over 5 years=£8,822.57

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?

Infliximab is administered at weeks 0, 2, 6 and then every 8 weeks. It is expected that patients will receive 8 infusions in the first year and an average of 7 in subsequent years. There is an associated £124 cost of administration of infliximab. The recommended dose is 5mg/kg and is infused over a 2 hour period in an outpatient unit. Treatment with infliximab is continuous at 8 weekly intervals.

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

Direct savings would be mainly comprised of the costs of hospitalisation associated with supportive care. The direct annual cost of a patient receiving supportive care is £7,099.93. The number of annual hospitalisations for supportive care is significantly higher than those for other patients than for those being treated with infliximab, therefore resulting in direct cost savings.

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

There are significant opportunities for resource savings with regards to decreased productivity in severe psoriasis patients that have not been quantified or included in the model. Individuals affected by psoriasis, many of whom are of working age, experience severe physical discomfort and impaired quality of life. The physical manifestations and psychological effects of psoriasis can result in missed days of work and decreased productivity at work. In a survey in the United Kingdom among patients with severe psoriasis, Finlay et al (1995) found that 59.3% of those who were employed had missed an average of 26 workdays during the preceding year due to their psoriasis. Among patients who were not working, 33.9% attributed not working to their psoriasis.

The cost of this lost productivity has not been studied extensively. The cost estimates derived from published studies vary. A recent cost-of-illness analysis of psoriasis in the US found that the direct medical cost of psoriasis was much lower, about $650 million (Javitz et al 2002). A recently reported cost-of-illness study in Germany found that the mean total cost was euro 6,709 per patient per year; these patients had a mean PASI score of 18.2. These costs were higher in 'high-need' patients (euro 8,831; PASI score of 22.2) (Sohn et al 2006).

The indirect costs of psoriasis can therefore be quite substantial. Thus, the total cost of psoriasis to society is much higher than can be expressed just through direct medical costs.

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9 Appendices

Appendix A – Clinical Effectiveness

Search strategy for clinical section

The Medline, Embase and Cochrane Clinical Trials Register (CCTR) were searched using the Ovid engine online. The terms were based on those carried out by the York assessment group in the NICE technology appraisal of etanercept and efalizumab.

Search strategies for each database are given in the tables below. Note that RCTs of comparator medications were searched for using identical search terms for the disease area. Hence these are included as extra lines subsequent to each search table.

Embase Search Strategy

1	randomized controlled trial/
2	randomization/
3	double blind procedure/ or single blind procedure/
4	exp clinical trial/
5	controlled study/
6	clin$ trial$.ti,ab
7	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab
8	placebo$.ti,ab.
9	placebo/
10	random$.ti,ab.
11	evaluation/
12	follow up/
13	exp methodology/
14	prospective study/
15	(control$ or prospective$ or volunteer$).ti,ab
16	or/1-15
17	(cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep or monkey).ti,ab,de.
18	exp animal/
19	animal experiment/
20	nonhuman/
21	human/
22	human experiment/
23	or/17-20
24	21 or 22
25	16 not (23 not (23 and 24))
26	exp psoriasis/
27	(psoria$ or anti psoria$ or antipsoria$).mp.
28	or/26-27
29	etanercept/ or etanercept.mp.
30	enbrel.mp.
31	efalizumab/ or efalizumab.mp.
32	raptiva.mp.
33	infliximab/ or infliximab.mp.
34	remicade.mp.
35	or/29-34
36	25 and 28 and 35
37	(letter or note or editorial).pt.
38	36 not 37

Medline Search Strategy

1	randomized controlled trial.pt.
2	exp randomized controlled trials/
3	random allocation/
4	double blind method/
5	single blind method/
6	clinical trial.pt.
7	exp clinical trials/
8	controlled clinical trials/
9	clin$ trial$.ti,ab.
10	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab
11	placebo$.ti,ab.

12	placebos/
13	random$.ti,ab.
14	exp evaluation studies/
15	follow up studies/
16	exp research design/
17	prospective studies/
18	(control$ or prospective$ ro volunteer$).ti,ab.
19	or/1-18
20	animals/
21	human/
22	20 not (20 and 21)
23	19 not 22
24	exp psoriasis/
25	(psoria$ or anti psoria$ or antipsoria$).mp.
26	or/24-25
27	etanercept.mp.
28	enbrel.mp.
29	efalizumab.mp.
30	raptiva.mp.
31	infliximab.mp.
32	remicade.mp.
33	or/27-32
34	23 and 26 and 33
35	(letter or note or editorial).pt.
36	34 not 35

CCTR Search Strategy

1	psoriasis/
2	psoriasis$.ti,ab.
3	(psoria$ or anti psoria$ or antipsoria$).ti,ab.
4	or/1-3
5	etanercept.mp.
6	enbrel.mp.
7	efalizumab.mp.
8	raptiva.mp.
9	infliximab.mp.
10	remicade.mp.
11	or/5-10
12	4 and 11

Methodology of Competitor RCTs

Efalizumab RCTs

Reference and Location	Design	Participants	Length	Intervention	Comparator	Endpoints (Primary endpoints in bold)
Lebwohl *et al*., 2003b USA	Phase 3, multicentre, placebo controlled, randomized trial	N=597 Adults Clinically stable moderate-to-severe plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Efalizumab 1 mg/kg SC once a wk (n=232) Efalizumab 2 mg/kg SC once a wk (n=243)	Placebo (n=122)	**Proportion achieving at week 12:** **PASI 50; PASI 75; PASI 90** Mean % change in PSA frequency, PSA severity, Itching score, PASI score
Gordon *et al*., 2003, USA	Phase 3, multicentre, placebo controlled, randomized trial	N=556 Adults Clinically stable moderate-to-severe plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Efalizumab 1 mg/kg SC once a wk (n=369)	Placebo (n=187)	**Proportion achieving at week 12:** **PASI 50; PASI 75; PGA Excellent or clear** Mean % change in PSA frequency, PSA severity, Itching score, DLQI score
Leonardi *et al*., 2005, USA	Phase 3, multicentre, placebo controlled, randomized trial	N=332 Adults Clinically stable moderate to severe plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Efalizumab 1 mg/kg SC once a wk (n=162)	Placebo (n=170)	**Proportion achieving at week 12:** **PASI 50; PASI 75; PASI 90** PGA, excellent or cleared. PASI 50 response
Papp *et al*., 2005a, Europe, Russia, Israel, Australia, Mexico, Canada	Phase 3, multicentre, placebo controlled, randomized trial	N=793 Adults (of whom 526 were 'high need', at least 2 systemic therapies unsuitable) Clinically stable moderate to severe plaque psoriasis; >10% BSA; baseline PASI >12	12 wks	Efalizumab 1 mg/kg SC once a wk (n=529)	Placebo (n=264)	**Proportion achieving at week 12:** **PASI 75** PGA, excellent or cleared. PASI 50 response. % improvement PASI, % improvement BSA

Etanercept RCTs

Reference and Location	Design	Participants	Length	Intervention	Comparator	Endpoints (Primary endpoints in bold)
Leonardi *et al*., 2003, USA	Phase 3, multicentre, placebo controlled, randomized trial	N=652 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >10	12 wks	Etanercept 25 mg SC once a wk (n=160) Etanercept 25 mg SC twice a wk (n=162) Etanercept 50 mg SC twice a wk (n=164)	Placebo (n=166)	**Proportion achieving at week 12:** **PASI 50, PASI 75, PASI 90, PGA Clear or excellent** Mean PASI score, % change in PASI score, % change in DLQI score
Papp *et al*., 2005b, USA, Canada and Europe	Phase 3, multicentre, placebo controlled, randomized trial	N=583 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >10	12 wks	Etanercept 25 mg SC twice a wk (n=196) Etanercept 50 mg SC twice a wk (n=194)	Placebo (n=193)	**Proportion achieving at week 12:** **PASI 50, PASI 75, PASI 90** Mean PASI score, % change in PASI score, %
Tyring *et al*., 2006, USA, Canada	Phase 3, multicentre, placebo controlled, randomized trial	N=112 Adults Clinically stable plaque psoriasis; >10% BSA; baseline PASI >10	96 wks	Etanercept 50 mg SC twice a wk (n=311)	Placebo (n=307)	**Proportion achieving at week 12:** **PASI 50, PASI 75, PASI 90** change in DLQI score change in BDI change in FACIT-F change in Ham-D
Gottlieb *et al*., 2003, USA	Phase 3, multicentre, placebo controlled, randomized trial	N=112 Adults Clinically stable plaque psoriasis; >10% BSA	24 wks	Etanercept 25 mg SC twice a wk (n=57)	Placebo (n=55)	**Proportion achieving at week 12:** **PASI 50, PASI 75, PASI 90, PGA Clear or excellent** Mean PASI score, % change in PASI score, % change in DLQI score

Primary results from comparator RCTs with pooled RR statistics.

Efalizumab versus Placebo

Study	Efalizumab	Placebo	RR (95% CI)
Proportion of Patients Achieving PASI 50			
Lebwohl *et al*., 2003b	120/232 (51.7%)	19/122 (15.6%)	3.32 (2.16, 5.11)
Gordon *et al*., 2003	216/369 (58.5%)	26/187 (13.9%)	4.21 (2.92, 6.08)
Leonardi *et al*., 2005	99/162 (61.1%)	25/170 (14.7%)	4.15 (2.84, 6.09)
Papp *et al*., 2005a	284/529 (53.7%)	38/264 (14.4%)	3.73 (2.35, 5.06)
Pooled OR Test for heterogeneity			3.92 (3.28, 4.69) Q=1.01 (df=4), *P*=0.908
Proportion of Patients Achieving PASI 75			
Lebwohl *et al*., 2003b	52/232 (22.4%)	6/122 (4.9%)	4.56 (2.02, 10.31)
Gordon *et al*., 2003	98/369 (26.6%)	8/187 (4.3%)	6.21 (3.09, 12.49)
Leonardi *et al*., 2005	63/162 (38.9%)	4/170 (2.4%)	16.53 (6.16, 44.37)
Papp *et al*., 2005a	166/529 (31.4%)	11/264 (4.2%)	7.53 (4.17, 13.61)
Pooled OR Test for heterogeneity			7.47 (5.20, 10.73) Q=4.16 (df=3), *P*=0.244
Proportion of Patients Achieving PASI 90			
Lebwohl *et al*., 2003b	10/232 (4.3%)	1/122 (0.8%)	5.26 (0.68, 40.60)
Leonardi *et al*., 2005	20/162 (12.3%)	2/170 (1.2%)	10.49 (2.49, 44.18)
Pooled OR Test for heterogeneity			8.39 (2.63, 26.79) Q=0.294 (df=1), *P*=0.59

Etanercept 25mg versus Placebo

Study	Etanercept 25 mg	Placebo	RR (95% CI)
Proportion of Patients Achieving PASI 50			
Leonardi *et al*., 2003	94/162 (58.0%)	24/166 (14.5%)	4.01 (2.71, 5.94)
Papp *et al*., 2005b	126/196 (64.3%)	18/193 (9.3%)	6.89 (4.39, 10.83)
Gottlieb *et al*., 2003	40/57 (70.2%)	6/55 (10.9%)	6.43 (2.97, 13.95)
Pooled OR Test for heterogeneity			5.41 (4.10, 7.14) Q=3.52 (df=2), *P*=0.172
Proportion of Patients Achieving PASI 75			
Leonardi *et al*., 2003	55/162 (34.0%)	6/166 (3.6%)	9.39 (4.16, 21.21)
Papp *et al*., 2005b	67/196 (34.2%)	6/193 (3.1%)	11.00 (4.89, 24.75)
Gottlieb *et al*., 2003	17/57 (29.8%)	1/55 (1.8%)	16.40 (2.26, 119.10)
Pooled OR Test for heterogeneity			10.68 (6.15, 18.57) Q=0.28 (df=2), *P*=0.869
Proportion of Patients Achieving PASI 90			
Leonardi *et al*., 2003	19/162 (11.7%)	1/166 (0.6%)	19.47 (2.64, 143.74)
Papp *et al*., 2005	21/196 (10.7%)	1/193 (0.5%)	20.68 (2.81, 152.22)
Gottlieb *et al*., 2003	6/57 (10.5%)	0/55 (0.0%)	11.58 (0.66, 202.41)*
Pooled OR Test for heterogeneity			18.35 (5.18, 65.01) Q=0.017 (df=1), *P*=0.90

*0.5 added to empty cell to calculate odds ratio (OR). CI, confidence interval; df, degrees of freedom

Etanercept 50mg versus Placebo

Study	Etanercept 50 mg	Placebo	RR (95% CI)
Proportion of Patients Achieving PASI 50			
Leonardi *et al*., 2003	121/164 (73.8%)	24/166 (14.5%)	5.10 (3.49, 7.47)
Papp *et al*., 2005b	150/194 (77.3%)	18/193 (9.3%)	8.29 (5.31, 12.96)
Tyring *et al*., 2006	229/311 (73.6%)	43/306 (14.1%)	5.24 (3.94, 6.97)
Pooled OR Test for heterogeneity			5.85 (4.77, 7.17) Q=3.41 (df=2), *P*=0.182
Proportion of Patients Achieving PASI 75			
Leonardi *et al*., 2003	81/164 (49.4%)	6/166 (3.6%)	13.67 (6.14, 30.43)
Papp *et al*., 2005b	96/194 (49.5%)	6/193 (3.1%)	15.92 (7.15, 35.44)
Tyring *et al*., 2006	147/311 (47.3%)	15/306 (4.9%)	9.64 (5.81, 16.02)
Pooled OR Test for heterogeneity			11.92 (8.17, 17.39) Q=1.29 (df=2), *P*=0.526
Proportion of Patients Achieving PASI 90			
Leonardi *et al*., 2003	36/164 (22.0%)	1/166 (0.6%)	36.44 (5.06, 262.67)
Papp *et al*., 2005	40/194 (20.6%)	1/193 (0.5%)	39.79 (5.53, 286.57)
Tyring *et al*., 2006	65/311 (20.9%)	4/306 (1.3%)	15.99 (5.90, 43.34)
Pooled OR Test for heterogeneity			23.32 (10.38, 52.37) Q=0.832 (df=1), *P*=0.66

DLQI results from comparator RCTs with pooled mean statistics

	Mean reduction in DLQI from baseline at week 12		
Agent	Placebo	Treatment	Mean difference
Efalizumab 1 mg/kg			
Menter *et al*., 2004	1.9	5.6	3.7
Ortonne *et al*., 2005	2.6	5.7	3.4
Pooled mean difference (95% CI)			3.54 (2.05, 5.02)
Etanercept 25 mg BIW			
Krueger *et al*., 2005	0.73	7.47	6.64
Feldman *et al*., 2005	1.4	6.45	5.05
Pooled mean difference (95% CI)			5.66 (3.27, 8.04)
Etanercept 50 mg BIW			
Tyring *et al*., 2006	2.67	8.64	5.97
Krueger *et al*., 2005	0.73	7.98	7.25
Feldman *et al*., 2005	1.4	6.89	5.49
Pooled mean difference (95% CI)			6.07 (3.99, 8.16)

Description of the ordered-probit model

The ordered probit model is designed to model a discrete dependent variable that takes ordered multinomial outcomes, for example, 3 , 2 , 1 , 0 = *y,* etc. The ordered-probit model can be expressed in terms of an underlying latent variable * *y* . This could be interpreted as the individual's underlying percentage reduction in PASI score from baseline. The higher the value of * *y* , the more likely they are to report a higher category of PASI response.

All infliximab trials provided outcome data on the number (%) of patients achieving PASI 75, and three provided data for PASI 50 and PASI 90.

For trials reporting the PASI 50, 75 and 90 endpoints, subjects may be in one of four mutually exclusive categories; no response, PASI 50 to PASI 75 response, PASI 75 to PASI 90 response, and PASI 90 and greater response. So the range of * *y* values is divided into 4 intervals corresponding to these categories. The threshold values (*c*'s) correspond to the cut-offs where an individual moves from reporting one category to another. The lowest value is set at minus infinity, the highest value is set at plus infinity and the upper bound on the first interval (c50) set to zero. The remaining thresholds (c75 and c90) were estimated based on the data. The treatment effects are introduced by making the latent variable, * *y* , a linear function of the treatment effect and intercept and a normally distributed error term. For trials reporting other patterns of endpoints, the appropriate mutually exclusive categories were modelled; for instance, if a trial only reported the PASI 90 endpoint, patients may be in one of two mutually exclusive categories (no response and PASI 90 or greater response).

The model was implemented as a Bayesian hierarchical model. The likelihood takes the form:

$$\prod_j p_{j,m(j)}^{n_j}$$
$$p_{j,1} = \Phi(y^*_j)$$
$$p_{j,2} = \Phi(y^*_j + c75) - \Phi(y^*_j)$$
$$p_{j,3} = \Phi(y^*_j + c90) - \Phi(y^*_j + c75)$$
$$p_{j,4} = 1 - \Phi(y^*_j + c90)$$
$$p_{j,5} = 1 - \Phi(y^*_j + c75)$$
$$p_{j,6} = 1 - \Phi(y^*_j)$$
$$p_{j,7} = \Phi(y^*_j + c75)$$
$$y^*_j = \mu_{s(j)} + \beta_{s(j)}^{t(j)}$$
$$\mu_{s(j)} = N(\mu, 1/\tau_\mu)$$
$$\beta_{s(j)}^{t} = N(\beta_t, 1/\tau_\beta)$$

where:

- n_j is the number of subjects in the m^{th} category represented by the j^{th} datapoint
- $p_{j,m(j)}$ is the probability of observing subjects in the m^{th} category represented by the j^{th} data point.
- $p_{j,1}$ is the probability of observing subjects not having a PASI 50 response for the j^{th} data point.

- $p_{j,2}$ is the probability of observing subjects having between a PASI 50 and a PASI 75 response for the j^{th} data point.
- $p_{j,3}$ is the probability of observing subjects having between a PASI 75 and a PASI 90 response for the j^{th} data point.
- $p_{j,4}$ is the probability of observing subjects having between a PASI 90 response for the j^{th} data point.
- $p_{j,5}$ is the probability of observing subjects having a PASI 75 response for the j^{th} data point.
- $p_{j,6}$ is the probability of observing subjects having a PASI 50 response for the j^{th} data point.
- $p_{j,7}$ is the probability of observing subjects having less than a PASI 75 response for the j^{th} data point.
- $\mu s(j)$ is the intercept for the k^{th} study represented by the j^{th} data point
- β is the treatment co-efficient for the t^{th} treatment and s^{th} study represented by the
- j^{th} data point
- $\beta.^1$ is constrained to zero
- Φ is the standard normal cumulative density function (CDF)

The following vague priors were defined:

$c75 \sim U(0,10)$
$c90 \sim U(c75,c75+10)$
$\beta^t \sim N(1/0.001)$
$\mu \sim N(1/0.001)$
$sd \sim U(0,10)$
$\tau_\mu = 1/sd^2$
$sd_{tx} \sim U(0,10)$
$\tau_\beta = 1/sd^2$

The predicted mean probabilities of PASI 50 response for the t^{th} treatment were estimated as:

$P_t^{pasi50} = 1- \Phi(\mu + \beta^t)$
PASI 75 as:
$P_t^{pasi75} = 1- \Phi(\mu + \beta^t + c_{75})$
and PASI 90 as:
$P_t^{pasi90} = 1- \Phi(\mu + \beta^t + c_{90})$.

Appendix B

Search strategy for economic evaluation

The following databases were used to identify the relevant studies:

- Medline (OVID)
- EMBASE (OVID)
- BIOSIS (OVID)
- Derwent Drug file (OVID)
- Current content/clinical medicine (OVID)
- Pubmed
- Health Economic Evaluation Database
- NHS Economic Evaluation Database (NHS HEED)

The searches were conducted on April 26th 2007. he date span of the search was set from 2004 to the date of the search April 26th 2007. The following search strategy was used in all the databases searched:

1 psoriasis
2 plaque psoriasis
3 biologic
4 infliximab
5 remicade
6 etanercept
7 enbrel
8efalizumab
9 raptiva
10 psoriasis treatment
11 systemic therapy
12 or/2-11
13 1 and 12
14 cost
15 cost-effectiveness
16 economic
17 economic model
18 health economic
19 cost utility analysis
20 cost consequence analysis
21 cost-benefit analysis
22 cost estimate
23 or/12-23
24 13 and 23
25 limit 24 to yr=2004-2007
26 quality of life
27 health status
28 or/26-27
29 1 and 28
30 24 and 28
31 limit 30 to yr=2004-2007

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

Not applicable.

Excluded Studies

Citation	Reason for exclusion
Sohn et al (2006)	German cost study
Dubertret et al (2006)	No economic outcomes
Stein et al (2005)	Quality of life study-no economic outcomes measured, only costs
Feldman et al (2006)	Clinical study-no economic outcomes
Boehncke et al (2006)	Review of biologic therapies
Nelson et al (2005)	US cost study
Rich et al (2004)	Cost study
Feldman et al (2003)	Clinical and cost study
Feldman et al (2005)	US cost study
Augustin et al (2006)	Quality of life study
Griffiths et al (2006)	Clinical study
Griffiths et al (2006)	Clinical study
Guenther et al (2004)	Review of psoriasis management-Canadian study
Smith et al (2005)	Guidelines for treatment
Sterry et al (2004)	Review of psoriasis management (international)
Pearce et al (2005)	US cost-effectiveness study-DLQI outcome
Pearce et al (2006)	US cost-effectiveness study-no meta-analysis for health effects
Gelfand et al (2006)	Clinical study-no economic outcomes
Jacobi et al (2006)	Clinical study-no economic outcomes
Kavanaugh et al (2006)	Clinical study-no economic outcomes
Kavanaugh et al (2006)	Clinical study-no economic outcomes
Kavanaugh, Krueger et al (2006)	Clinical study-no economic outcomes
Mrowietz et al (2007)	Clinical study-no economic outcomes
Rapp et al (2004)	Quality of life study-no economic outcome
Reich et al (2006)	Quality of life study-no economic outcome

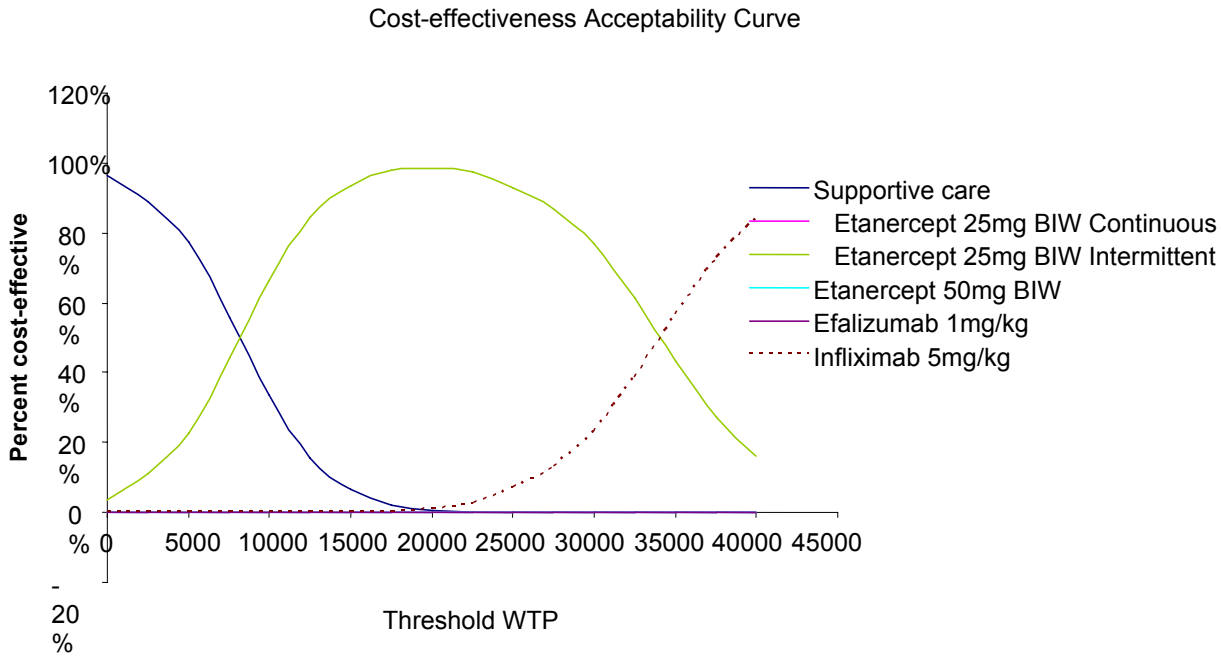
Appendix C

Table 10.1: Baseline results: Severe patients (4th Quartile DLQI): ICERs vs supportive care

	mean incremental QALYS	mean incremental costs	ICERs ordered	ICER vs supportive care
Supportive care	0.000	£ 0		
Intermittent Etanercept 25mg twice weekly	0.089	£ 716	£ 8,044	£ 8,044
Efalizumab 1mg/kg	0.073	£ 1269	Dominated	£ 17,467
Continuous Etanercept 25mg twice weekly	0.089	£ 1531	£ 16,059	£ 17,208
Etanercept 50mg twice weekly	0.124	£ 4439	£ 81,858	£ 35,652
Infliximab 5mg/kg	0.205	£ 4562	£ 1,528	£ 22,240

Table 10.2: Probabilistic Sensitivity Analysis (4th Quartile DLQI): ICERs vs supportive care

	mean incremental QALYs			mean incremental Costs				
	mean	2.5% CI	97.5% CI	mean	2.5% CI	97.5% CI	ICER (ordered)	ICER against supportive care
Supportive care	0	0	0	£ 0	£ 0	£ 0		
Intermittent Etanercept 25mg twice weekly (PASI 75)	0.089	0.065	0.117	£ 704	£ -112	£ 1341	£ 7,873	£ 7,873
Efalizumab 1mg/kg (PASI 75)	0.073	0.053	0.094	£ 1263	£ 655	£ 1799	Dominated	£ 17,368
Continuous Etanercept 25mg twice weekly (PASI 75)	0.089	0.065	0.117	£ 1521	£ 767	£ 2176	£ 15,509	£ 17,022
Etanercept 50mg twice weekly (PASI 75)	0.125	0.094	0.16	£ 4438	£ 3240	£ 5491	£ 81,359	£ 35,438
Infliximab 5mg/kg (PASI 75)	0.205	0.163	0.249	£ 4591	£ 2726	£ 6132	£ 1,925	£ 22,418



Scatter plot-ICERs infIximab vs supportive care (4th Quartile DLQI)

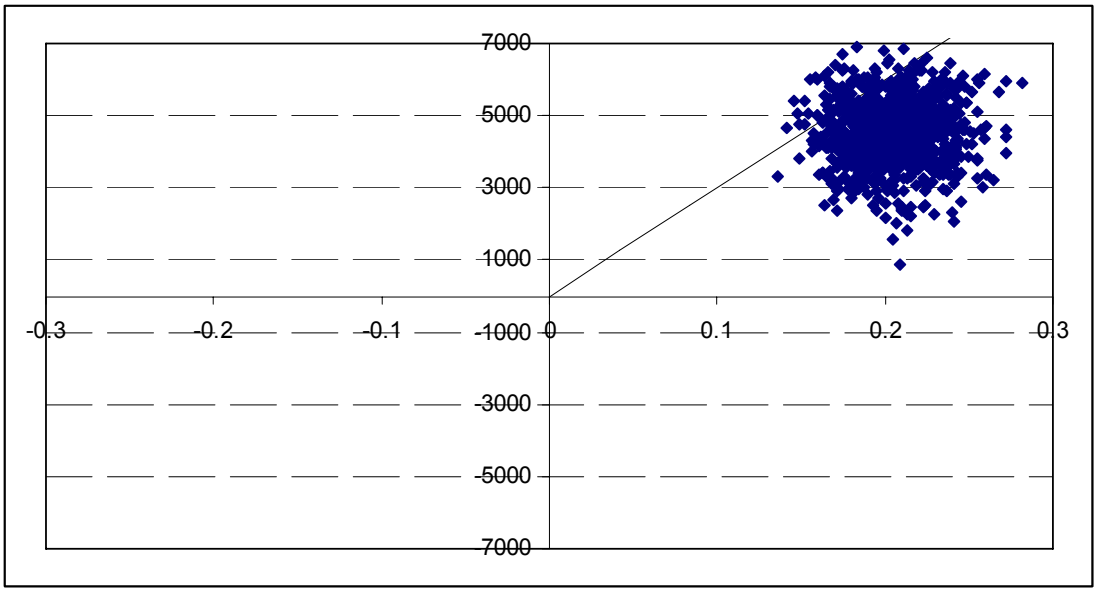
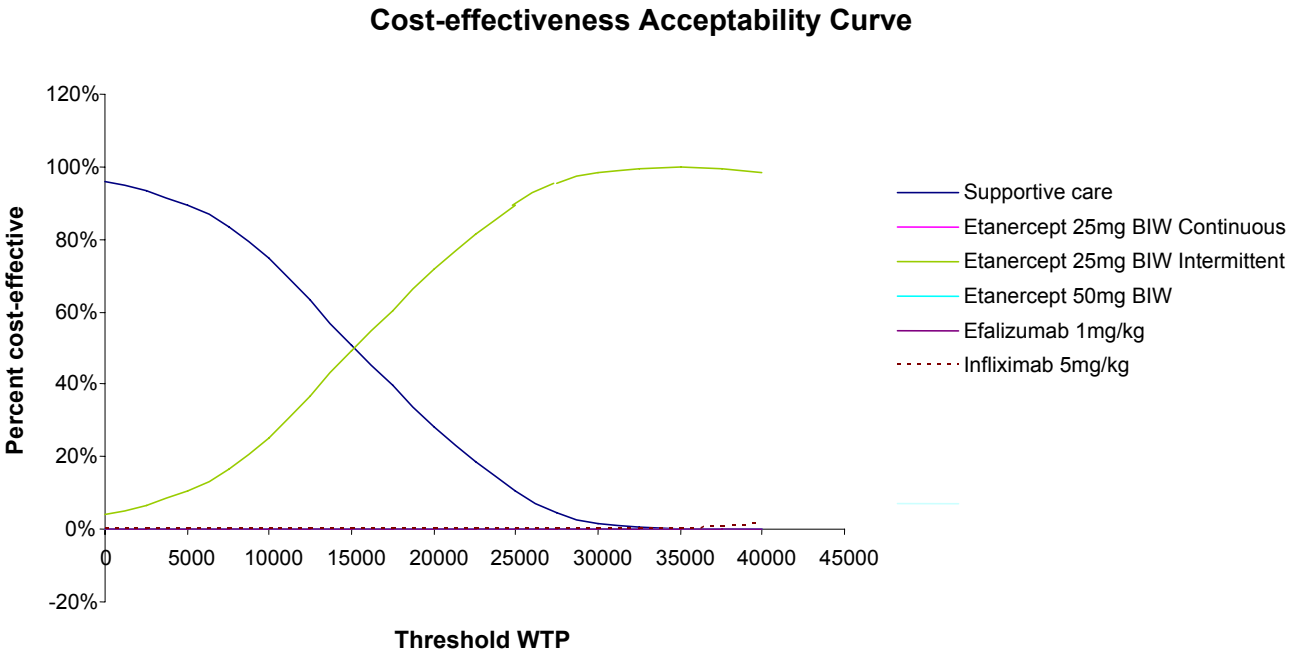


Table 10.3: Baseline results: All patients: ICERs vs supportive care

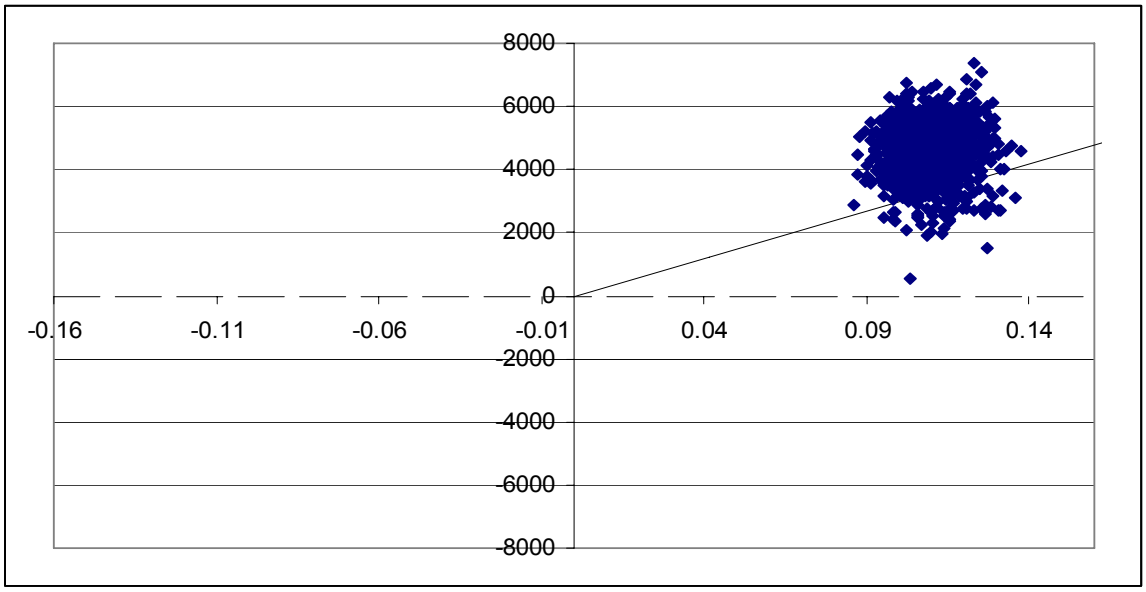
	mean incremental QALYS	mean incremental costs	ICER ordered	ICER vs SC
Supportive care	0.000	£ 0		
Intermittent Etanercept 25mg twice weekly (PASI 75)	0.048	£ 716	£ 14,997	£ 14,997
Efalizumab 1mg/kg (PASI 75)	0.039	£ 1269	Dominated	£ 32,563
Continuous Etanercept 25mg twice weekly (PASI 75)	0.048	£ 1531	£ 29,955	£ 32,084
Etanercept 50mg twice weekly (PASI 75)	0.067	£ 4439	£ 152,534	£ 66,461
Infliximab 5mg/kg (PASI 75)	0.110	£ 4562	£ 2,829	£ 41,351

Table 10.4: Probabilistic Sensitivity Analysis All patients: ICERs vs supportive care

	Incremental QALYs			Incremental Costs				
	mean	2.5% CI	97.5% CI	mean	2.5% CI	97.5% CI	ICER (ordered)	ICER against SC
Supportive care	0	0	0	£ 0	£ 0	£ 0		
Intermittent Etanercept 25mg twice weekly (PASI 75)	0.048	0.038	0.06	£ 709	£ -117	£ 1366	£ 14,726	£ 14,726
Efalizumab 1mg/kg (PASI 75)	0.039	0.031	0.048	£ 1267	£ 630	£ 1795	Dominated	£ 32,357
Continuous Etanercept 25mg twice weekly (PASI 75)	0.048	0.038	0.06	£ 1532	£ 708	£ 2236	£ 29,473	£ 31,818
Etanercept 50mg twice weekly (PASI 75)	0.067	0.055	0.079	£ 4434	£ 3257	£ 5474	£ 155,232	£ 66,323
Infliximab 5mg/kg (PASI 75)	0.11	0.094	0.127	£ 4609	£ 2685	£ 6155	£ 4,026	£ 41,726



Scatter plot: ICERs infliximab vs supportive care (all patients)



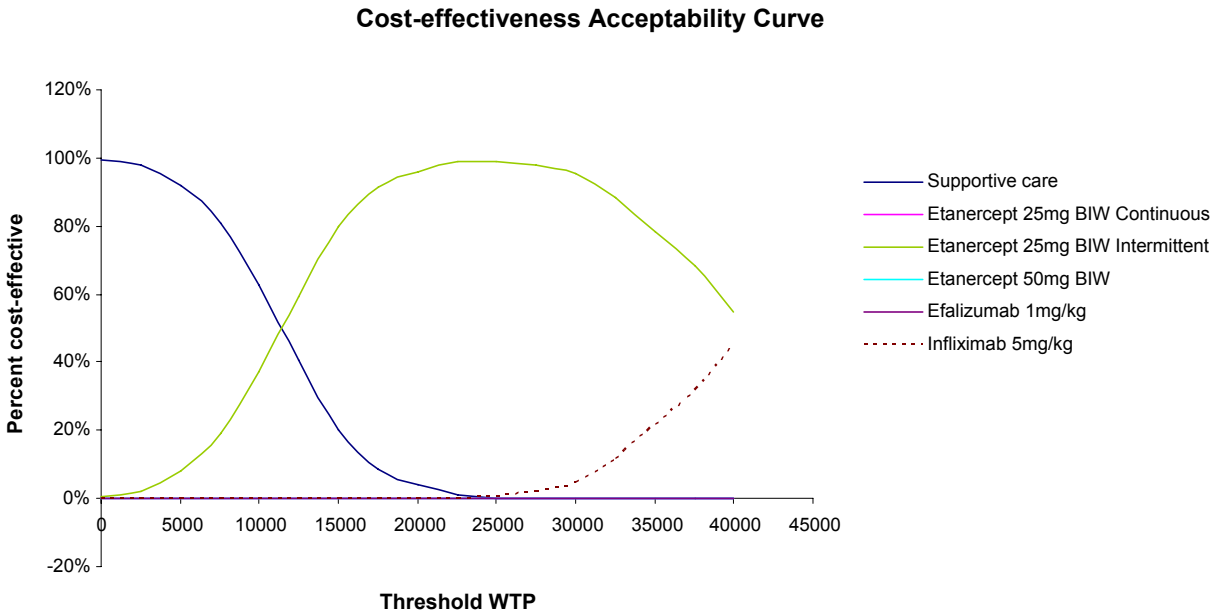
Appendix D

Table 10.5: Baseline results: ICERs vs supportive care (4th quartile DLQI) (efalizumab 2nd line therapy)

	mean incremental QALYS	mean incremental costs	ICER ordered	ICER vs SC
Supportive care	0.000	£ 0		
Efalizumab 1mg/kg (PASI 75)	0.073	£ 1269	£ 17,467	£ 17,467
Intermittent Etanercept 25mg twice weekly (PASI 75)	0.136	£ 1529	£ 4,135	£ 11,280
Continuous Etanercept 25mg twice weekly (PASI 75)	0.136	£ 2344	Dominated	£ 17,297
Infliximab 5mg/kg (PASI 75)	0.219	£ 4803	£ 29,484	£ 21,939
Etanercept 50mg twice weekly (PASI 75)	0.161	£ 5073	Dominated	£ 31,546

Table 10.6: Probabilistic Sensitivity Analysis: ICERs vs supportive care (4th quartile DLQI) (efalizumab 2nd line therapy)

	Incremental QALYs			Incremental Costs				
	mean	**2.5% CI**	**97.5% CI**	**mean**	**2.5% CI**	**97.5% CI**	**ICER (ordered)**	**ICER against SC**
Supportive care	0	0	0	£ 0	£ 0	£ 0		
Efalizumab 1mg/kg (PASI 75)	0.072	0.051	0.093	£ 1267	£ 702	£ 1810	£ 17,524	£ 17,524
Intermittent Etanercept 25mg twice weekly (PASI 75)	0.135	0.101	0.171	£ 1517	£ 356	£ 2509	£ 3,965	£ 11,200
Continuous Etanercept 25mg twice weekly (PASI 75)	0.135	0.101	0.171	£ 2339	£ 1233	£ 3315	Dominated	£ 17,265
Infliximab 5mg/kg (PASI 75)	0.218	0.172	0.263	£ 4857	£ 2951	£ 6513	£ 30,337	£ 22,231
Etanercept 50mg twice weekly (PASI 75)	0.16	0.123	0.2	£ 5065	£ 3744	£ 6346	Dominated	£ 31,610



Scatter plot: infIximab versus supportive care (4th quartile DLQI) (efalizumab 2nd line)

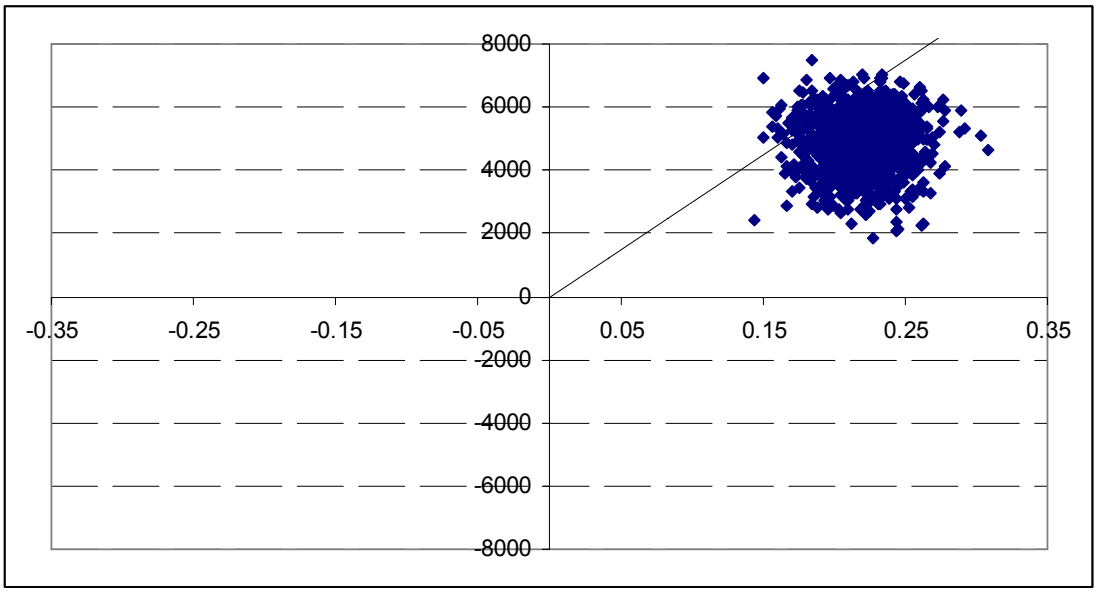
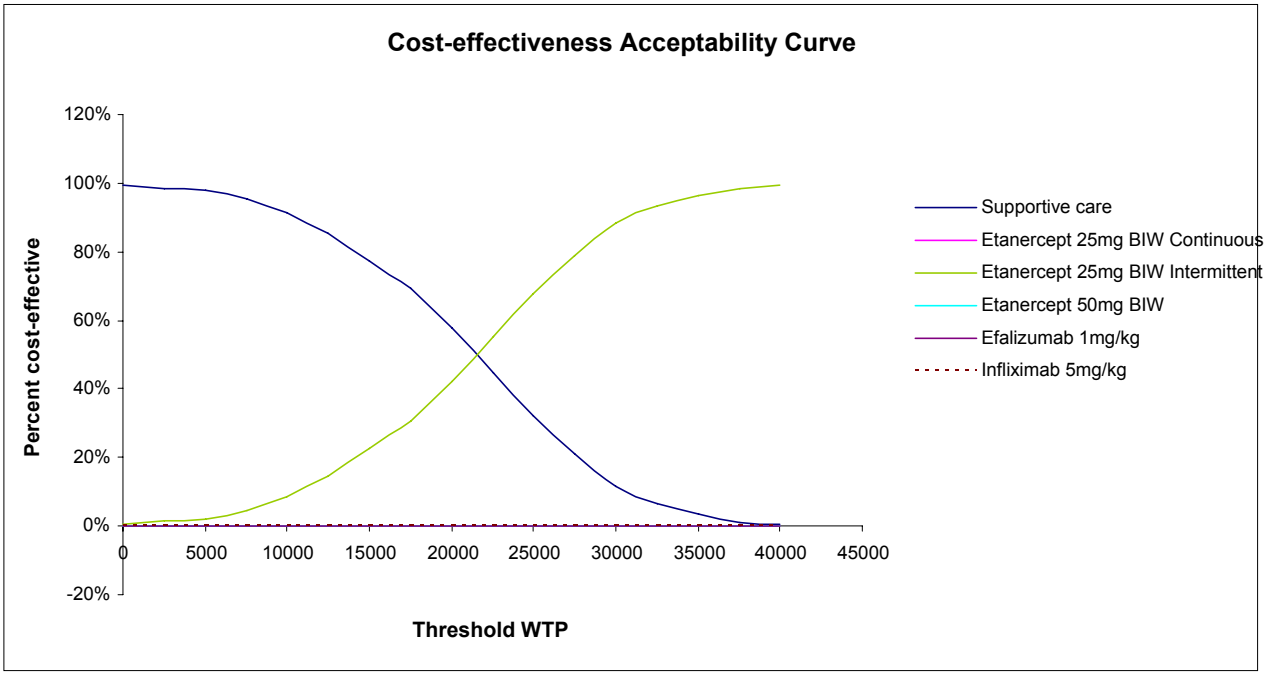


Table 10.8: ICERs vs supportive care (all patients)(efalizumab 2nd line)

	Inc QALYS	Inc Costs	ICER ordered	ICER vs SC
Supportive care	0.000	£ 0		
Efalizumab 1mg/kg (PASI 75)	0.039	£ 1269	£ 32,563	£ 32,563
Intermittent Etanercept 25mg twice weekly (PASI 75)	0.073	£ 1529	£ 7,710	£ 21,030
Continuous Etanercept 25mg twice weekly (PASI 75)	0.073	£ 2344	Dominated	£ 32,249
Infliximab 5mg/kg (PASI 75)	0.118	£ 4803	£ 54,603	£ 40,799
Etanercept 50mg twice weekly (PASI 75)	0.086	£ 5073	Dominated	£ 58,808

Table 10.9: Probabilistic Sensitivity Analysis: ICERs vs supportive care (all patients) (efalizumab 2nd line therapy)

	Incremental QALYs			Incremental Costs				
	mean	**2.5% CI**	**97.5% CI**	**mean**	**2.5% CI**	**97.5% CI**	**ICER (ordered)**	**ICER against SC**
Supportive care	0	0	0	£ 0	£ 0	£ 0		
Efalizumab 1mg/kg (PASI 75)	0.039	0.03	0.048	£ 1261	£ 676	£ 1746	£ 32,610	£ 32,610
Intermittent Etanercept 25mg twice weekly (PASI 75)	0.072	0.058	0.086	£ 1511	£ 426	£ 2436	£ 7,446	£ 20,913
Continuous Etanercept 25mg twice weekly (PASI 75)	0.072	0.058	0.086	£ 2328	£ 1220	£ 3236	Dominated	£ 32,213
Infliximab 5mg/kg (PASI 75)	0.117	0.101	0.133	£ 4836	£ 2978	£ 6410	£ 55,797	£ 41,257
Etanercept 50mg twice weekly (PASI 75)	0.086	0.072	0.1	£ 5056	£ 3649	£ 6314	Dominated	£ 58,915



Scatter plot: infliximab vs supportive care (all patients) (efalizumab 2nd line)

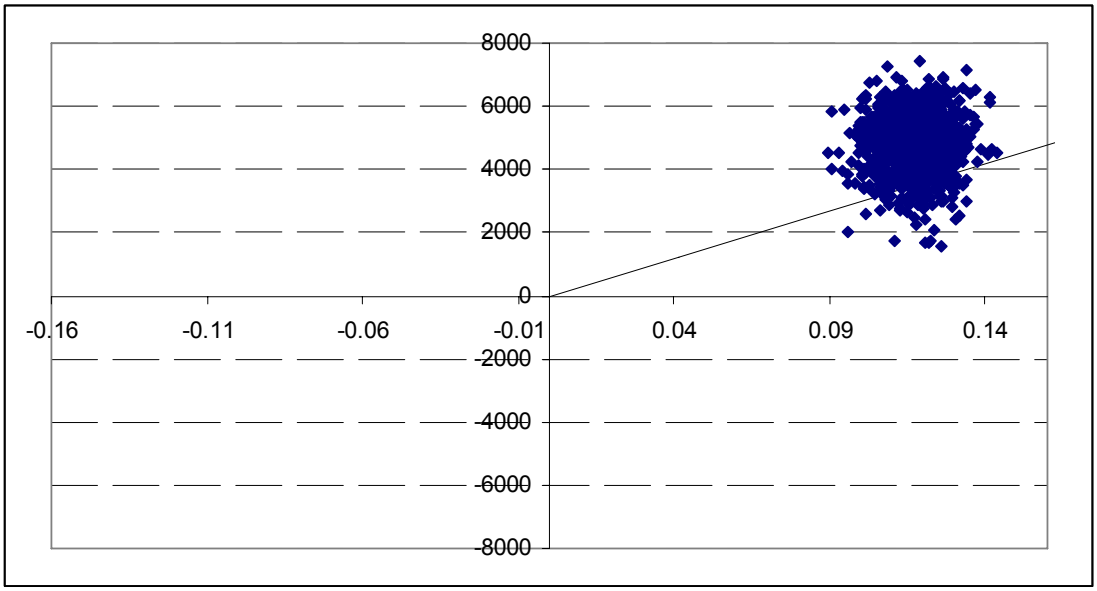
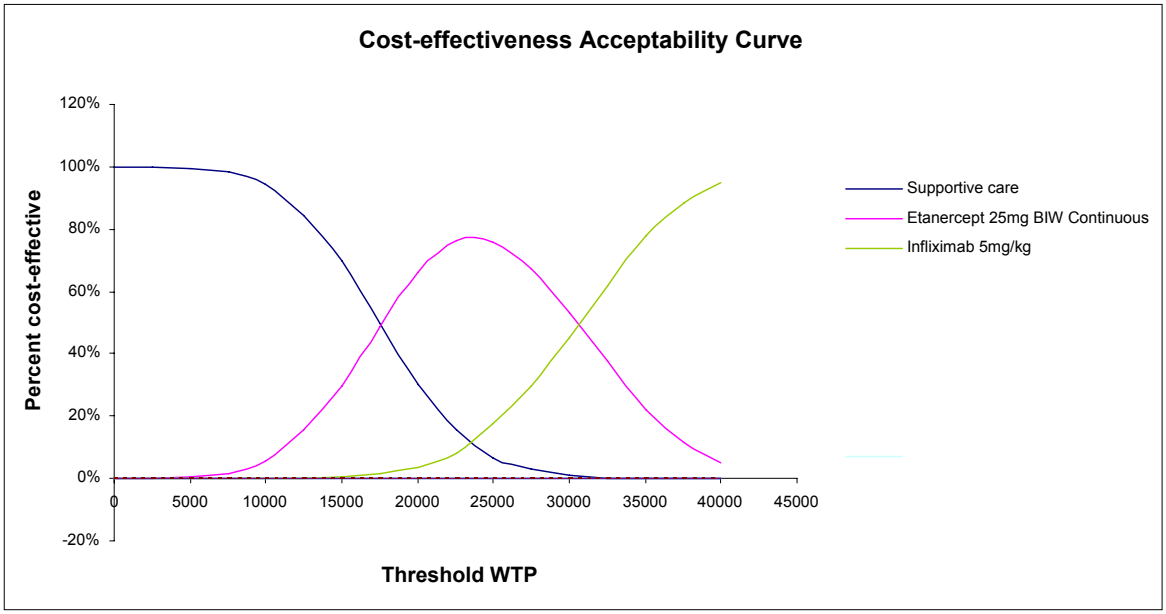


Table 10.10: Baseline results: Severe patients (4th Quartile DLQI): inflixmab vs continuous etanercept 25 mg twice weekly (efalizumab 2nd line)

	mean incremental QALYS	mean incremental costs	ICER
Continuous Etanercept 25mg twice weekly (PASI 75)	0.136	£ 2344	
Infliximab 5mg/kg (PASI 75)	0.219	£ 4803	£ 29,484

Table 10.11: Probabilistic Sensitivity Analysis: Severe patients (4th Quartile DLQI): infliximab vs continuous etanercept 25mg twice weekly (efalizumab 2nd line)

	mean incremental QALYs			mean incremental Costs			
	mean	2.5% CI	97.5% CI	mean	2.5% CI	97.5% CI	ICER
Continuous Etanercept 25mg twice weekly	0.135	0.099	0.169	£ 2329	£ 1146	£ 3313	
Infliximab 5mg/kg	0.218	0.17	0.263	£ 4834	£ 2831	£ 6492	£ 30,196



Scatter plot: ICERs infliximab versus continuous etanercept 25mg twice weekly (efalizumab 2nd line)