NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Ustekinumab (Stelara™) for the Treatment of Moderate to Severe Plaque Psoriasis in England & Wales

January 2009

Table of Contents

Section A

1 Description of technology under assessment

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

Brand name: Stelara
Approved name: Ustekinumab
Therapeutic class: Fully human IgG1κ monoclonal antibody, 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).

Ustekinumab does not currently have marketing authorisation in the UK. However, following the submission of a regulatory dossier to the European Medicine Evaluation Agency (EMEA) on 7th December 2007(1)Janssen-Cilag received a positive opinion for ustekinumab from the Committee for Medicinal Products for Human Use (CHMP) on 20th November 2008. It is anticipated that ustekinumab will receive EU marketing authorisation on 26th January 2009.

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

It is anticipated that ustekinumab will be indicated for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to, or have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA. (See Appendix 1)

This proposed indication is subject to final European Commission approval.

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.

Following EU marketing authorisation on 26th January 2009, we anticipate that ustekinumab will be launched on 2nd February 2009 in the UK. Patients from the UK with moderate to severe plaque psoriasis are currently participating in two ongoing phase III clinical trials of ustekinumab (PHOENIX 2 and ACCEPT).

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

Currently, ustekinumab has only been approved for use in Canada. The submission to EMEA covers all EU member states and the licence is expected to be granted on 26th January 2009.

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?

[redacted]

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

Ustekinumab will be available as a liquid in vial with each vial containing 45mg in 0.5 ml. [redacted].

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.

Adults: The recommended dose of ustekinumab is an initial dose of 45mg administered subcutaneously at week 0 followed by another 45mg dose at week 4, followed by 45mg every 12 weeks thereafter.

For patients with a body weight >100kg the dose is 90mg administered subcutaneously at week 0 followed by another 90mg dose at week 4, followed by 90mg every 12 weeks thereafter. In patients weighing >100 kg, 45mg was also shown to be efficacious. However, 90mg resulted in greater efficacy in these patients.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Children and adolescents (<18 years): Safety and efficacy of ustekinumab have not been studied in this age group. It is therefore not recommended for use in children and adolescents below the age of 18 years.

(See Appendix 1)

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

The list price of an ustekinumab 45mg vial is £2,147 with the list price of 90mg (2x45mg) being £4,294. [redacted]

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

The anticipated licence recommends that ustekinumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis (See Appendix 1).

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?

The monitoring of patients receiving ustekinumab will not differ markedly from other available biologic therapies. In common with other biologics, the major requirement is that patients should be evaluated for tuberculosis infection prior to initiation of therapy.

Ustekinumab requires less frequent administration than other current biologics, being administered only once every 12 weeks via subcutaneous injection following the initial induction two-dose period (weeks 0 and 4).

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with moderate to severe plaque psoriasis who have had an inadequate response to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA	The submission will address the clinical and cost-effectiveness of treatment with ustekinumab within its licensed indication. Patients with a Psoriasis Area and Severity Index (PASI) ≥10 and Dermatology Life Quality Index (DLQI) >10 will be considered to have moderate to moderate to severe psoriasis, consistent with the definitions used in previous NICE appraisals (TA103 and TA146) and in the British Association of Dermatology guidelines.
Intervention	Ustekinumab	45mg solution for injection
Comparator(s)	Biologic therapies: Adalimumab Efalizumab Etanercept Infliximab Best supportive care	In this submission, comparisons between treatments will be assessed via a mixed treatment comparison evidence synthesis. The efficacy of supportive care will be estimated from the placebo responses in the included clinical trials. The comparator treatments are assumed to be administered as follows: Adalimumab: 80mg initially, then 40mg at week 1, and every two weeks thereafter Efalizumab: 0.7mg/kg initially then 1 mg/kg every week Etanercept: 25mg twice weekly administered continuously and intermittently; 50mg twice weekly administered continuously for the first 12 weeks, then 25mg twice weekly thereafter

		Infliximab: 5mg/kg infused initially, repeated 2 and 6 weeks following initial infusion and then every 8 weeks Supportive care (placebo)
Outcomes	The outcome measures to be considered include: • severity of psoriasis • remission rate • relapse rate • adverse effects of treatment • health-related quality of life.	In this submission, a range of outcome measures will be used to assess the clinical effectiveness of ustekinumab. These are as follows: Severity of psoriasis will be assessed via the PASI score, and clinical outcomes according to PASI 50/75/90 responses will be presented. The primary focus will be PASI 75 as this was the primary outcome measure in all the clinical trials. PASI 50 and 90 values will also be presented as secondary analyses. All three levels of PASI response will be estimated for each treatment via a mixed treatment comparison evidence synthesis. The efficacy of ustekinumab will also be presented in terms of the Physician's Global Assessment (PGA) scores. Currently, there is no universally agreed definition of what constitutes remission. However, in this submission, we will use PASI 90 responses as an indicator of remission. Relapse prevention will be assessed based on durability of response. Adverse events will be reported for ustekinumab and comparators based on the results from the ustekinumab clinical trial programme Health related quality of life will be assessed using the DLQI which is a widely used disease-specific health related quality of life questionnaire and which was used in the ustekinumab clinical trial programme. Quality Adjusted-Life Years (QALYs) is the outcome measure used in the economic analysis and are derived through mapping DLQI measurements to EQ-5D UK tariff scores for PASI response categories

Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The cost-effectiveness of treatment is assessed by the incremental cost per quality adjusted life year (QALY), by applying the results of the mapping exercise described above to the response to treatment as measured by PASI score in a decision analytic model framework The model includes the biologic therapies defined by the scope of this appraisal. Analyses are also provided that compare ustekinumab against best supportive care based on the efficacy reported from the placebo arms from the clinical trials The time horizon applied in this submission reflects that used in previous submissions for biologics in psoriasis Costs are estimated from the perspective of the NHS We have agreed the following with the NICE technical team: • The assessment for the response of ustekinumab will be estimated at 16 weeks, just prior to the third dose • The weight based dosing of ustekinumab will be used in the base case cost-effectiveness analysis to reflect the guidance for use in the SmPC, with the ITT analysis being presented as a scenario analysis
Special considerations, including issues related to equity or equality	It is anticipated that individuals may also be treated with topical therapies; where the evidence permits any resulting confounding factors will be taken into consideration. Where the evidence allows, sequencing of different drugs and the place of ustekinumab in such a sequence will be considered.	There is evidence to suggest that an adjustment in dosing may be required for patients over 100kg. We anticipate that the final SmPC will, therefore, specify a 90mg dose for patients over 100kg The economic analysis will consider the cost-effectiveness of ustekinumab in line with the anticipated licence indication

	If the evidence allows, consideration will be given to the subgroup of people with very severe psoriasis. Guidance will only be issued in accordance with the marketing authorisation.	

Section B

3 Executive summary

Psoriasis

- Psoriasis is a chronic, systemic inflammatory disease mediated by T-helper cells of the Th1 and Th17 sub-types. These cells produce a range of cytokines, which promote the formation of psoriatic skin lesions.
- New options are needed for the treatment of this inflammatory condition, especially for the 20% of patients classified as having moderate to severe disease (PASI≥10; DLQI>10) because poorly controlled psoriasis can have a devastating impact on the quality of life, work prospects and overall health of patients. The clinical manifestations of moderate to severe psoriasis are illustrated on page 14.

Development of ustekinumab

- IL-12 and IL-23 are key cytokines that promote differentiation and expansion of Th1 and Th17 cell lines and as a result have been identified as a target for new psoriasis treatments
- Ustekinumab, a fully humanised monoclonal antibody is the first treatment to specifically target IL-12 and IL-23. It binds to the p40 subunit, common to both IL-12 and IL-23, which prevents these cytokines from binding to the cell surface of T cells thereby disrupting differentiation, clonal expansion and consequently the inflammatory cascade implicated in this disease.
- Ustekinumab has a unique dosing schedule, which means that patients require considerably fewer injections than with existing agents. Following induction doses at weeks 0 and 4, the dosing interval during maintenance therapy is once every 12 weeks. In comparison, etanercept requires subcutaneous injection once or twice weekly and adalimumab once every two weeks.
- The SmPC for ustekinumab recommends a weight based dosing approach. The recommended dose of ustekinumab is an initial dose of 45mg administered subcutaneously at week 0 followed by another 45mg dose at week 4, followed by 45mg every 12 weeks thereafter. For patients with a body weight >100kg the dose is 90mg administered subcutaneously at week 0 followed by another 90mg dose at week 4, followed by 90mg every 12 weeks thereafter. In patients weighing >100 kg, 45mg was also shown to be efficacious. However, 90mg resulted in greater efficacy in these patients.

Clinical Evidence

- The efficacy and safety of ustekinumab have been studied in three Phase III, international randomised controlled clinical trials. In this submission we present both the ITT results as well as the clinical trial data analysed specifically by weight according to the posology in the SmPC.
- Two of these trials (PHOENIX 1 and PHOENIX 2) were placebo controlled and the third (the ACCEPT trial) was a randomised head to head study of ustekinumab (45mg and 90mg) versus etanercept 50mg twice weekly.
- The ACCEPT trial is the first randomised, comparative trial of two biologic agents to have been conducted in psoriasis and is of particular relevance to this appraisal as it compares ustekinumab to the most commonly used agent in UK clinical practice

- In PHOENIX 1, 67% and 66% of patients achieved PASI 75 at week 12 for ustekinumab 45mg and 90mg respectively compared to 3% for placebo. In PHOENIX 2, the results were 66%, 76% and 4% for the same three groups respectively.
- In both studies, there were statistically significant and clinically meaningful improvements in patients' quality of life as measured by the DLQI with both doses of ustekinumab. The benefits of ustekinumab on patients' quality of life are stated in section 5.1 of the SmPC.
- Long-term follow-up data demonstrate that the effectiveness of ustekinumab is maintained over time (at least 52 weeks).
- In the ACCEPT trial, which evaluated over 900 patients with moderate to severe psoriasis, ustekinumab 45mg and ustekinumab 90mg were both significantly more effective than etanercept 50mg twice weekly at week 12.
    - 68% and 74% of patients treated with ustekinumab 45mg and ustekinumab 90mg respectively achieved PASI 75 response compared to 57% treated with etanercept 50mg twice weekly ($p<0.001$)
    - A significantly higher proportion of patients treated with ustekinumab 45mg and ustekinumab 90mg also achieved a PGA of cleared or minimal (65% and 71% respectively) compared with etanercept 50mg twice weekly (49%).
    - Significantly more patients also achieved the more stringent response criteria of PASI 90 at week 12 for both ustekinumab groups versus etanercept 50mg twice weekly ($p<0.001$).
- Across all three Phase III studies, ustekinumab was generally well tolerated. Rates of serious infections, malignancies and cardiovascular events were low and comparable to placebo and etanercept 50mg twice weekly.
- To compare the effectiveness of ustekinumab to other treatment options for moderate to severe psoriasis, a mixed treatment comparison was undertaken following a comprehensive systematic review of the literature. The mixed treatment comparison followed the methodology employed by the assessment group in the original Multiple Technology Appraisal of efalizumab and etanercept.
- Results from this analysis suggest that ustekinumab has the highest mean PASI 75 response rates after infliximab. In the weight-based mixed treatment comparison, mean PASI 75 response rates were 75% and 69% for ustekinumab 45mg and ustekinumab 90mg groups, compared to mean response rates of 59%, 26%, 38%, and 52% for adalimumab, efalizumab, etanercept 25mg and etanercept 50mg respectively.
- In summary, in the first head to head trial of biologic agents for the treatment of psoriasis, both doses of ustekinumab were more effective than the most effective licensed dose of etanercept. In a mixed treatment comparison, which built upon the methodology developed by the University of York in the original Multiple Technology Appraisal, ustekinumab resulted in higher PASI 75 responses than adalimumab, efalizumab and etanercept.

Weight based dosing

- In the proposed SmPC, it is recommended that people should be dosed according to their weight. For patients >100kg, it is recommended that they should receive a dose of 90mg, with patients ≤100kg recommended to receive 45mg.
- At launch, only a 45mg strength will be available, which raises a potential difficulty because those patients who are over 100kg and who are prescribed the 90mg strength would require two vials of 45mg which would double the cost

[redacted]

- This scheme is built into the economic evaluation presented in section 7.

Cost-effectiveness

- The annual cost of ustekinumab is very similar to the currently available NICE approved biologics in psoriasis. Average annual costs of ustekinumab is estimated to be £9,336 compared to £9,327 for etanercept 25mg (continuous) and £9,327 for adalimumab.
- Ustekinumab has lower acquisition costs than etanercept 50mg twice weekly dosing and infliximab.
- The ACCEPT trial demonstrates the clinical superiority of ustekinumab versus etanercept 50mg twice weekly dosing.
    - PASI 75 response for ustekinumab 45mg and ustekinumab 90mg groups was 72.2% and 65.0% respectively versus 57% for etanercept 50mg twice weekly at week 12.
    - This is achieved for a very similar overall cost to the lower (and less effective) 25mg strength.
- The mixed treatment comparison also suggests greater efficacy with ustekinumab than adalimumab, efalizumab and etanercept. These additional benefits are achieved at a similar annual acquisition cost.
- An economic evaluation was undertaken to evaluate the cost-effectiveness of ustekinumab compared to alternative biologic treatments and best supportive care in line with the NICE reference case.
- The model followed the same structure as that developed by the assessment group in the Multiple Technology Assessment, and was updated with the results from the mixed treatment comparison described above.
- The following base case modelling assumptions were agreed with the NICE technical team prior to the submission:
    - A trial period of 16 weeks for ustekinumab
    - It is plausible that etanercept 25 mg intermittent is less effective than continuous treatment based on the finding of a recently published comparative clinical trial(2)
    - Weight based efficacy (45mg for patients ≤100kg and 90mg for patients >100kg) for ustekinumab used in the base case.

[redacted]

- Base case results from the model demonstrated that ustekinumab dominates adalimumab, efalizumab, etanercept 25mg and 50mg twice-weekly continuous treatment. The ICER for ustekinumab versus best supportive care was £29,587.
- When compared directly to etanercept 25mg intermittent, the ICER for ustekinumab was £26,637. In this analysis etanercept was extended dominated by ustekinumab and best supportive care.
- The ICER for infliximab versus ustekinumab was £304,566

- The cost-effectiveness acceptability curve showed that of all available biologic treatment options, ustekinumab had the highest chance of being cost-effective across conventional ranges of willingness to pay.

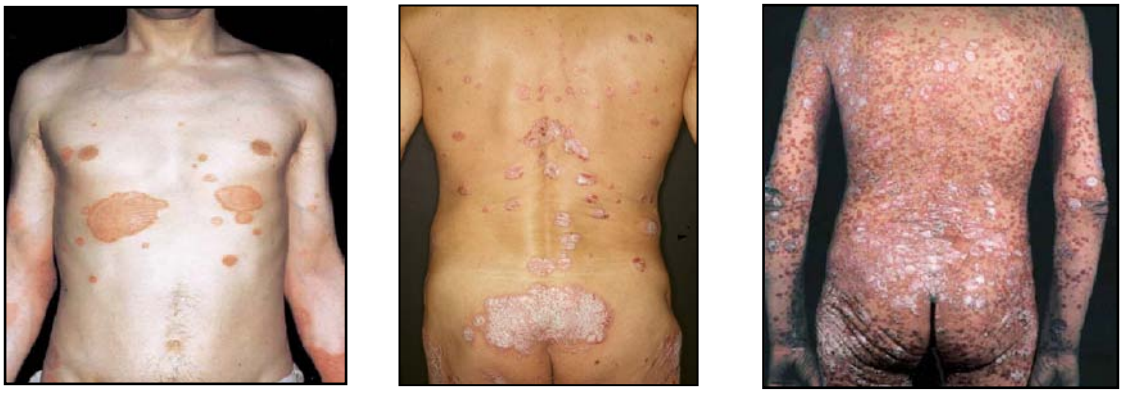
4 Context

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

Psoriasis is a chronic, inflammatory, immune-mediated skin disease affecting approximately 2% of the population in the United Kingdom(3). Although psoriasis has conventionally been thought of as being a disorder that affects only the skin, it is increasingly understood to be a systemic autoimmune disorder(3), the pathogenesis of which is mediated by T-cells(3). Current understanding of the pathogenesis of psoriasis suggests that the initial trigger is an environmental factor such as a viral antigen that induces production of cytokines by skin-resident immune cells which then act on many different cell types such as T-cells(4;5). These cytokines stimulate proliferation of keratinocytes (one type of skin cells) and also promote expression of adhesion molecules on cells of the immune system and the blood vessels within the skin. Interaction of adhesion molecules promotes further activation of T cells and stimulates the production of further cytokines setting up a vicious cycle of response. Psoriasis is an incurable disease and most patients endure debilitating chronic psoriasis with intermittent periods of remission and relapse of their disease(6).

Chronic plaque psoriasis, or psoriasis vulgaris, is the most common form of the condition affecting approximately 90% of sufferers(7). The plaques can occur at any skin site but commonly appear on the elbows, knees, scalp and trunk. The remaining 10% of psoriasis sufferers have other forms including guttate, erythrodermic, pustular, nail, scalp and inverse psoriasis(5).

Figure 4.1.1 Examples of psoriasis by severity categories



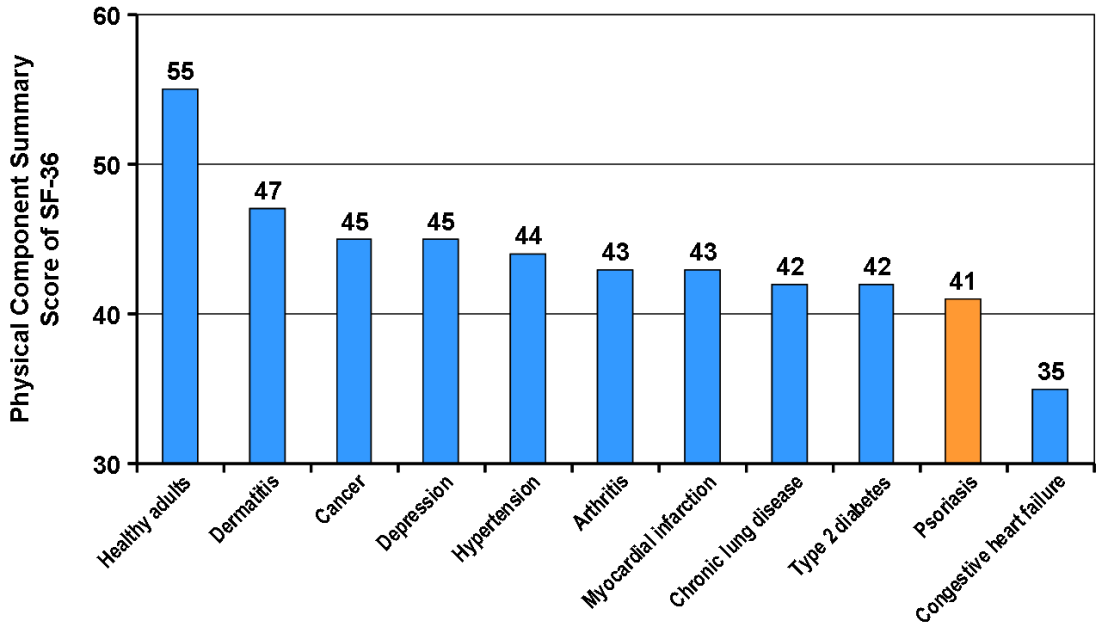
PASI ≤10 **PASI >10-20** **PASI ≥20**

PASI = Psoriasis Area and Severity Index

The severity of psoriasis is determined by several factors, including the Psoriasis Area and Severity Index (PASI), the extent of body surface area affected (BSA), and the impact of the condition on patients' quality of life, commonly measured by the Dermatology Life Quality Index (DLQI). In 2005, the British Association of Dermatologists (BAD) published guidelines which defined patients with severe psoriasis as having a PASI score≥10 (or BSA ≥10), a DLQI >10, have had severe disease for >6 months, are resistant to topical treatment and are candidates for systemic therapy(8). Overall, between 20 and 30% of sufferers have severe psoriasis(8) and in these patients the plaques can cover almost the total body surface area(6).

Psoriasis is also associated with a significant negative impact on health-related quality of life (HRQoL). In a study of the quality of life of psoriasis patients using the Short Form Health Survey Questionnaire (SF-36), a standardised generic quality of life assessment tool, quality of life was significantly worse in psoriasis patients for the domains of physical and social functioning and mental and general health compared with healthy adults(9). In addition, this study found that the negative impact of psoriasis on physical health was worse than that associated with some other chronic diseases including arthritis, myocardial infarction, chronic lung disease and type 2 diabetes(9) (Figure 4.1.2).

Figure 4.1.2 Impact of psoriasis on physical health. Comparison with other diseases(9)



Psoriasis also has a negative impact on productivity at work. The condition commonly restricts the sufferer's choice of career and over half of patients with severe psoriasis report that they are unable to work at all(10-12).

Psoriasis is also associated with co-morbidities such as obesity, diabetes, hypertension and heart failure. For example: a cross-sectional study carried out in the US examining the impact of obesity and smoking on psoriasis showed that the prevalence of obesity in psoriasis patients was significantly higher than that of the general population (34% vs. 18%, respectively, $p<0.001$(13)). Additionally, a retrospective analysis of more than 40,000 patients with psoriasis in Germany, showed that there was a 1.5-fold increase in the risk of developing diabetes ($p<0.05$(14)) and a 2-fold increase in the risk of developing hypertension compared

with matched individuals without psoriasis (p<0.01(14)). Finally, a large prospective, population-based cohort study in the UK of patients with psoriasis, showed that the relative risk (RR) of myocardial infarction is higher than that of the general population, particularly in young patients. For a 30-year-old patient with mild or severe psoriasis, the adjusted RR of having a myocardial infarction is 1.29 (95% CI, 1.14–1.46) and 3.10 (95% CI, 1.98–4.86), respectively(15).

Management of psoriasis

There are a variety of treatment options available for patients with psoriasis:

Topical treatment

Mild psoriasis is generally treated initially with topical creams, ointments or lotions in primary care. Topical treatments include coal tar derivatives, dithranol, vitamin D analogues (calcipotriol, calcitriol and tacalcitol), vitamin A analogues (tazarotene) and corticosteroids. The choice of topical treatment is dependent upon the extent and pattern of psoriasis, and patient preference(6). Patients would normally only be referred to a dermatologist in the event of treatment failure (defined as a lack of response to at least 2–3 months of topical therapy), uncertainty over diagnosis, extensive disease that is unresponsive to initial therapy or difficult for the patient to manage, adverse reactions to topical treatment or the need for more potent steroids or systemic therapy(6).

Phototherapies

Phototherapy can be used in patients with moderate to severe psoriasis, or psoriasis unresponsive to topical treatment, and is delivered in specialist treatment centres. Different types are as follows:

- *Phototherapy (broadband or narrowband UVB)* - Broadband UVB (290–320 nm) and narrowband UVB (311 nm) are effective treatments for plaque psoriasis. Narrowband UVB (311 nm) demonstrates greater efficacy in the treatment of psoriasis than broadband UVB. Treatments are frequent (two or three per week). The principal unwanted effects are acute skin burn and a presumed dose-related increase in the risk of developing non-melanoma skin cancer, which can be mitigated by shielding the face during treatment and limiting the number of treatment courses(6;16).
- *Photochemotherapy (psoralens + UVA [PUVA])* - Administration of oral or topical psoralens, followed by irradiation with long wave ultraviolet light (320-400 nm) (UVA), is an established, effective, widely used form of treatment. While it does have acute adverse effects (i.e. skin burning, nausea and pain) and chronic consequences (i.e. skin ageing and pigmentation), PUVA continues to be used for more difficult to clear psoriasis resistant to topical preparations and UVB. There is also evidence that PUVA is associated with a significant increase in the risk of developing squamous cell carcinoma (SCC)(17). The risk of SCC is also increased in patients who have received cyclophosphamide or methotrexate in addition to PUVA(18;19).

The combination of phototherapy and PUVA with other anti-psoriasis treatments such as coal tar, topical calcipotriol and oral retinoids has been proven effective, with an increased rate of clearance and a reduction in the total light dose required. However, most patients find the freedom from the use of topical agents an advantage, therefore combination treatments are often reserved for resistant cases(6).

Systemic treatments

Patients who have failed to respond to topical therapy, or have had repeated hospital admissions whilst on topical therapy, or patients with extensive plaque psoriasis would be eligible for systemic treatment(6). Candidates for systemic therapy will usually be expected to have a body surface area affected ≥10%, or the PASI score >10, or the DLQI > 10(10). Options for systemic treatment include:

- *Oral retinoids* - The most common is acitretin, which is the carboxylic acid metabolite of etretinate, the first oral retinoid used in clinical practice(6). However, acitretin is associated with numerous side effects and toxicity reactions, foetal death or abnormalities and hepatotoxicity

- *Methotrexate* - is an anti-metabolite treatment and is effective in the treatment of severe psoriasis unresponsive to other therapies(20). However, methotrexate is associated with acute bone marrow suppression and the risk of liver toxicity with prolonged use(21)

- *Ciclosporin* - is an immunosuppressant that is effective at treating severe psoriasis at doses of 2.5–5 mg/kg/day. However, it is associated with nephrotoxity and hypertension. Doses higher than this are associated with increased side effects that may negate the additional clinical benefits(20).

Biologic therapies

A number of biologic therapies are recommended by NICE for patients with moderate to severe psoriasis that have failed to respond to standard systemic therapies including ciclosporin, methotrexate and/or PUVA, or patients who are intolerant to, or have a contraindication to systemic treatments(22-24)

Biologic therapies target specific inflammatory mediators involved in the pathophysiology of psoriasis. There are two principal modes of action currently available and these are blockade of tumour necrosis factor and a leukocyte cell surface protein present on activated T lymphocytes.

Tumour necrosis factor alpha (TNF-α) inhibitors- TNF is a cytokine released from T lymphocytes that mediates inflammation and modulates the cellular immune response. Monoclonal antibodies and receptor fusion proteins bind specifically to TNF-α, blocking interaction with its cell-surface receptors and thereby limiting the promotion of inflammatory pathways. Currently available anti-TNFs are as follows:

- *Etanercept* is a recombinant human TNF receptor fusion protein that inhibits the activity of TNF. It is administered subcutaneously either with 50mg once weekly or 25mg twice weekly. Also 50mg is administered twice weekly for the first twelve weeks of treatment and then 25mg twice weekly thereafter.

- *Infliximab* is a chimeric human-murine monoclonal antibody that binds specifically to TNF-α. It is administered in hospital via intravenous infusion over two hours at weeks 0,2 and 6 and every 8 weeks thereafter at a dose of 5mg/kg.

- *Adalimumab* is a recombinant human monoclonal antibody that binds specifically to TNF-α, and is administered subcutaneously with 80mg at treatment initiation followed by 40mg at week one and 40mg every other week thereafter.

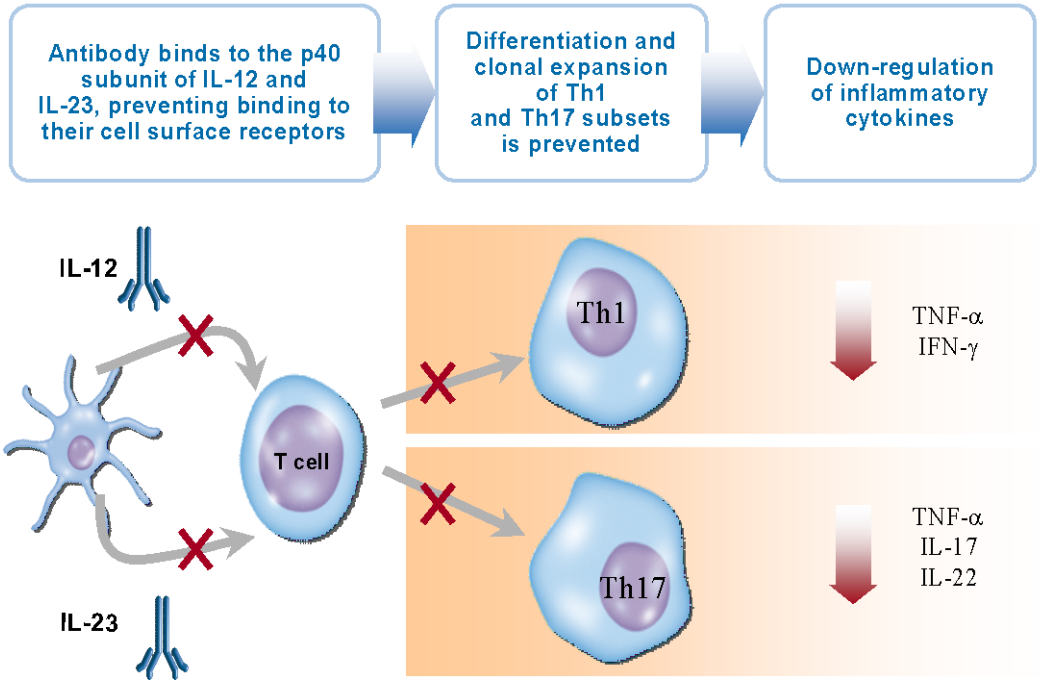
Others

Efalizumab is a humanised monoclonal antibody that binds to the CD11a subunit of lymphocyte function-associated antigen-1 (LFA-1). Efalizumab interferes with T cell binding to other cells, inhibiting several stages in the immunologic cascade including migration and activation and is administered subcutaneously at 0.7 mg/kg initially then 1 mg/kg every week thereafter.

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

Psoriasis is an inflammatory disease in which different elements of the immune system interact to produce the classic psoriatic plaque. The inflammatory component of psoriasis is mediated by T-helper cells of the Th1 and Th17 sub-types which promote the formation of psoriatic skin lesions by the production of cytokines such as IL-17, IL-22, IFN-γ, and TNF-α. Currently available biologic therapies target T cell activity and the effects of TNF-α. Recent findings indicate that IL-12 and IL-23, produced by dendritic cells, are key cytokines in the psoriasis disease process. They are involved in the differentiation and expansion of Th1 and Th17 cell populations. IL-12 and IL-23 possess a common subunit (known as p40) that is a potential target for therapeutic intervention. Targeting the p40 subunit of IL-12 and IL-23 offers a novel way of treating severe psoriasis (Figure 4.2.1).

Figure 4.2.1 Targeting IL-12 / IL-23 p40: A Novel Approach to Psoriasis Therapy(25-28)



Therefore, the rationale for development of ustekinumab was to provide a new, highly selective and effective treatment for chronic inflammatory diseases such as psoriasis with a different mode of action than currently available biological therapies. There is a clear unmet medical need for new treatments for a condition where burden of disease is substantial even when skin involvement is not extensive, and is associated

with widespread treatment dissatisfaction(29). A survey of psoriasis patients identified that 40% of patients were frustrated with the ineffectiveness of treatment and that a further 32% felt that the therapies provided for psoriasis were not aggressive enough. In addition, more than half of the patients surveyed were not happy with their treatment(30).

As has been described previously, moderate to severe psoriasis may be treated with a range of products including topical therapy, phototherapy, conventional systemic agents, or biologic therapies, and combinations of these agents are commonly employed, each of which has limitations. Acceptability of many topical therapies is limited and adherence can be poor(31). Phototherapy is effective and generally well tolerated, but inconvenient (2 to 3 treatments weekly), is sometimes unavailable, and its efficacy is rarely sustained over the long-term. Conventional systemic therapies, although effective, are associated with significant toxicities, particularly organ damage with long-term administration.

Biologic therapies are effective and generally well tolerated with currently approved subcutaneous biologic therapies having shown significant efficacy, proportion of subjects achieving ≥ 75% improvement in PASI from baseline (PASI 75 response).

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

Ustekinumab is a fully human monoclonal antibody directed against the p40 subunit of IL-12 and IL-23. By binding to the p40 subunit of IL-12 and IL-23, ustekinumab prevents these cytokines from binding to their cell surface receptors on T cells. This prevents the differentiation and clonal expansion of Th1 and Th17 T cell subsets due to the absence of the IL-12/IL-23 "third signal" of T cell activation and differentiation(25;28). Down-regulation of inflammatory cytokines such as TNF-α, IFN-γ, IL-17 and IL-22 breaks the vicious circle of psoriatic plaque development and maintenance(15;26).

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

Ustekinumab is a treatment option for moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA. In practice, we believe ustekinumab should be a treatment option in patients who meet the above criteria and who have a PASI ≥10 and DLQI >10. This is in line with the current NICE recommendations for the use of etanercept and adalimumab and we anticipate that ustekinumab would be an alternative to these two agents.

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

We are not aware of any specific issues relating to the use of this technology.

4.6 Provide details of any relevant guidelines or protocols.

National guidelines

In the UK, the British Association of Dermatologists (BAD) guidelines on the management of patients with psoriasis are widely accepted(6). This guidance was last updated in 2006. The BAD also published guidelines for the use of biological therapies in psoriasis in 2005(8). The guidelines state that eligible patients for treatment with etanercept, efalizumab or infliximab should have severe disease defined by a PASI ≥10 and a DLQI >10, which should have been severe for at least 6 months. Additionally, patients should fulfil at least one of the following criteria:

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

Treatment should be initiated and monitored by consultant dermatologists experienced in managing difficult psoriasis. This should include knowledge and experience of standard therapies and management of those who fail to respond. They must be familiar with and/or have access to healthcare professionals trained in the use of the tools recommended for determining treatment eligibility and disease response. Supervising consultants will be responsible for ensuring that all patients receiving therapy are registered with the BAD Biological Intervention Register (BADBIR) throughout the treatment period(8).

HTA guidance in England & Wales

NICE has issued guidance on the following treatments in psoriasis:

- Efalizumab, and etanercept T103(22). Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly, is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met:
    - The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10.
    - The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments.

Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either:

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

Efalizumab, within its licensed indications, is recommended for the treatment of adults with plaque psoriasis under the circumstances detailed as for etanercept only if their psoriasis has failed to respond to etanercept or they are shown to be intolerant of, or have contraindications to, treatment with etanercept. Further treatment with efalizumab is not recommended in patients unless their psoriasis has responded adequately at 12 weeks. It is recommended that the use of etanercept and efalizumab for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. If a person has both psoriasis and psoriatic arthritis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

- Infliximab TA134(23). Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met:
  - The disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18.
  - The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant to or has a contraindication to these treatments.

  Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either:
  - a 75% reduction in the PASI score from when treatment started (PASI 75) or
  - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.

- Adalimumab TA146(24). Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met:
  - The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10.
  - The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant of, or has a contraindication to, these treatments.

  Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started, or

- a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment.

HTA guidance in Scotland

The Scottish Medicines Consortium (SMC) has issued guidance on the use of adalimumab, efalizumab and infliximab:

- Adalimumab (Humira®) 40 mg solution for injection is accepted for restricted use within NHS Scotland for treatment of chronic plaque psoriasis in adult patients who failed to respond to or have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA(32)

- Efalizumab (Raptiva®) was not recommended for use in NHS Scotland(33), however, the NICE Multiple Technology Appraisal guidance supersedes this negative guidance(22)

- Infliximab (Remicade®) is accepted for restricted use within NHS Scotland for the treatment of severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapy including ciclosporin, methotrexate or psoralen ultraviolet A (PUVA)(34).

Janssen-Cilag is not aware of any other guidelines or protocols in the UK, other than the aforementioned, that would be relevant to the current submission.

5 Equity and equality

5.1 *Identification of equity and equalities issues*

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

We have identified one issue relating to weight based dosing recommended in the SmPC. We discuss this issue and our response in more detail below.

The published literature has commonly linked psoriasis with higher weight(35;36) with psoriasis patients being on average heavier than the general population(37). The estimate of the percentage of psoriasis patients who are over 100kg varies from 17% to 20% based on two database studies both conducted in the UK (see Appendices 5 and 6). When treating with some biologics, the weight of a patient will influence the amount of drug administered (e.g. the dosing for infliximab is 5mg/kg).

Administration of the appropriate dose of ustekinumab will require an assessment of a patient's weight. The recommended posology of ustekinumab is an initial dose of 45mg administered subcutaneously at week 0, followed by a 45mg dose at week 4, then every 12 weeks thereafter. For patients with a body weight >100 kg the dose is 90mg administered subcutaneously at week 0, followed by a 90mg dose at week 4, then every 12 weeks thereafter (see section 5.1). In patients weighing >100 kg, 45mg was also shown to be efficacious. However, 90mg resulted in greater efficacy in these patients. Ustekinumab is supplied as vials of 45mg and thus the higher dose requires additional vials and a potential doubling of the drug acquisition cost (based on list price).

How has the analysis addressed these issues?

The agreed patient access scheme for the ustekinumab 90mg dose has been incorporated into the cost-effectiveness analysis as well as the budgetary impact analysis. In section 7, the base case cost-effectiveness analysis for ustekinumab overall, weighted by the percentage of patients ≤100kg and >100kg, are presented, based on efficacy analyses for patients over 100kg who were randomised to the 90mg dose and patients at or below 100kg who were randomised to the 45mg. This is consistent with the recommendations of the SmPC and should reflect the use of ustekinumab in clinical practice. In addition, two scenario analyses are also presented for the weight based dosing and also on the primary ITT analysis. In both of these scenario analyses the cost-effectiveness of both the 45mg and 90mg doses are presented separately to provide a transparent estimate of the cost-effectiveness of ustekinumab with tight alignment to the recommendations made within the SmPC.

6 Clinical evidence

6.1 *Identification of studies*

A full systematic review of the clinical effectiveness of ustekinumab in moderate to severe psoriasis has been conducted. The aim of this review was to assess the best available evidence to evaluate the efficacy and safety of tumour necrosis factor (TNF) inhibitors, T-cell target therapy and the IL-12 and IL-23 antibody ustekinumab in patients with moderate to severe psoriasis. The evidence base for ustekinumab is discussed in the following sections, whilst a meta-analysis of comparator medications presented in section 6.5 and 6.6. Eligible studies were English language placebo or head to head randomised controlled trials (RCTs) with ustekinumab administered as monotherapy or in combination with other agents. Study eligibility was determined by three reviewers, who used abstracts of publications and full papers when necessary.

A comprehensive literature search of electronic databases [MEDLINE (via PubMed) and Embase (via Ovid)] was performed for all studies published between 1st January 1995 and 19th September 2008, the search cut-off date. In addition, the Cochrane Library was searched for any recent systematic review on the subject, as a source of further references. The source of data was limited to randomised controlled trials published in English since 1995.

For any clinical trials in progress, the following sites were searched:

- Cochrane Central Register of Controlled Trials (accessed via the Cochrane website)
- www.centerwatch.com
- www.controlled-trial.com
- www.clinicaltrials.gov

Full details of the search strategies are reported in Appendix 2.

A manual check of the reference lists of all accepted studies and of recent reviews and meta-analyses was performed to supplement the above searches and ensure optimal and complete literature retrieval.

Furthermore, the abstracts from the annual proceedings of the following meetings between 2005 and 2008 were searched for eligible studies that were not yet published as full papers:

- American Academy of Dermatology (AAD)
- Society for Investigative Dermatology (SID)
- European Academy of Dermatology & Venereology (EADV)
- International Congress on Psoriasis (ICP)

Identification of included studies

Two levels of study screening were performed. Level I screening was performed on abstracts downloaded from the literature searches noted above. At Level I screening, any study with a definite exclusion criterion was rejected. If no definite exclusion criterion was identified, then the full paper was retrieved for closer review. Level II screening was then applied to full papers. None of the exclusion criteria and all of the

protocol-specified inclusion criteria had to be present for studies to pass Level II screening.

Data and outcomes of interest

The main efficacy outcome of interest was:

- Psoriasis Area and Severity Index (PASI) 50, 75, and 90 response

In addition, the following efficacy outcomes were also of interest:

- Physician Global Assessment (PGA)
- PGA 'cleared' or 'minimal' response (PGA 0 or 1)

The Quality of Life (QoL) outcomes of interest were:

- Dermatology Life Quality Index (DLQI)
- SF-36 total: mental and physical domain scores were collected whenever available.

Data extraction and validity assessment

For each eligible study that passed Level II screening, data elements of interest were extracted on data extraction forms (DEFs) developed specifically for use in this project. One investigator extracted the data from each study, and then a second reviewer (a physician) independently reviewed each DEF against the original paper for completeness and accuracy. Any discrepancies in extracted data were resolved by a consensus conference between the two investigators, with a third party arbitrating disagreements as necessary.

At the time of data extraction, the quality of each RCT was scored using an instrument developed by Jadad(38) which assigns quality points based on three reported methodological features of the trial: randomisation method, blinding procedures, and accounting for withdrawals. The range of possible scores is 0–5, with higher scores representing higher quality. The QUORUM statement and checklist was also applied.

Further details on the search strategy and outcomes are shown in Appendix 2, section 9.2.

6.2 *Study selection*

6.2.1 Complete list of RCTs

The systematic review reported in section 6.1 identified one Phase II and two Phase III randomised placebo-controlled trials for ustekinumab in moderate to severe psoriasis (T04(39), PHOENIX 1(40) and PHOENIX 2(41)). In addition one head to head randomised controlled trial for ustekinumab was identified (ACCEPT(42)). A summary of the Phase III trials is shown in table 6.2.1.

6.2.2 Inclusion and exclusion criteria

Inclusion criteria

- A population of adult patients with psoriasis
- Study design: placebo-controlled or active comparator-controlled RCT with at least one arm randomised to treatment with ustekinumab as monotherapy or in combination with other agents
- Treatment duration of at least 6 weeks
- Reporting at least one efficacy and/or safety outcome
- For studies reported only in abstract form (AAD, SID, EADV, and ICP proceedings), the same inclusion and exclusion criteria must be satisfied as for full papers.

Exclusion criteria

- Animal or in vitro studies
- Study designs other than RCTs
- Publications before 1995
- Languages other than English
- Pharmacokinetic or pharmacodynamic studies
- Dose finding studies without a placebo arm
- Studies of non-psoriatic patients or studies with mixed populations in which outcomes for psoriatic patients are not reported separately
- Therapies other than ustekinumab
- Any study which has one or more arms of <50 participants
- Intended treatment duration less than 6 weeks.

6.2.3 List of relevant RCTs

Results from the two placebo-controlled PHOENIX trials have been published in the Lancet in 2008(40;41). The head to head ACCEPT trial was presented at the European Academy of Dermatology & Venereology (EADV) in September 2008(42).

The results from the T04 trial have not been included due to the different dosing regimens used within this trial which are not included in the SmPC.

A summary of the relevant clinical trials for ustekinumab is given in table 6.2.1 below.

Table 6.2.1: Summary of ustekinumab clinical trials

Study ID **Number of Centres/Locations** **Duration** **Total Enrolment**	**Design, Control Type**	**Treatment arms** **Dose, Route and Regimen**	**Study Objective**	**Number of Subjects by Treatment Arm Entered**	**Diagnosis** **Inclusion Criteria**	**Primary Endpoints**
Randomised controlled studies against supportive care (placebo)						
PHOENIX-1 (T08)(40) 48: USA, Canada, Belgium n=766	Phase III, parallel, double-blind, randomised, placebo-controlled	Ustekinumab: 45mg sc at weeks 0 and 4, then every 12 weeks thereafter 90mg sc at weeks 0 and 4, then every 12 weeks thereafter Placebo: Given at weeks 0 and 4, then crossover to ustekinumab 45mg sc (50%) or 90mg sc (50%) at weeks 12 & 16 and every 12 weeks thereafter Trial length is 5 years	Efficacy and safety	Ustekinumab 45mg n=255 Ustekinumab 90mg n=256 Placebo n=255	Adult patients with moderate to severe plaque psoriasis for ≥ 6 months; ≥ 10% BSA lesion, PASI ≥ 12; have received prior systemic therapy or were candidates for such therapy	Proportion of patients achieving ≥75% improvement in PASI at week 12
PHOENIX-2 (T09)(41) 70: Europe & North America (Austria, Canada, France, Germany, Switzerland, UK, USA) n=1,230	Phase III, parallel, double-blind, randomised, placebo-controlled	Ustekinumab: 45mg sc at weeks 0 and 4, then every 12 weeks thereafter 90mg sc at weeks 0 and 4, then every 12 weeks thereafter Placebo:	Efficacy and safety	Ustekinumab 45mg n=409 Ustekinumab 90mg n=411 Placebo n=410	Adult patients with moderate to severe plaque psoriasis for ≥ 6 months; ≥ 10% BSA lesion, PASI ≥ 12; have received prior systemic therapy or were candidates for such therapy	Proportion of patients achieving ≥75% improvement in PASI at week 12

		Given at weeks 0 and 4, then crossover to ustekinumab 45mg (50%) or 90mg (50%) at week 12 Trial length is 5 years				
Randomised controlled studies against other biological agents						
ACCEPT (T12)(42) 67: Austria, Belgium, Canada, Denmark, Finland, Germany, the Netherlands, the United Kingdom and the USA n=903	Phase III, parallel, randomised, controlled	Ustekinumab: 45mg sc at weeks 0 and 4 90mg sc at weeks 0 and 4 Patients not achieving an appropriate response by week 16 were given an additional dose of ustekinumab while those patients achieving response were only re-treated with two doses of ustekinumab 4 weeks apart when the response decreased Etanercept: 50mg sc twice weekly for first twelve weeks then discontinued treatment until loss of response then placed on ustekinumab 90mg sc at weeks 0 and 4 Trial length is 64 weeks	Efficacy and safety	Ustekinumab 45mg n=209 Ustekinumab 90mg n=347 Etanercept n=347	• Age ≥18 years • Diagnosis of plaque psoriasis for at least 6 months • Candidate for phototherapy or systemic therapy • Failure to respond to, or had a contraindication to, or intolerant to ciclosporin A, methotrexate, or PUVA • Baseline PASI ≥12 • BSA ≥10%	Proportion of patients achieving ≥75% improvement in PASI at week 12

6.2.4 List of relevant non-randomised controlled trials

There are no non-randomised studies included in this submission.

6.2.5 Ongoing studies

The PHOENIX-1 and PHOENIX-2 studies are ongoing with a planned follow-up duration of 5 years. The ACCEPT trial is a 64-week study and is also ongoing.

6.3 *Summary of methodology of relevant RCTs*

Summary information on the three Phase III ustekinumab clinical trials (PHOENIX-1 (T08), PHOENIX-2 (T09) and ACCEPT(T12)) are given in Table 6.3.1 below.

Details of methodology include the following:

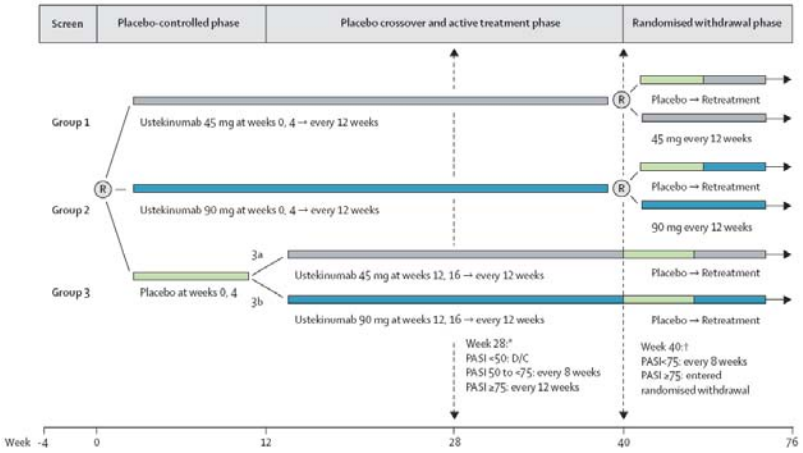
- Methods (study duration, blinding, randomisation, details of interventions and a study description)
- Participants (baseline characteristics and inclusion and exclusion criteria)
- Patient numbers (number of patients eligible to enter the study and CONSORT flow chart)
- Outcomes (primary and secondary outcomes, measures used, description of outcomes with relevance to the decision problem)
- Statistical analysis and definition of study groups (hypotheses, sample size calculation and statistical analysis)
- Critical appraisal of trials (allocation concealment, randomisation techniques, justification of sample size and adequacy of follow-up)

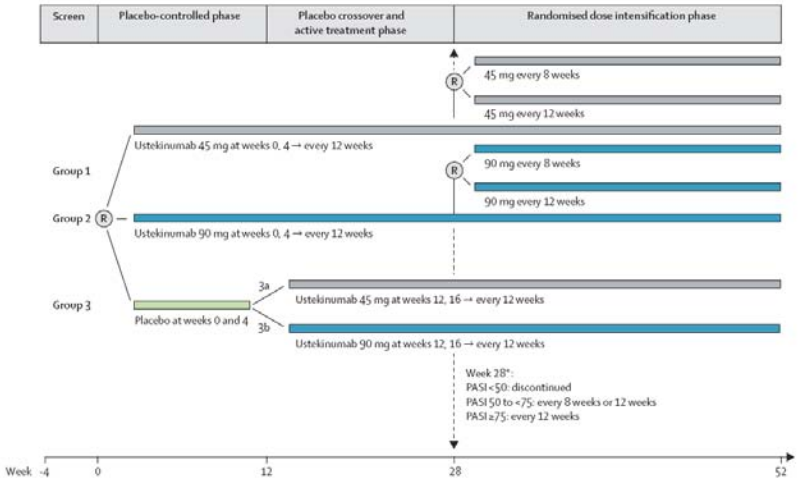
All patient results from the randomised phases of the PHOENIX-1 (T08) and PHOENIX-2 (T09) studies have been published in peer reviewed journals(40;41) and the data on these studies given in this submission have been taken from the published articles where possible. The ACCEPT (T12) study has not yet been published in a peer reviewed journal, although data have been presented in the form of a poster presented at the European Academy of Dermatology and Venereology (EADV) Congress in Paris on 17-21 September 2008(42). Data from this study have been extracted from the poster and clinical study report; specific reference to the clinical study reports will be made where this is the data source. Where data that directly relate to the decision problem are not available in the literature the clinical study reports have been used for reference.

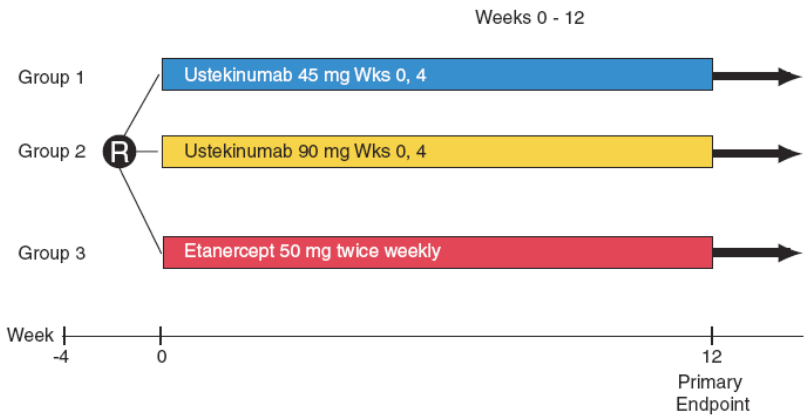
6.3.1 Methods

The clinical trials methodologies are summarised in table 6.3.1.

6.3.1 Methods

Study	Intervention/Duration	Study type/Design	Randomisation Method	Blinding Method
PHOENIX-1(T08)(40;43)	Ustekinumab: 45mg sc at weeks 0 and 4, then every 12 weeks thereafter 90mg sc at weeks 0 and 4, then every 12 weeks thereafter Placebo: Given at weeks 0 and 4, then crossover to ustekinumab 45mg (50%) or 90mg (50%) at weeks 12 & 16 and every 12 weeks thereafter	Phase III, parallel, double-blind, randomised, placebo-controlled study conducted at 48 sites in Canada, the USA and Belgium to evaluate long-term efficacy and safety of ustekinumab versus placebo. Patients receiving ustekinumab at week 0 and who achieved long-term response (PASI 75 at Weeks 28 and 40) were re-randomised at week 40 to maintenance therapy with ustekinumab or withdrawal from treatment until loss of therapeutic effect.  	Patients were randomly assigned on a 1:1:1 ratio to either ustekinumab 45mg, 90mg or placebo using a biased-coin minimisation assignment via centralised interactive voice response system. Randomisation stratified by site, weight of patient (≤90kg or >90kg) and whether the patient had an inadequate response, intolerance, or contraindication to less than three or more than three conventional systemic therapies. Randomised withdrawal phase At week 40 where patients achieving ≥75% improvement in PASI at Weeks 28 and 40 were re-randomized to continue ustekinumab at 12 week intervals or placebo. Subjects randomized to placebo re-initiated ustekinumab at their original randomized dose when they lost at least 50% of their PASI improvement. Randomisation stratified by site and weight of patient (≤90kg or >90kg)	The site monitors, investigators, and site personnel associated with the conduct of the study and subjects in the study are blinded to treatment assignment until the week 76 database is finalised and locked. To maintain the blinding, all administrations were to be given as 2 SC injections, 1 syringe containing 0.5 mL and 1 syringe containing 1.0mL of study agent. Unblinding of treatment information for individual subjects was allowed for specific safety reasons and required a request from the investigator on an individual subject basis

PHOENIX-2 (T09)(41;44)	Ustekinumab: 45mg sc at weeks 0 and 4, then every 12 weeks thereafter 90mg sc at weeks 0 and 4, then every 12 weeks thereafter Placebo: Given at weeks 0 and 4, then crossover to ustekinumab 45mg (50%) or 90mg (50%) at week 12 Duration of study 52 weeks	Phase III, parallel, double-blind, randomised, placebo-controlled trial conducted at 70 sites in Europe and North America (Austria, Canada, France, Germany, Switzerland, UK, USA) to evaluate long-term efficacy and safety of ustekinumab versus placebo. Partial responders were re-randomised at week 28 to continue dosing every 12 weeks or to escalate dosing to every 8 weeks.  	Patients were randomly assigned to either placebo or ustekinumab 45mg or 90mg on a 1:1:1 ratio using a biased-coin minimisation assignment via centralised interactive voice response system. Randomisation stratified by site and weight of patient (≤90kg or >90kg) and whether the patient had an inadequate response, intolerance, or contraindication to less than three or more than three conventional systemic therapies. Dose intensification phase at week 28 where patients achieving partial response (≥50%<75% improvement in PASI) were re-randomised to continue at 12 week intervals or intensified intervals every 8 weeks. Randomisation stratified by site and weight of patient (≤90kg or >90kg)	The site monitors, investigators, site personnel associated with the conduct of the study and subjects in the study were blinded to treatment assignment until the Week 52 database is locked and finalised. To maintain the blind, all administrations were to be given as 2 SC injections, 1 syringe containing 0.5 mL and 1 syringe containing 1.0 mL of study agent.
ACCEPT (T12)(42;45)	Ustekinumab: 45mg sc at weeks 0 and 4 90mg sc at weeks 0 and 4 Etanercept: 50mg sc twice weekly for first twelve weeks then discontinued treatment until loss of response then	Randomised, active controlled, parallel three-arm study to compare the efficacy and safety of ustekinumab and etanercept in moderate to severe psoriasis patients.	Patients were randomised in a 3:5:5 ratio to receive ustekinumab 45 mg, ustekinumab 90 at weeks 0 and 4 or etanercept 50 mg twice weekly through to week 12 Please note: Patients were randomised to a 3:5:5 (ustekinumab 45mg:	The different formulations of etanercept prevented development of etanercept placebo to allow a double-dummy blinded design. Maintaining the blind of the blinded efficacy evaluator (BEE) to

	placed on ustekinumab 90mg sc at weeks 0 and 4, then every 12 weeks thereafter		ustekinumab 90mg:etanercept 50mg twice weekly) ratio in the trial design of the ACCEPT trial. The initial hypothesis was to test non-inferiority between the etanercept 50mg twice weekly and the ustekinumab 45mg dose and superiority between the etanercept 50mg twice weekly and the ustekinumab 90mg dose. In consideration of the requirements of the HTA organisations such as NICE, a decision was made during the study to test superiority between the etanercept 50mg twice weekly and the ustekinumab 45mg dose as well. Instead of changing the 3:5:5 randomisation ratio, the total sample size of the trial was increased to meet statistical power. It is important to note that this trial design change was not due to interim analysis (no interim analysis was conducted) and all subjects remained blinded throughout the trial.	treatment assignment was critical to the integrity of the study. This was done on multiple levels. The interactions between the subjects, all of whom were unblinded to study treatment, and the BEEs were structured so as to preclude discussion between the subjects and the efficacy evaluators. The evaluators performing the safety evaluations, the blinded safety evaluators (BSEs), were also blinded to study treatment. The principal investigator at each site, who may have served as either the BEE or BSE, was also blinded.

6.3.2 Participants

Study	Inclusion Criteria	Exclusion criteria	Baseline Demographics and Disease Characteristics			
PHOENIX-1 (T08)(40;43)	• Age ≥18 years • Diagnosis of plaque psoriasis for at least 6 months • Candidate for phototherapy or systemic therapy • Baseline PASI ≥12 • BSA ≥10%	• Non-plaque psoriasis • Recent serious systemic or local infection • History or symptoms of active tuberculosis, or known malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years) within the previous 5 years • Prior treatment with any biological or investigational agent within the previous 3 months or 5 drug half-lives • Prior treatment with any agent	**Characteristic**	**Ustekinumab 45mg (n=255)**	**Ustekinumab 90mg (n=256)**	**Placebo (n=255)**
			Age -years	44.8 (12.5)	46.2 (11.3)	44.8 (11.3)
			Male sex – no. (%)	175 (68.6)	173 (67.6)	183 (71.8)
			Weight - kg	93.7±23.8	93.8±23.9	94.2±23.5
			Duration of psoriasis - years	19.7±11.7	19.6±11.1	20.4±11.7
			Involved body surface area - %	27.2±17.5	25.2±15.0	27.7±17.4
			Physicians global assessment – marked or severe (%)*	114 (44.7)	109 (42.6)	112 (43.9)
			PASI score	20.5±8.6	19.7±7.6	20.4±8.6
			DLQI score	11.1±7.1	11.6±6.9	11.8±7.4
			Patient with psoriatic arthritis (%)	74 (29.0)	94 (36.7)	90 (35.3)
			Patients treated previously – no. (%)			
			Topical agent†	245 (96.1)	239 (93.4)	242 (94.9)
			Phototherapy‡	173 (67.8)	169 (66.0)	150 (58.5)
			Conventional systemic therapy§	141 (55.3)	141 (55.1)	142 (50.2)
			Biological therapy¶	134 (52.5)	130 (50.8)	128 (50.2)
			Patients with latent tuberculosis (%)¤	8 (3.1)	7 (2.7)	10 (3.9)
			Plus-minus data are Mean±SD. * Rated as cleared (0), minimal (1), mild (2), moderate (3), marked (4), or severe (5). † Patients had to have discontinued topical therapies (except moisturisers and shampoos) 2 weeks, conventional systemic therapy 4 weeks and biological agents at least 3 months before randomisation ‡ Includes UVB. § Includes PUVA, methotrexate, acitretin and ciclosporin ¶ Includes etanercept, alefacept, efalizumab, infliximab or adalimumab. ¤ Latent tuberculosis was identified by a purified protein derivative test without evidence of active tuberculosis			

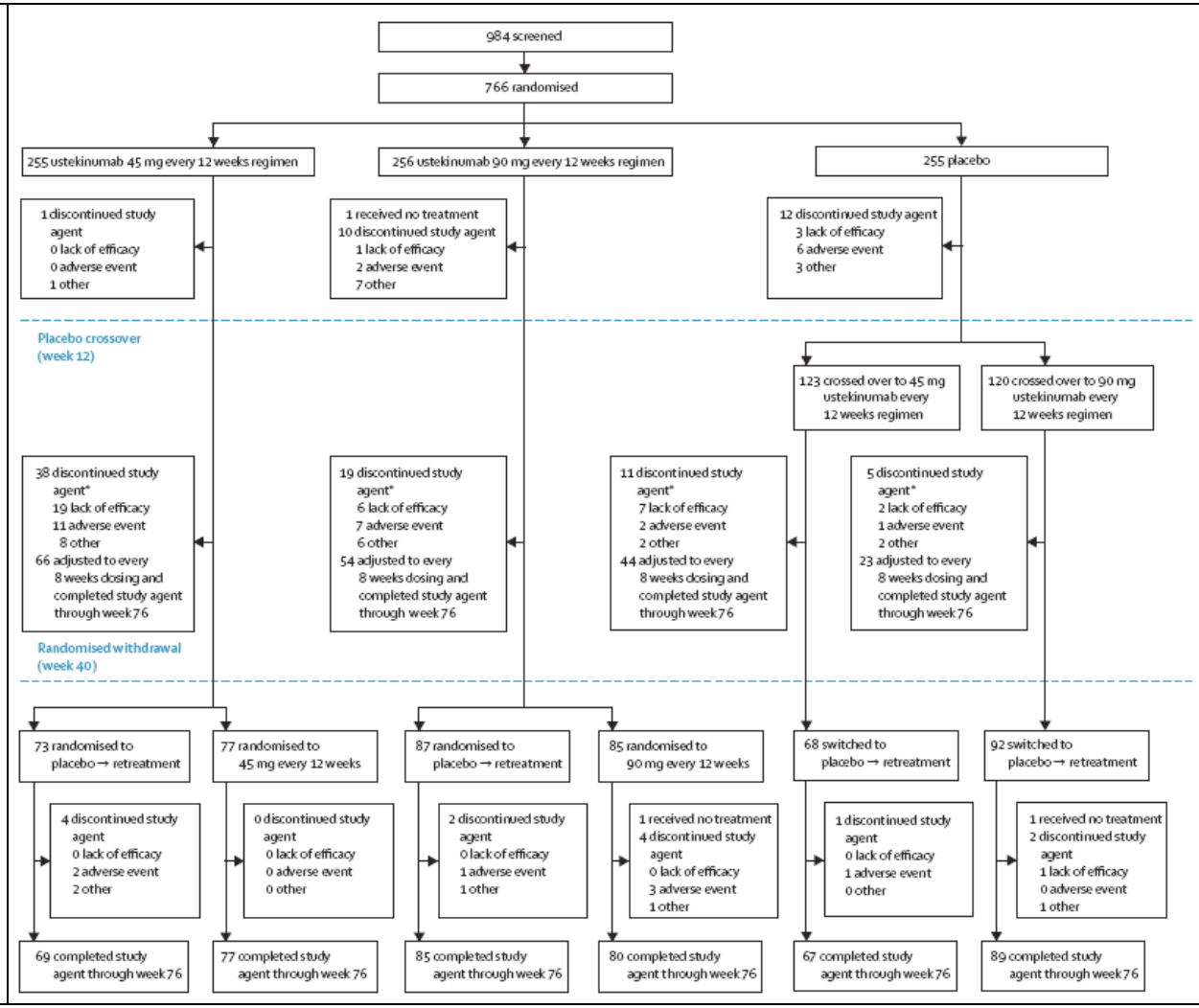
<table>
<tr><td></td><td></td><td>specifically targeting IL-12/23
• Conventional systemic or phototherapy within the last 4 weeks
• Topical therapy within the last 2 weeks</td><td colspan="4">As the table above shows, baseline demographics and patient characteristics were well balanced amongst all three study groups.</td></tr>
<tr><td rowspan="20">PHOENIX-2 (T09)(41;44)</td><td rowspan="20">• Age ≥18 years
• Diagnosis of plaque psoriasis for at least 6 months
• Candidate for phototherapy or systemic therapy
• Baseline PASI ≥12
• BSA ≥10%</td><td rowspan="20">• Non-plaque psoriasis
• Recent serious systemic or local infection
• History or symptoms of active tuberculosis, or known malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years) within the previous 5 years
• Prior treatment with any biological or</td><td>Characteristic</td><td>Ustekinumab 45mg (n=409)</td><td>Ustekinumab 90mg (n=411)</td><td>Placebo (n=410)</td></tr>
<tr><td>Age -years</td><td>45.1 (12.1)</td><td>46.6 (12.1)</td><td>47.0 (12.5)</td></tr>
<tr><td>Male sex – no. (%)</td><td>283 (69.2)</td><td>274 (66.7)</td><td>283 (69.0)</td></tr>
<tr><td>Weight - kg</td><td>90.3±21.0</td><td>91.5±21.3</td><td>91.1±21.6</td></tr>
<tr><td>Duration of psoriasis - years</td><td>19.3±11.7</td><td>20.3±12.3</td><td>20.8±12.2</td></tr>
<tr><td>Involved body surface area - %</td><td>25.9±15.5</td><td>27.1±17.4</td><td>26.1±17.4</td></tr>
<tr><td>Physicians’ global assessment – marked or severe (%)</td><td>169 (41.3)</td><td>159 (38.7)</td><td>160 (39.0)</td></tr>
<tr><td>PASI score</td><td>19.4±6.8</td><td>20.1±7.5</td><td>19.4±7.5</td></tr>
<tr><td>DLQI score</td><td>12.2±7.1</td><td>12.6±7.3</td><td>12.3±6.9</td></tr>
<tr><td>Patient with psoriatic arthritis (%)</td><td>107 (26.2)</td><td>94 (22.9)</td><td>105 (25.6)</td></tr>
<tr><td colspan="4">Patients treated previously – no. (%)</td></tr>
<tr><td>Topical agent†</td><td>393 (96.1)</td><td>384 (93.4)</td><td>396 (96.6)</td></tr>
<tr><td>Phototherapy‡</td><td>286 (69.9)</td><td>267 (65.0)</td><td>276 (67.3)</td></tr>
<tr><td>Conventional systemic therapy§</td><td>223 (54.5)</td><td>224 (54.5)</td><td>241 (58.8)</td></tr>
<tr><td>Biological therapy¶</td><td>157 (38.4)</td><td>150 (36.5)</td><td>159 (38.8)</td></tr>
<tr><td>Patients with latent tuberculosis (%)¤</td><td>16 (3.9)</td><td>16 (3.9)</td><td>11 (2.7)</td></tr>
</table>

<table>
<tr><td></td><td></td><td>investigational agent within the previous 3 months or 5 drug half-lives
• Prior treatment with any agent specifically targeting IL-12/23
• Conventional systemic or phototherapy within the last 4 weeks
• Topical therapy within the last 2 weeks</td><td colspan="4">Plus-minus data are Mean±SD.
† Patients had to have discontinued topical therapies (except moisturisers and shampoos) 2 weeks, conventional systemic therapy 4 weeks and biological agents at least 3 months before randomisation
‡ Includes UVB.
§ Includes PUVA, methotrexate, acitretin and ciclosporin
¶ Includes etanercept, alefacept, efalizumab, infliximab or adalimumab.
¤ Latent tuberculosis was identified by a purified protein derivative test without evidence of active tuberculosis</td></tr>
<tr><td></td><td></td><td></td><td colspan="4">As the table above shows, baseline demographics and patient characteristics were well balanced amongst all three study groups.</td></tr>
<tr><td>ACCEPT (T12)(42;45)</td><td>• Age ≥18 years
• Diagnosis of plaque psoriasis for at least 6 months
• Candidate for phototherapy or systemic therapy
• Failure to respond to, or had a contraindication to, or intolerant to ciclosporin A, methotrexate, or PUVA
• Baseline PASI ≥12
• BSA ≥10%</td><td>• History or symptoms of active tuberculosis or known malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no</td><td colspan="4"><table>
<tr><th>Characteristic</th><th>Etanercept 50mg (n=347)</th><th>Ustekinumab 45mg (n=209)</th><th>Ustekinumab 90mg (n=347)</th></tr>
<tr><td>Age –years*</td><td>45.7 (45.0)</td><td>45.1 (45.0)</td><td>44.8 (45.0)</td></tr>
<tr><td>Male sex – no. (%)</td><td>246 (70.9)</td><td>133 (63.6)</td><td>234 (67.4)</td></tr>
<tr><td>Weight – kg*</td><td>90.8 (89.0)</td><td>90.4 (87.0)</td><td>91.0 (88.2)</td></tr>
<tr><td>Duration of psoriasis – years*</td><td>18.81 (17.41)</td><td>18.87 (16.71)</td><td>18.74 (17.63)</td></tr>
<tr><td>Involved body surface area - %*</td><td>23.8 (19.0)</td><td>26.7 (20.0)</td><td>26.1 (20.0)</td></tr>
<tr><td>Physicians' global assessment – marked or severe (%)</td><td>148 (42.7)</td><td>98 (46.9)</td><td>144 (41.6)</td></tr>
<tr><td>PASI score*</td><td>18.64 (16.80)</td><td>20.49 (17.00)</td><td>19.87 (17.15)</td></tr>
<tr><td>Patients with psoriatic arthritis (%)</td><td>95 (27.4)</td><td>62 (29.7)</td><td>95 (27.4)</td></tr>
<tr><td colspan="4">* Data are means (medians).</td></tr>
</table></td></tr>
</table>

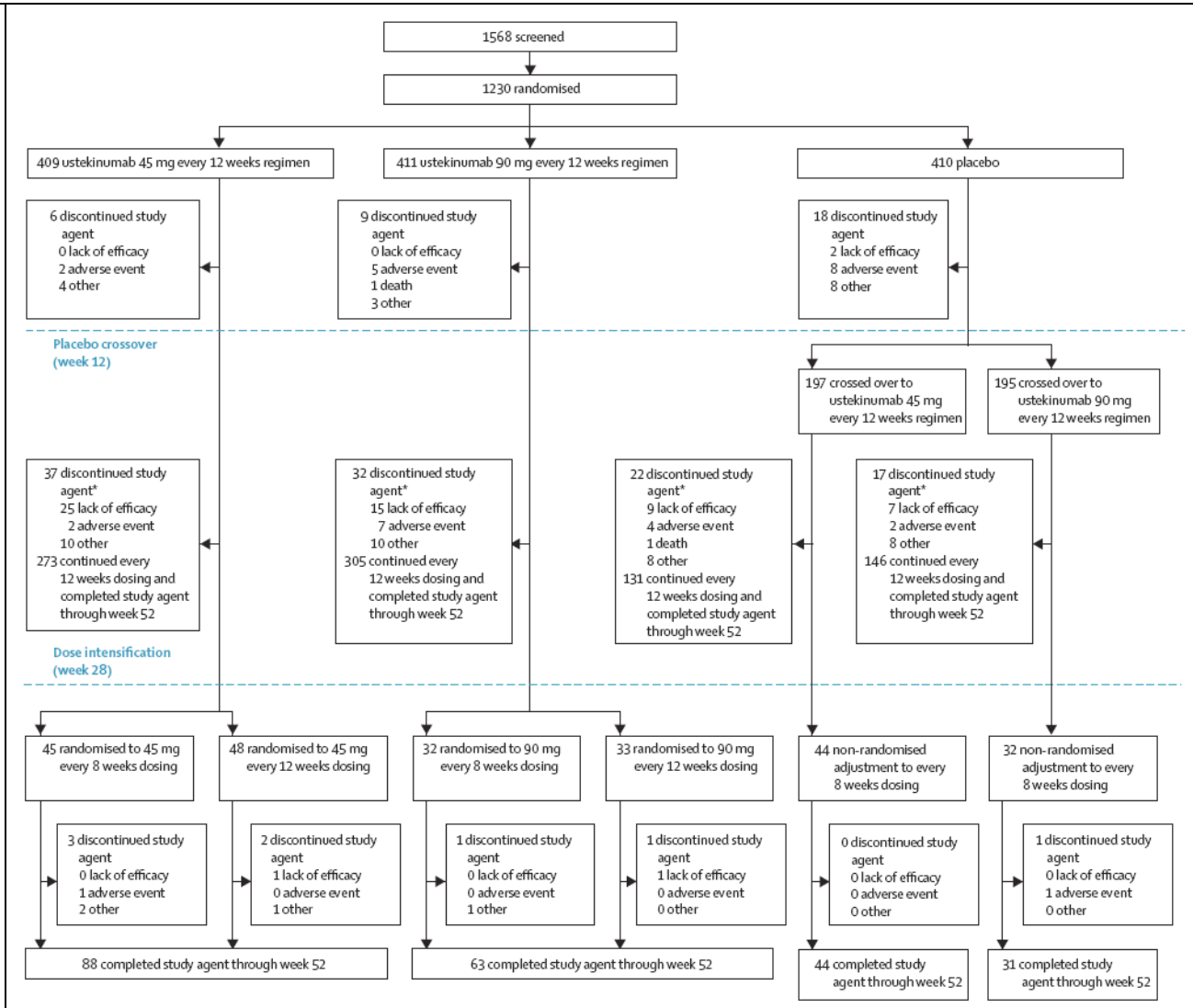
		evidence of recurrence within 5 years) • Prior treatment with any biological or investigational agent within the previous 3 months or 5 drug half-lives • Prior treatment with etanercept or any agent specifically targeting IL-12/23 • Conventional systemic or phototherapy within the last 4 weeks • Topical therapy within the last 2 weeks	As the table above shows, baseline demographics and patient characteristics were well balanced amongst all three study groups.

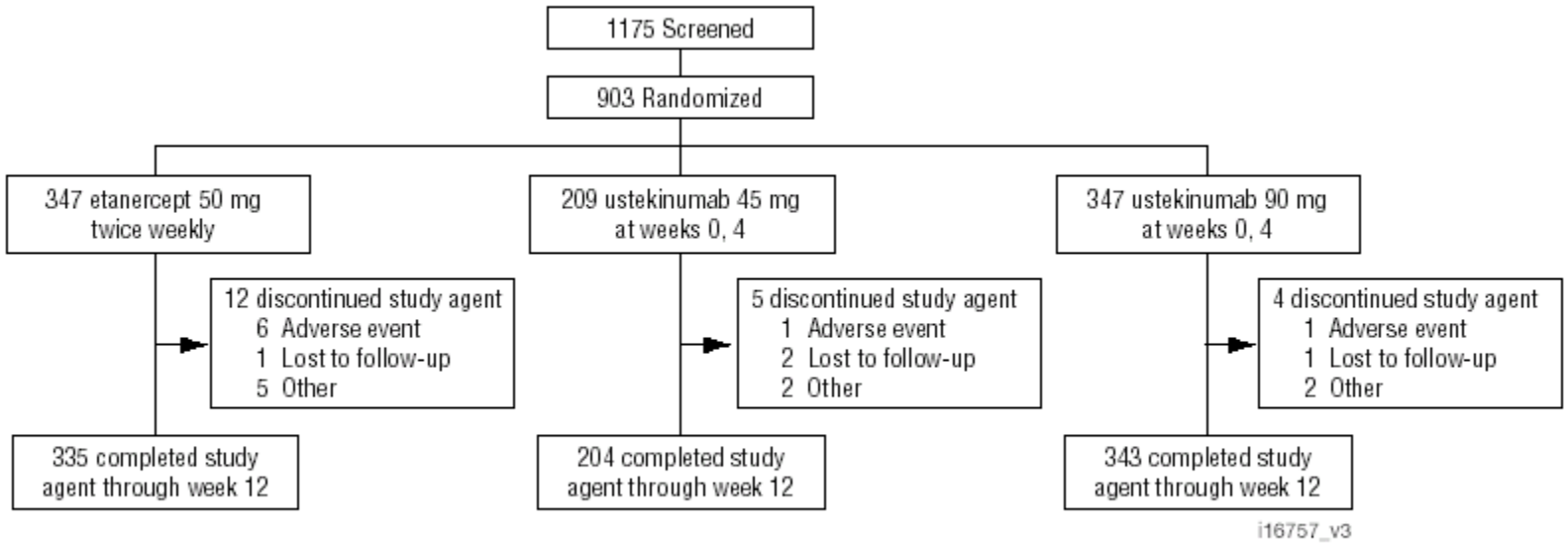
6.3.3 Patient numbers

PHOENIX-1 (T08)(40;43)



PHOENIX-2 (T09)(41;44)



ACCEPT (T12)(42;45)	

6.3.2 Outcomes

Study	
PHOENIX-1 (T08)(40;43)	**Primary outcome measure** • The primary efficacy end point was the proportion of patients achieving at least 75% improvement from baseline in PASI score at week 12. **Secondary outcome measures** • Proportion of patients with a physician's global assessment (PGA) score of "cleared" or "minimal" at 12 weeks • Change in Dermatology Life Quality Index (DLQI) score from baseline at week 12 • Time to loss of PASI 75 response in subjects who continued ustekinumab versus subjects withdrawn from ustekinumab **Other key outcome measures** • Proportion of patients achieving at least 90% improvement from baseline in PASI score at week 12 • Proportion of patients achieving at least 50% improvement from baseline in PASI score at week 12 • SF-36 Please see Appendix 7 for details on outcome measures collected within this trial
PHOENIX-2 (T09)(41;44)	**Primary outcome measure** • The primary efficacy end point was the proportion of patients achieving at least 75% improvement from baseline in PASI score at week 12. **Secondary outcome measures** • Proportion of patients with a physician's global assessment (PGA) score of "cleared" or "minimal" at 12 weeks • Change in Dermatology Life Quality Index (DLQI) score from baseline at week 12 **Other key outcome measures** • Proportion of patients achieving at least 90% improvement from baseline in PASI score at week 12 • Proportion of patients achieving at least 50% improvement from baseline in PASI score at week 12 Please see Appendix 7 for details on outcome measures collected within this trial

ACCEPT (T12)(42;45)	**Primary outcomes measure** • The primary efficacy end point was the proportion of patients achieving at least 75% improvement from baseline in PASI score at week 12. **Secondary outcomes measures** • Proportion of patients with a physician's global assessment (PGA) score of "cleared" or "minimal" at 12 weeks • Proportion of patients achieving at least 90% improvement from baseline in PASI score at week 12 • Weight based analysis: Proportion of patients achieving at least 75% improvement from baseline in PASI score at week 12 **Other key outcome measures** • Proportion of patients achieving at least 50% improvement from baseline in PASI score at week 12 Please see Appendix 7 for details on outcome measures collected within this trial

Psoriasis Area and Severity Index (PASI) - The PASI combines assessments of the extent of body-surface involvement in four anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque thickness in each region, yielding an overall score of 0 (no psoriasis) to 72 (severe disease).

Physician's Global Assessment (PGA) - The physician's global assessment rates the patient's psoriasis overall relative to baseline as 0 (clear), 1 (minimal), 2 (moderate), 3 (marked), or 5 (severe), and considers involvement of body surface area, induration (thickness), scaling, and erythema.

Dermatology Life Quality Index (DLQI) - The 10-item Dermatology Life Quality Index questionnaire, completed by the patient, measures whether psoriasis has an effect on the patient's quality of life, with scores ranging from 0 ("not at all") to 30 ("very much")

Short-Form-36 - A multi-purpose, short-form health survey consisting of 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure of quality of life.

6.3.3 Statistical analysis and definition of study groups

Study	Primary hypothesis	Statistical analyses used for testing this hypothesis	Sample size calculation – rationale and assumptions
PHOENIX-1 (T08)(40;43)	• The primary endpoint for the study was the proportion of subjects who were PASI 75 responders at Week 12	• On the basis of simulation studies in SAS (version 8.02) using Cochran-Mantel-Haenszel χ^2 tests stratified by weight, the trial with 250 patients per group provided more than 99% power to detect at least one pairwise treatment effect in the primary endpoint based on Holm's procedure at an overall 5% level of significance. • To maintain an overall type I error rate of 0·05, the primary and major secondary analyses were done sequentially with each endpoint tested at an alpha	• The study was designed to enrol 750 patients to assess both the primary and major secondary endpoints and to characterise the efficacy and safety of long-term treatment. The sample size calculations took into account the results of the phase II trial T04 and assumed PASI 75 response rates of 50% (≤90 kg) and 40% (>90 kg) in each ustekinumab group and 10% for the placebo group.

Study	Primary hypothesis	Statistical analyses used for testing this hypothesis	Sample size calculation – rationale and assumptions
		level of 0·05. All other statistical tests were two-sided.	
PHOENIX-2 (T09)(41;44)	• The primary endpoint for the study was the proportion of subjects who were PASI 75 responders at Week 12.	• The significance level for the analyses of the primary endpoint and the major secondary endpoints was controlled at 0·05 by sequential tests of the primary endpoint and then the major secondary endpoints. • All other statistical tests were two-sided at a significance level of 0·05. • Dichotomous endpoints were analysed with the Cochran-Mantel-Haenszel test, with site (pooled) and weight (≤90 kg, >90 kg) as stratification factors. • Continuous variables were analysed by an analysis of variance (ANOVA) on the van der Waerden normal scores, with weight as a binary covariate. The Cochran-Mantel-Haenszel test, with a row mean score (integer score) statistic, was used to analyse response in the dose intensification phase. • A post-hoc analysis was conducted to determine the baseline characteristics predictive of the week 28 response (PASI 75 vs. partial responders), in addition to different doses, with stepwise logistic regression at a significance level of 0·1.	• Enrolment was planned for 1,200 patients to assess the primary and major secondary endpoints and the efficacy and safety of long-term treatment. Assuming PASI 75 response rates of 50% and 40%, respectively, in each weight stratum (≤90 kg or >90 kg) for both ustekinumab groups and 10% for the placebo group across weight strata, this study had more than 99% power to determine whether at least one ustekinumab group was effective compared with placebo for the primary endpoint on the basis of Holm's procedure at an overall significance level of 0·05.
ACCEPT (T12)(42;45)	• The primary endpoint for the study was the proportion of subjects who achieved a PASI 75 response at Week 12. • To maintain an overall Type I error rate of 0.05, a stepwise procedure was planned to compare the efficacy of ustekinumab with that of etanercept at Week 12	**1. Ustekinumab 90 mg versus etanercept** • A) To claim the superiority of ustekinumab 90 mg over etanercept, a 2-sided (α = 0.05) CMH chi-square test stratified by weight (< 90 kg or ≥ 90 kg) was performed. If superiority was established, then step 1B would not be conducted and the superiority of ustekinumab 90mg over etanercept would be declared. • B) If superiority was not established in 1A, then a 1-sided (α=0.025) CMH weight adjusted (< 90 kg or ≥ 90 kg) Z-test would be conducted to test the non-inferiority of ustekinumab 90mg to etanercept. If the test for the superiority of ustekinumab 90mg was positive, then the comparison between	The sample size was adjusted from 650 subjects to 850 subjects to power the tests of the superiority of both ustekinumab doses over etanercept with an overall type I error rate of 0.05. The randomisation ratio was maintained at 3:5:5. With 325 subjects each in the ustekinumab 90 mg and etanercept treatment groups, the power to detect a significant treatment effect at α = 0.05 level (2-sided) was calculated for various response rates in each treatment group. Assuming the PASI 75 response rate of the etanercept group is 50%, the complete power to detect a significant treatment difference between ustekinumab 90 mg (n = 325) and etanercept (n = 325) at α = 0.05, and then a significant treatment difference between

Study	Primary hypothesis	Statistical analyses used for testing this hypothesis	Sample size calculation – rationale and assumptions
		ustekinumab 45mg and etanercept would be performed. Otherwise, no claim would be made in step 2. Only the nominal p-value(s) for comparing ustekinumab 45mg and etanercept would be reported. **2. Ustekinumab 45 mg versus etanercept** • A. If the superiority of ustekinumab 90mg over etanercept was established in 1A, then the superiority of ustekinumab 45mg over etanercept would be tested through a 2-sided (α = 0.05) CMH chi-square test stratified by weight (< 90 kg or ≥ 90 kg). If the result was positive, then step 2B would not be conducted and the superiority of ustekinumab 45mg would be declared. Otherwise, the non-inferiority of ustekinumab 45 mg to etanercept would be tested in step 2B. • B. If superiority was not established in 2A, then a 1-sided (α= 0.025) CMH weight adjusted (< 90 kg or ≥ 90 kg) Z-test would be conducted to test the non-inferiority of ustekinumab 45mg to etanercept.	ustekinumab 45 mg (n = 200) and etanercept (n = 325) at α = 0.05, was 87%.

6.3.4 Critical appraisal of relevant RCTs

Critical appraisal	Study assessment		
	PHOENIX-1 (T08)(40;43)	**PHOENIX-2 (T09)(41;44)**	**ACCEPT (T12)(42;45)**
How was allocation concealed?	The site monitors, investigators, and site personnel associated with the conduct of the study, and subjects in the study were to be blinded to treatment assignment until the Week 76 database is finalised and locked. To maintain the blind, all administrations were to be given as 2 SC injections, 1 syringe containing 0.5 mL and 1 syringe containing 1.0 mL of study agent. Unblinding of treatment information for individual subjects was allowed for specific safety reasons and required a request from the investigator on an individual subject basis	The site monitors, investigators, site personnel associated with the conduct of the study and subjects in the study are to be blinded to treatment assignment until the week 52 database is locked and finalised. To maintain the blind, all administrations were to be given as 2 SC injections, 1 syringe containing 0.5 mL and 1 syringe containing 1.0 mL of study agent An unblinding procedure was in place in the event that an investigator felt it was necessary, for safety reasons, to know a subject's treatment group.	This study was open-label, however maintaining the blind of the blinded efficacy evaluators (BEEs) to treatment assignment was critical to the integrity of the study. This was done on multiple levels. The interactions between the subjects, all of whom were unblinded to study treatment, and the BEEs were structured so as to preclude discussion between the subjects and the efficacy evaluators. The evaluators performing the safety evaluations, the blinded safety evaluators (BSEs), were also blinded to study treatment. The principal investigator at each site, who may have served as either the BEE or BSE, was also blinded. The BEEs only assessed efficacy, and did not have access to other subject data The BEEs only had access to efficacy

Critical appraisal	Study assessment		
	PHOENIX-1 (T08)(40;43)	**PHOENIX-2 (T09)(41;44)**	**ACCEPT (T12)(42;45)**
			worksheets while performing the efficacy evaluations. The BSEs assessed causality of all noninjection site-related AEs and provided follow-up on all AEs as appropriate. It was anticipated that study agent treatment assignment for some subjects might become known to blinded site personnel during the trial. Unblinding of the BSEs or BEEs to study agent treatment assignment was captured in the eCRF. All subjects were unblinded to study agent assignment. For subjects randomised to ustekinumab, all site personnel and subjects were blinded to the dose of ustekinumab. To maintain the blind of ustekinumab dose, all subjects who received ustekinumab (45 mg or 90 mg) received 2 SC injections at each administration. All subjects were managed in a similar manner regardless of treatment assignment. Unblinded site personnel were unblinded regarding subject treatment assignment to ustekinumab or etanercept. The unblinded site personnel administered, dispensed, and accounted for study agents; completed exposure data; reviewed Study Diaries and Administration Calendars and entered the data into the eCRF; recorded injection-site reactions; and identified all AEs for referral to the BSE as needed. These rigorous parameters will be kept in place until the Week 64 database lock. Access to eCRF exposure pages was restricted by password to unblinded site personnel. See Appendix 8 for a graphical representation of the blinding within this study
Which randomisation technique was used?	Patients were randomly assigned to either placebo or treatment groups using a biased-coin minimisation assignment via centralised interactive voice response system. The randomisation at week 0 was stratified by investigational site, weight (≤90kg or >90kg), and whether there were < 3 or ≥ 3 conventional therapies (i.e., psoralen plus ultraviolet A light [PUVA], methotrexate, acitretin, and ciclosporin) to	Patients were randomly assigned to either placebo or treatment groups using a biased-coin minimisation assignment via centralised interactive voice response system. Subjects were assigned to a treatment group using a similar adaptive treatment allocation as at week 0, with separate randomisations for each of the 45 mg and 90 mg groups. The randomisation was stratified by investigational site and	Patients were randomly assigned to either ustekinumab 45mg or 90mg or etanercept 50mg using a biased coin minimisation assignment via a centralised interactive voice response system. Subjects were assigned to the treatment group using an adaptive treatment allocation with investigational site and weight (<90kg or ≥90kg) as strata.

Critical appraisal	Study assessment		
	PHOENIX-1 (T08)(40;43)	**PHOENIX-2 (T09)(41;44)**	**ACCEPT (T12)(42;45)**
	which the subject had an inadequate response, intolerance, or contraindication.	baseline weight (≤90kg or >90kg).	
Was a justification of the sample size provided?	Justification has been provided on the sample size. See section 6.3.5	Justification has been provided on the sample size. See section 6.3.5	Justification has been provided on the sample size. See section 6.3.5
Was follow-up adequate?	The follow-up is adequate and did concur with EMEA recommendations	The follow-up is adequate and did concur with EMEA recommendations	The follow-up is adequate and did concur with EMEA recommendations
Were the individuals undertaking the outcomes assessment aware of allocation?	This study was fully blinded and therefore those undertaking the efficacy and safety assessment were not aware of the treatment allocation	This study was fully blinded and therefore those undertaking the efficacy and safety assessment were not aware of the treatment allocation	See the response to 'How was allocation concealed?'
Was the design parallel-group or crossover? Indicate for each trial whether a carry-over effect is likely	Parallel groups for ustekinumab, the placebo group crossed over to ustekinumab 45mg (50%) or 90mg (50%) at weeks 12 & 16 and every 12 weeks thereafter	Parallel groups for ustekinumab, the placebo group crossed over to ustekinumab 45mg (50%) or 90mg (50%) at week 12	Parallel groups up to week 12
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	The study was not conducted in the UK but at 48 sites in the USA, Canada, and Belgium. Clinical practice in these countries is unlikely to differ from UK practice.	The study was conducted at 70 sites in Europe (including the UK, Austria, France, Germany and Switzerland) and North America (Canada and the USA). Clinical practice in these countries is unlikely to differ from UK practice.	The study was conducted in 67 sites in the UK, Austria, Belgium, Canada, Denmark, Finland, Germany, the Netherlands and the USA
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	Patients in this trial were broadly similar in baseline demographics and disease severity to patients in the UK Patients had to be candidates for systemic/biologic therapy.	Patients in this trial were broadly similar in baseline demographics and disease severity to patients in the UK. Patients had to be candidates for systemic/biologic therapy.	Patients in this trial were broadly similar in baseline demographics and disease severity to patients in the UK.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	In this study patients received either 45mg or 90mg of ustekinumab given at weeks 0, 4 and every 12 weeks thereafter. These dosage regimens are within those detailed in the summary of product characteristics.	In this study patients received either 45mg or 90mg of ustekinumab given at weeks 0, 4 and every 12 weeks thereafter. These dose regimens are within those detailed in the summary of product characteristics. Partial responders (i.e., patients achieving ≥50% but <75% improvement from baseline in PASI) were re-randomised at week 28 to continue dosing every 12	In this study patients received ustekinumab at 45mg or 90mg given at weeks 0 and 4. These dosage regimens are within those detailed in the summary of product characteristics.

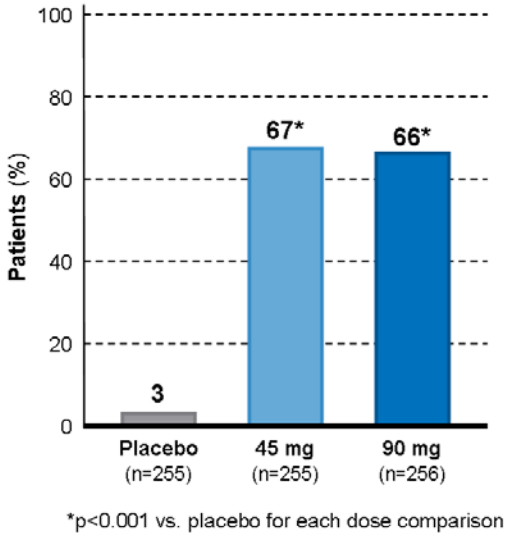
Critical appraisal	Study assessment		
	PHOENIX-1 (T08)(40;43)	**PHOENIX-2 (T09)(41;44)**	**ACCEPT (T12)(42;45)**
		weeks or escalate to dosing every 8 weeks. Escalated dosing every 8 weeks is not within the summary of product characteristics.	
Were the study groups comparable?	Baseline demographics and patient characteristics were well balanced amongst all three study groups.	Baseline demographics and patient characteristics were well balanced amongst all three study groups.	Baseline demographics and patient characteristics were well balanced amongst all three groups
Were the statistical analyses used appropriate?	The statistical analyses used in this study were appropriate.	The statistical analyses used in this study were appropriate.	The statistical analyses used in this study were appropriate.
Was an intention-to-treat analysis undertaken?	An intent-to-treat analysis was undertaken.	An intent-to-treat analysis was undertaken.	An intent-to-treat analysis was undertaken.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	None	None	None

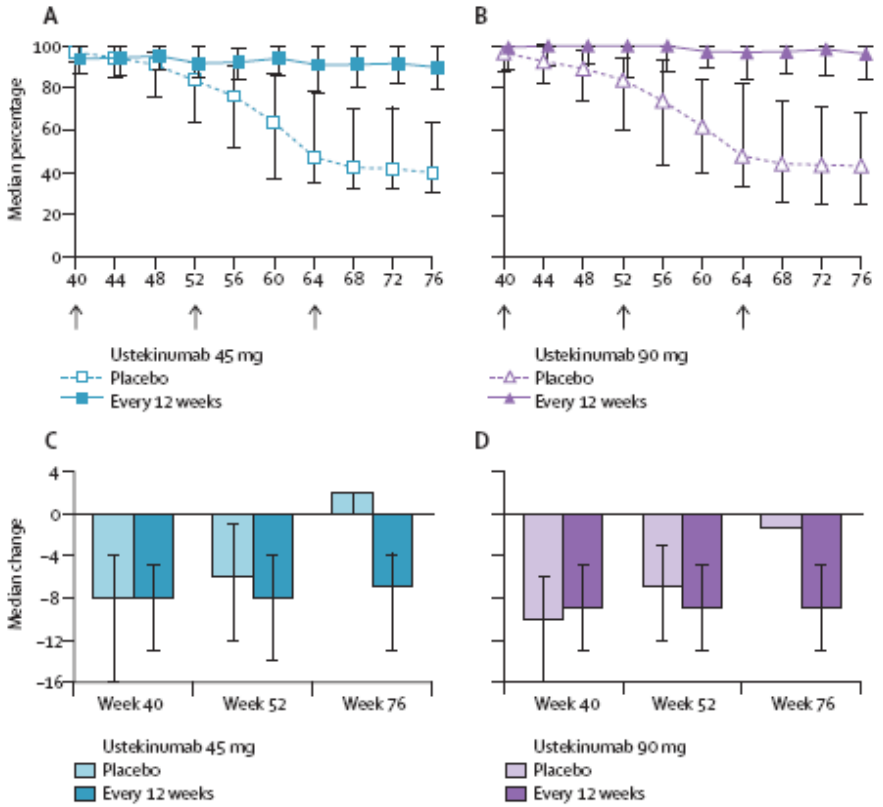
6.4 *Results of the relevant comparative RCTs*

Results from the relevant ustekinumab comparative trials are outlined in tabular form below.

6.4.1 PHOENIX-1 (T08)(40;43)

A total of 766 patients were randomised and 742 were included in the efficacy analysis at week 12. Twenty three patients discontinued the study agent (4 due to lack of efficacy, 8 due to adverse events, 8 for other reasons). The study was conducted between December 2005 and September 2007.

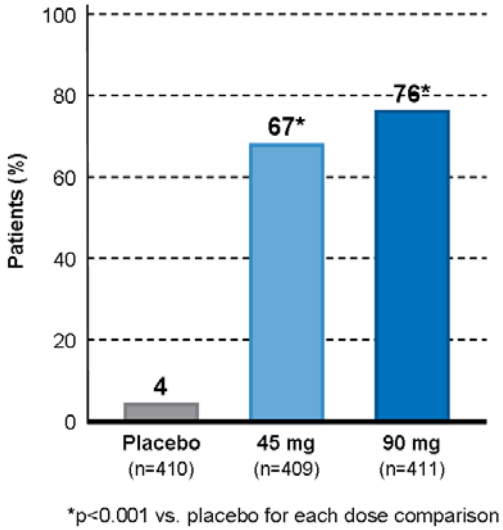
Primary outcome measure	• 67.1% of patients receiving ustekinumab 45mg (n=171/255) and 66% of patients receiving ustekinumab 90mg achieved a PASI 75 response (169/256) versus 3% in the placebo group (8/255) at week 12 (p<0·0001 for 45mg and p<0·0001 for 90mg vs placebo)	

Secondary outcome measures	• At week 12 the Physician's Global Assessment was "cleared" or "minimal" in more patients receiving ustekinumab than in those receiving placebo (60.4% for ustekinumab 45mg (154/255), 61.7% for ustekinumab 90 mg (158/256), 3.9% for placebo (10/255); (Difference in response 56·5%, 95% CI 50·0–62·9, p<0·0001 for 45 mg vs. placebo and 57·8%, 95% CI (51·4–64·2), p<0·0001 for 90 mg vs. placebo) • At week 12, the mean change in DLQI score was -8.0 (SD=6.87) in patients treated with 45mg ustekinumab, -8.7 (SD=6.47) in patients treated with 90mg ustekinumab compared with -0.6 (SD=5.97) with placebo (p<0.001 vs. placebo for both ustekinumab doses)	
	• Among patients re-randomised at week 40, time to loss of PASI 75 response was better maintained in patients receiving maintenance therapy than in patients withdrawn from therapy up to at least one year (p<0·0001) (figures A and B). The median percentage improvement in PASI remained stable to at least week 76 in the maintenance therapy groups (Please note: re-randomisation took place at week 40) (figures C and D)	

Other outcome measures	• At week 12, 41.6% of patients receiving ustekinumab 45mg (n=106/255) and 36.7% of patients receiving ustekinumab 90mg achieved a PASI 90 response (94/256) versus 2% in the placebo group (5/255) (p<0·0001 for both ustekinumab doses vs placebo) • At week 12, 83.5% of patients receiving ustekinumab 45mg (n=213/255) and 85.9% of patients receiving ustekinumab 90mg achieved a PASI 50 response (220/256) versus 10.2% in the placebo group (26/255) (p<0·0001 for both ustekinumab doses vs placebo) • Ustekinumab resulted in significant improvements from baseline in the SF-36 physical and mental component summary scores at week 12 (p<0.001 in both groups vs placebo); these improvements at week 12 were generally sustained at weeks 28 and 40. Additionally, the placebo → 45 mg and placebo → 90 mg groups had improvements in the two SF-36 component summary scores at weeks 28 and 40 that were similar in magnitude to those seen in subjects initially randomised to ustekinumab • The ustekinumab groups demonstrated significant improvements from baseline in all 8 SF-36 domain scores at week 12 ($p \leq 0.017$ in both ustekinumab dose groups vs placebo), with the greatest improvements observed in the 'bodily pain' and 'social functioning' domains
Conclusions	In this multi-centre, double-blind, randomised, placebo-controlled study, ustekinumab demonstrated statistically and clinically significant efficacy in the treatment moderate to severe psoriasis as measured by PASI and patients with PGA of cleared or minimal. Treatment with ustekinumab was also associated with significant improvement in quality of life as reported by DLQI and SF-36, compared with placebo.

6.4.2 PHOENIX-2 (T09)(41;44)

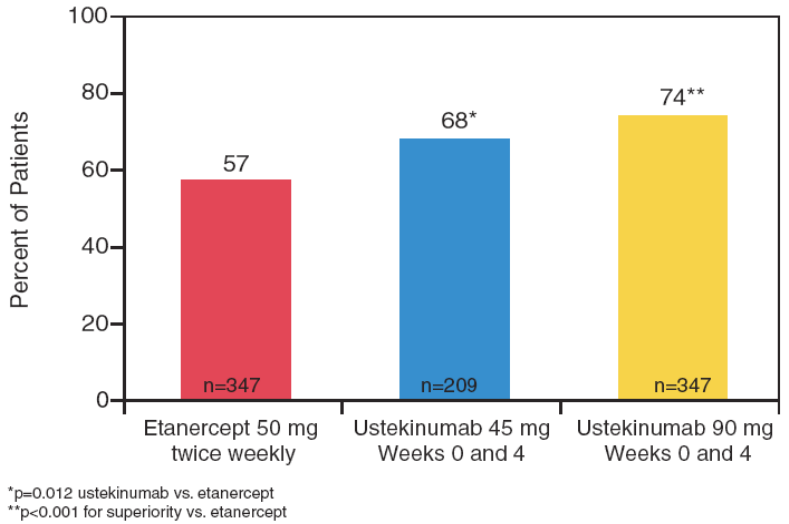
A total of 1,230 patients were randomised and 1,197 were included in the efficacy analysis at week 12. Thirty three patients discontinued the study agent (2 due to lack of efficacy, 15 due to adverse events, 1 death and 15 for other reasons). The study was conducted between March 2006 and September 2007.

Primary outcome measure	• 66·7% of patients receiving ustekinumab 45mg (273/409), 75.7% receiving ustekinumab 90mg (311/411), and 3.7% receiving placebo (15/410) achieved a PASI 75 at week 12 (difference in response rate vs. placebo 63·1%, 95% CI (58.2-68.0), p<0·0001 for 45mg and 72.0%, 95% CI (67.5-76.5), p<0·0001 for 90mg)	
Secondary outcome measures	• At week 12, Physician's Global Assessment was "cleared" or "minimal" in more patients receiving ustekinumab than in those receiving placebo (68.0% for ustekinumab 45mg, 73.5% for ustekinumab 90 mg, 4.9% for placebo; difference in response 63.1%, 95% CI 58.1-68.1, p<0·0001 for 45 mg vs. placebo and 68.6%, 95% CI 63.9-73.4, p<0·0001 for 90 mg vs. placebo) • At week 12, the mean change in DLQI score was –9.3 (SD=7.12) in patients treated with 45mg ustekinumab, -10.0 (SD=6.67) in patients treated with 90mg ustekinumab compared with -0.5 (SD=5.66) with placebo (p<0.001 versus placebo for both ustekinumab dose groups)	

Other outcome measures	• At week 12, 42.3% of patients receiving ustekinumab 45mg (n=173/409) and 50.9% of patients receiving ustekinumab 90mg achieved a PASI 90 response (209/411) versus 0.7% in the placebo group (3/410) (p<0·0001 for both ustekinumab doses vs placebo) • At week 12, 83.6% of patients receiving ustekinumab 45mg (n=342/409) and 89.3% of patients receiving ustekinumab 90mg achieved a PASI 50 response (367/411) versus 10.0% in the placebo group (41/410) (p<0·0001 for both ustekinumab doses vs placebo)
Conclusions	In this multi-centre, double-blind, randomised, placebo-controlled study, ustekinumab demonstrated statistically and clinically significant efficacy in the treatment moderate to severe psoriasis as measured by PASI and patients with PGA of cleared or minimal. Treatment with ustekinumab was also associated with significant improvement in quality of life as reported by DLQI, compared with placebo. Additionally, significant improvements were observed for ustekinumab vs. placebo in anxiety and depression from the HADS and in work limitations from the WLQ.

6.4.3 ACCEPT (T12)(42;45)

A total of 903 patients were randomised

Primary outcome measure	• At Week 12, a significantly greater proportion of patients in the ustekinumab 45mg and ustekinumab 90mg arms (68% (141/209) and 74% (256/347), respectively) achieved PASI 75 compared with 57% (197/347) who received etanercept 50mg (p=0.012 for ustekinumab 45mg; p<0.001 for ustekinumab 90mg, each compared with etanercept 50mg)	
Secondary outcome measures	• At week 12, a greater proportion of patients in the ustekinumab 45mg and ustekinumab 90mg groups achieved a PGA of cleared or minimal (65% (136/209) and 71% (245/347), respectively) compared with 49% (170/347) of etanercept-treated patients (p<0.001, for each comparison vs etanercept 50 mg twice weekly) • At week 12, the proportion of subjects who achieved a PASI 90 response at week 12 was significantly greater in the ustekinumab treatment groups (36.4% (73/209) and 44.7% (155/347) in the 45mg and 90mg groups, respectively) compared with the etanercept 50mg twice weekly group (23.1% (80/347); p<0.001 for each ustekinumab group versus etanercept) • Please see section 6.4.4 for the results from the weight based analysis	

Other outcome measures	• At week 12, the proportion of subjects who achieved a PASI 50 response at week 12 was greater in the ustekinumab treatment groups (86.6%% (181/209) and 92.2% (320/347) in the 45mg and 90mg groups, respectively) compared with the etanercept 50mg twice weekly group (82.4% (286/347)
Conclusions	In this multi-centre, randomised, comparative study, both ustekinumab 45mg and 90mg demonstrated statistically superior efficacy in the treatment of moderate to severe psoriasis as measured by PASI and patients with PGA of "cleared"or "minimal" compared with etanercept 50mg twice weekly.

6.4.4 Weight based dosing analysis for PHOENIX 1, PHOENIX 2 and ACCEPT trials

Based on data from Phase II studies, the ustekinumab Phase III clinical trials investigated both the 45mg and 90mg doses of ustekinumab in patients with moderate to severe plaque psoriasis. These trials contained patients of all weights in both the 45mg and 90mg treatment arms. The primary outcome results from the all-patient analyses for the PHOENIX trials have recently been published[1,2] and are shown in section 6.4.1 and 6.4.2.

The design of the phase III studies and the planned statistical analyses recognised the need to assess efficacy by dose and patient weight, and as such, randomisation was stratified by a patient weight at above and below 90kg (so as to include 40-60% of patients in each stratification level). The statistical analysis plan specified a sub-group analysis by dose and 90kg weight stratification; additionally, summary tables by dose and 10kg weight increments and weight quartiles were specified. The results from the phase III studies suggested a degree of heterogeneity of response for the 45mg strength by weight, and a patient weight of above 100kg was identified as optimising the risk benefit ratio for the use of the higher dose of ustekinumab.

Given that the SmPC for ustekinumab will recommend the 45mg dose for patients who are ≤100kg and 90mg for patients who are >100kg, we considered that this dosing stratification would be most appropriate for use in our base case cost-effectiveness analysis (see section 7.3.1.1). We also believe this dosing stratification will most closely match the way ustekinumab will be used in clinical practice. This issue was highlighted during the decision problem step and the approach taken was discussed and agreed between the company and the NICE technical team.

The results from the weight based dosing are shown in the following table.

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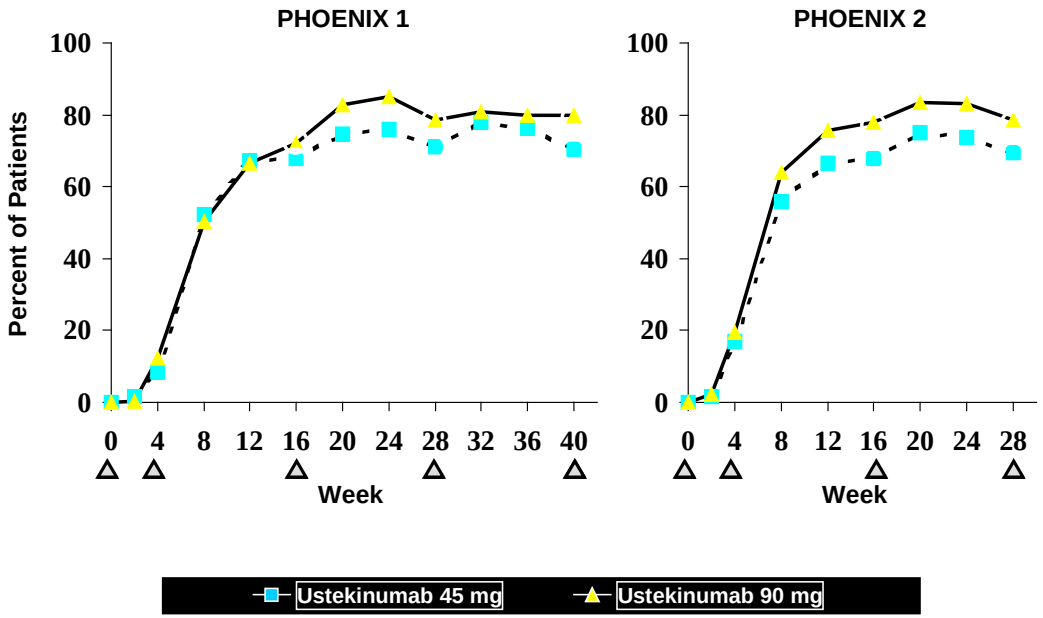
	Primary efficacy outcome
PHOENIX 1 (T08)(43)	• At week 12, the results for the weight by dose are as follows: o For patients who were ≤100kg and had received ustekinumab 45mg 73.8% (124/168) achieved a PASI 75 o For patients who were >100kg and received ustekinumab 90mg 68.5%(63/92) achieved a PASI 75
PHOENIX 2 (T09)(44)	• At week 12: o For patients who were ≤100kg and had received ustekinumab 45mg 73.4% (218/297) achieved a PASI 75 o For patients who were >100kg and received ustekinumab 90mg 71.1% (86/121) achieved a PASI 75
ACCEPT (T12)(45)	• At week 12: o For patients who were ≤100kg and had received ustekinumab 45mg 72.2% (109/151) achieved a PASI 75 o For patients who were >100kg and received ustekinumab 90mg 65.0% (67/103) achieved a PASI 75

6.4.5 Long term efficacy based on the PHOENIX 1 and PHOENIX 2 trials

To date efficacy data are available for 76 weeks for PHOENIX 1 and 52 weeks for PHOENIX 2(40;41). The results for up to week 40 for PHOENIX 1 and week 28 for PHOENIX 2 can be seen in the following figure. In general, ustekinumab has been proven to maintain a high response rate as defined by PASI 75 and yields a durable response over time**.**

Figure 6.4.1 Long term efficacy of ustekinumab(40;41)



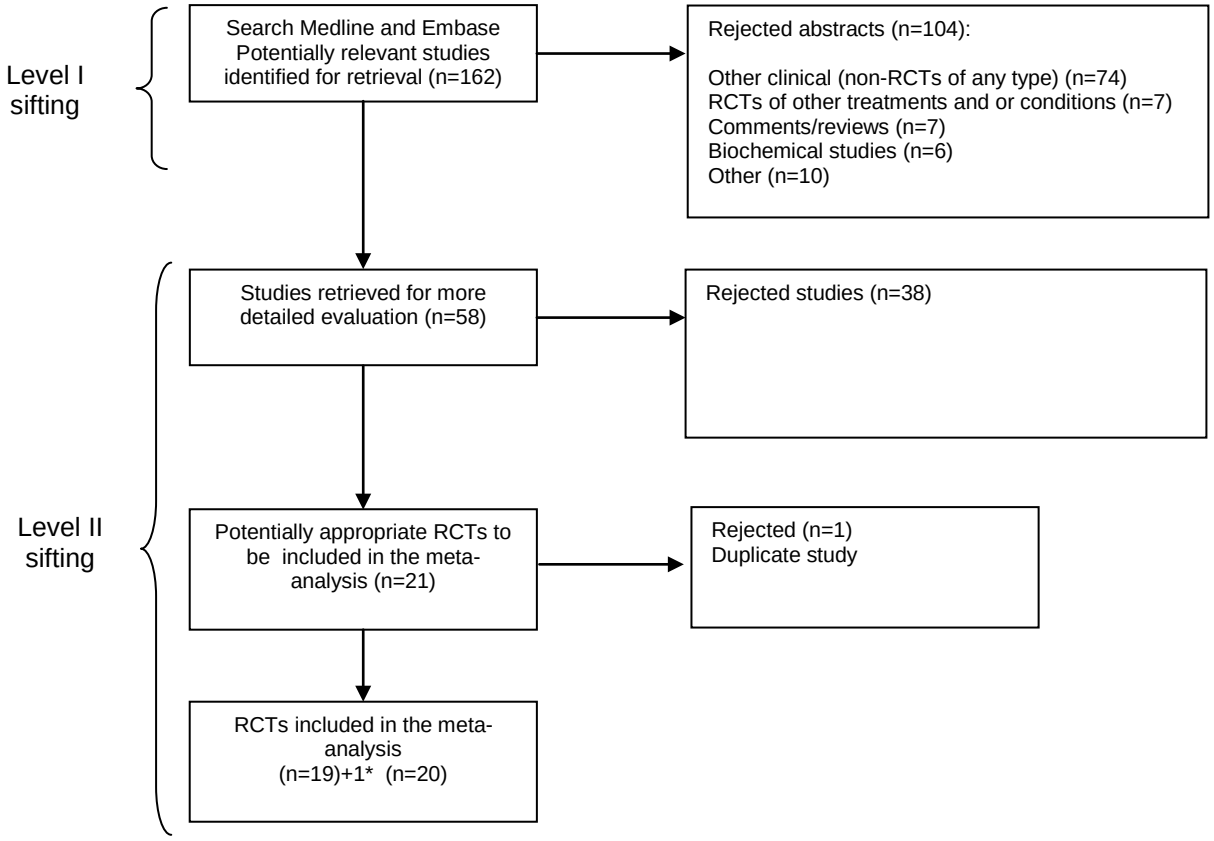
6.5 *Meta-analysis*

A specific dedicated meta-analysis of ustekinumab study data has not been carried out. However, based on the methodology described in Woolacott et al 2006(46) that was developed by the Assessment group for the Multiple Technology Appraisal on efalizumab and etanercept(47) a mixed treatment comparison of currently available biological agents, including ustekinumab, for the treatment of moderate or severe plaque psoriasis in the UK has been conducted, details of which are provided in 6.6 below.

6.6 *Indirect/mixed treatment comparisons*

The systematic review methodology outlined in sections 6.1 and 6.2.2, was used to identify all of the relevant randomised controlled trial evidence for all of the available biologics (adalimumab, efalizumab, etanercept and infliximab as well as ustekinumab). The only additional inclusion criteria was that the trials needed to include at least on of these biologics. Based on the results of this systematic review, a mixed treatment comparison has been carried out. The ACCEPT head to head trial results have been incorporated into this mixed treatment comparison to include all of the relevant data for ustekinumab. Ineligible studies along with the reason for exclusion can be found in Appendix 9.

Figure 6.6.1 Literature search tree



* +1 is a head to head study of ustekinumab vs etanercept presented in September 2008 but not identified via the systematic review

The Cochrane Library search yielded 11 documents (searched by the key term psoriasis) of which all were excluded. In addition, one protocol on the role of biologics with psoriasis was identified but also excluded. Abstracts were available from the AAD, SID and ICP until 2007. EADV was searched up until 2008. The majority of RCTs described in the abstracts have been subsequently published in full.

A summary of the trials included in the systematic review is given in Table 6.6.1 below. A total of 21 primary studies enrolling 11,275 psoriatic patients were identified by the systematic review. All were recent publications (published since 2000), of which 19 were published in full papers and two were meeting abstracts. All 19 RCTs presented as full papers were of good quality (Jadad score 4 or higher). Of the 21 studies: 12 evaluated TNF inhibitors (adalimumab n=3, etanercept n=5 and infliximab n=4) and 6 studies focused on T-cell modulators (efalizumab n=6). There were three studies on the new IL-12 & 23 antibody (ustekinumab n=3). All studies compared one biologic with placebo with one exception of the ACCEPT trial. Efalizumab and ustekinumab were the most commonly studied drug in this population with 25% of all psoriatic patients each in this review were enrolled in six efalizumab trials and three ustekinumab studies. Industry sponsorship was noted in a majority of studies. One study of efalizumab identified did not contain the relevant outcome data required (Leonardi et al 2007). Therefore, a total of 20 of these studies contained relevant outcome data and were included in the meta-analysis described below.

Doses of biological agents evaluated in these studies ranged as follows:

- Adalimumab 40 mg subcutaneously (s.c.) once a week (QW) or every other week (EOW)
- Etanercept 25–50 mg s.c. QW or twice a week (BIW),
- Infliximab 3–10 mg/kg intravenously (IV)
- Efalizumab 1–2 mg/kg s.c.
- Half of the studies (n=12) compared various doses or dose schedules of biologic agents within the study.

For the meta-analysis only the UK licensed doses of each product were included, specifically infliximab 5mg/kg and efalizumab 1mg/kg. To generate the most robust and precise estimates of treatment effects possible we have combined 50mg once weekly and 25mg twice weekly under the title etanercept 25mg, investigation of the forest plots in figure 6.6.6 to 6.6.8 suggest that alternative approaches would be unlikely to have altered conclusions.

Meta-analysis

A mixed treatment comparison meta-analysis has been carried out as has been reported previously(46) where estimates of PASI 50, 75 and 90 response were generated for biologic treatments and supportive care. A mixed treatment comparison was conducted to examine relative efficacy among the comparators. A total of 20 trials are included in this mixed treatment comparison. The mixed treatment comparison uses data based on direct comparisons (A vs. B and B vs. C) and indirect comparisons (A vs. C) to facilitate simultaneous inference regarding all treatments. Network meta-analysis is an extension of conventional, pairwise, meta-analysis, which is based on the assumption that, on a suitable scale, we can add and subtract the within-trial estimates of relative treatment effects. A statistical analysis of the network of trial evidence is used to produce comparable estimates of the effectiveness across a range of treatments.

All trials, except for the ACCEPT head to head trial, are linked with a common comparator of placebo or supportive care. The meta-analysis provides estimates for response rates for each biologic and also supportive care based on all observed comparisons adjusting for variation in supportive care/placebo response rates on the log-odds scale (see WinBUGS code in Appendix 10). The results have been incorporated into the cost-effectiveness model described in section 7.

There are two main assumptions within the evidence synthesis: firstly the treatment effects are constant across the endpoints on the probit scale, and secondly the treatment effects can be considered exchangeable between the trials(46). As is common to analyses of this type, there exists some between trial heterogeneity. However, differences between the inclusion and exclusion criteria are small.

Heterogeneity among trials is a general concern when comparing treatment effects of different therapies. However, this is not an issue when comparing ustekinumab and etanercept because a head to head study was conducted to compare ustekinumab against the highest and most effective dose of etanercept. This was the first head to head trial for biologics.

Table 6.6.2a lists the baseline characteristics of the patients in the trials included for the mixed treatment comparison. Inclusion and exclusion criteria are very similar for all trials including age, gender, ethnicity, and duration of psoriasis at baseline, implying that the populations in these trials were relatively homogeneous. However, there are a few exceptions. In the study of etanercept as reported in Tyring et al (2006)(48), patients were excluded if they had any other therapy within the past 4 weeks. In the infliximab study described in Chaudhari et al (2001)(49), patients were excluded if they had a topical therapy in the past 14 days or systemic therapy in the past 28 days. In Gordon et al (2006)(50) and Lebwohl et al (2003)(51) which studied adalimumab and efalizumab respectively, there were no data presented on prior treatments. Table 6.6.2b shows the baseline severity of the patients included in each trial. In general the baseline severity is similar across the trials with a range of mean PASI 18-20. There were a few exceptions: in one infliximab study(52) the baseline PASI is approximately 23; in an adalimumab study(50) the average PASI score is between 14 and 16 for the various treatment arms, in one etanercept study(53) the median PASI score is approximately 16, however there is no data available on the mean PASI score and finally in one efalizumab study(54) the mean PASI is approximately 23. The available evidence permits the estimation of comparative efficacy using the mixed treatment comparison model.

The trials included in the mixed treatment comparison are shown in table 6.6.1 along with the Jadad score for each trial, with the data incorporated in the analysis being shown in table 6.6.2. The results from the mixed treatment comparison can be seen in table 6.6.3 and 6.6.4.

As described in section 6.4.4 a weight based dosing analysis, that is 45mg for patients $\leq$100kg and 90mg for patients >100kg, has been carried out and forms the basis of the base case cost-effectiveness analysis. Therefore, firstly the mixed treatment comparison has been carried out on the weight based dosing results for ustekinumab. In addition, as the PHOENIX and ACCEPT trials included patients of all weights in each dose arm, a mixed treatment comparison has been carried out on the results from the all-patient ITT analysis from these trials.

We have identified an inconsistency in the Woolacott et al review between what is reported in the main document and the WinBUGS code reported in the appendix. In

the main text of this report the prior for the study specific, corresponding to a study specific fixed effect baseline, is described as:

$$\mu_s \sim N(\frac{1}{0.001})$$

Whereas in the WinBUGS code included in the appendix it is given as mu[s]~dnorm(muMean,muTau) which corresponds to a random effect baseline.

In the analysis presented in this submission, the fixed effect baseline has been used in preference as it does not require the strong assumption of exchangeability of baseline rates between studies required by the random effects baseline model, and this was the methodology used to generate the effect measures presented by Woolacott et al(46). This approach is also supported by expert opinion in the field of mixed treatment comparison(55).

Table 6.6.1: Double-blind, placebo-controlled RCTs included in the systematic review

Adalimumab (n=3)

Author **Year** Full paper unless stated	**Study duration** (wks)	**Patient Population**	**Treatment** (n) **Control** (n)	**Outcome measures and time points of evaluation**
Gordon KB 2006(50) Jadad Score = 5	12 wks	Adults with moderate to severe chronic psoriasis for ≥ 1 year, affected BSA ≥ 5%, naive to anti-TNF therapy	Adalimumab sc 40 mg (EOW) n=45 40 mg (QW) n=50 Placebo n=52	PASI, DLQI, SF-36, Safety At 12 wks
Saurat 2007(56) & Revicki 2008(57) Jadad Score = 5	16 wks	Adult patients with moderate to severe psoriasis (≥10% BSA & PASI score of ≥10 at baseline. Naïve to TNF-antagonists and MTX.	Adalimumab sc 40mg n=108 Placebo n=53 Methotrexate n=110	PASI, DLQI at 16 wks
Menter MA 2008(58) (REVEAL) Jadad Score = 5	16 wks	Adults with PASI ≥ 12 who failed topical therapy and were naive to anti-TNF therapy	Adalimumab sc 40mg (EOW) n=814 Placebo n=398	PASI, PGA, Safety at 16 wks

Efalizumab n=5

Author **Year** Full paper unless stated	**Study duration** (wks)	**Patient Population**	**Treatment** (n) **Control** (n)	**Outcome measures and time points of evaluation**
Dubertret L 2006(54) Jadad Score = 5	12 wks	Adults 18-75 years with plaque psoriasis for ≥ 6 months; ≥ 10% BSA lesion, PASI ≥ 12.0; received previous systemic therapy	Efalizumab sc 1 mg/kg* n=529 Placebo n=264	PASI, PGA, DLQI, SF-36, Safety at 12 wks
Lebwohl M 2003(51) Jadad Score = 5	12 wks	Adults with moderate to severe psoriasis for ≥ 6 months; PASI > 12.0; ≥ 10% BSA lesion and candidacy for systemic therapy	Efalizumab sc 1 mg/kg * n=232 2 mg/kg * n=243 Placebo n=122	PASI, PGA, DLQI, Safety at 12 wks
Leonardi CL 2005(59) Jadad Score = 4	12 wks	Adults with moderate to severe psoriasis for ≥ 6 months, clinically stable for ≥ 3 months before screening; PASI ≥ 12.0 with > 10% BSA lesion	Efalizumab sc 1 mg/kg * n=162 2 mg/kg * n=162 Placebo n=170	PASI, PGA, DLQI, Safety at 12 wks
Menter MA 2005(60)	12 wks	Adult patients with plaque psoriasis for ≥ 6 months, ≥ 10% BSA lesions, and PASI ≥ 12.0	Efalizumab sc 1 mg/kg * n=187 Placebo n=187	PASI, PGA, DLQI, Safety at 12 wks

Jadad Score = 4				
Papp KA 2006(61) Jadad Score = 4	12 wks	Adults with ≥10% BSA lesion, diagnosis for ≥ 6 months, PASI ≥ 12.0 and body weight ≤ 140 kg	Efalizumab sc 1 mg/kg * n=450 Placebo n=236	PASI, PGA, Safety at 12 wks

Etanercept (n=5)

Author **Year** Full paper unless stated	**Study duration** (wks)	**Patient Population**	**Treatment** (n) **Control** (n)	**Outcome measures and time points of evaluation**
Gottlieb AB 2003 (62) Jadad Score = 5	24 wks	Age ≥ 18 years, active stable plaque psoriasis ≥ 10% BSA lesion with ≥1 previous systemic or phototherapy	Etanercept sc 25 mg n=57 Placebo n=55	PASI, Safety At 12, 24 wks
Leonardi CL 2003(63) Jadad Score = 4	12 wks	Age ≥ 18 years with clinically stable plaque psoriasis ≥ 10% BSA lesion, PASI ≥ 10, had ≥ 1 phototherapy or systemic therapy, or had been candidates for such therapy	Etanercept sc 25 mg (QW) n=169 25 mg (BIW) n=167 50 mg (BIW) n=168 Placebo n=168	PASI, PGA, DLQI, Safety at 12 wks
Papp KA 2005(53) Jadad Score = 4	12 wks	Age ≥ 18 years; active, clinically stable plaque psoriasis with ≥ 10% BSA lesion; PASI ≥ 10; have received or were receiving ≥ 1 phototherapy or systemic therapy	Etanercept sc 25 mg n=204 50 mg n=203 Placebo n=204	PASI, PGA, DLQI, SF-36, Safety at 12 wks
Tyring S 2006(48) Jadad Score = 5	12 wks	Age ≥18 years, active and clinically stable plaque psoriasis with ≥ 10% BSA lesion; PASI ≥ 10.	Etanercept sc 25 mg n=311 Placebo n=309	PASI, DLQI, Safety at 12 weeks
Van der Kerkhof 2008(64) abstract Jadad Score = 5	12 weeks	Adult patients with moderate to severe plaque psoriasis (>10% of the body surface and a PASI score of >10)	Etanercept sc 50mg QW n=96 Placebo n=46	PASI, DLQI at 12 weeks

Infliximab (n=4)

Author **Year** Full paper unless stated	**Study duration** (wks)	**Patient Population**	**Treatment** (n) **Control** (n)	**Outcome measures and time points of evaluation**
Chaudhari U 2001(49) Jadad Score = 5	10 wks	Patients with moderate to severe plaque psoriasis for ≥ 6 months, affected BSA ≥ 5%, with topical corticosteroid treatment failure	Infliximab IV 5 mg/kg (n=11) 10 mg/kg I V (n=11) Placebo n=11	PASI, Safety At 10 wks
Gottlieb AB (SPIRIT) 2004(65) Jadad Score = 5	30 wks	Age ≥ 18 years; plaque psoriasis for ≥ 6 months; previously treated with PUVA or other systemic therapy; PASI ≥ 12 with ≥ 10% BSA	Infliximab IV 3 mg/kg n=99 5 mg/kg n=99 Placebo n=51	PASI, PGA, DLQI, Safety at 2, 4, 10 wks
Menter MA (EXPRESS II) 2007(66) Jadad Score = 5	14 wks	Adult candidates for phototherapy or systemic therapy, PASI score ≥ 12 with ≥ 10% BSA lesions, and no history of serious infection	Infliximab IV 3 mg/kg n=313 5 mg/kg n=314 Placebo n=208	PASI, PGA, DLQI, Safety at 10 wks
Reich K (EXPRESS) 2005(52) Jadad Score = 5	24 wks	Patients with moderate-severe plaque psoriasis for at least 6 months; PASI score ≥12; ≥ 10% BSA affected	Infliximab IV 5 mg n=301	PASI, PGA, DLQI, SF-36, Safety at 10 and 24 wks

Ustekinumab (n=2 + 1) – All patients

Author **Year** Full paper unless stated	**Study duration** (wks)	**Patient Population**	**Treatment** (n) **Control** (n)	**Outcome measures and time points of evaluation**
Leonardi (PHOENIX-1) 2008(40) Jadad Score = 5	12 wks	Adult patients with moderate to severe plaque psoriasis for ≥ 6 months; ≥ 10% BSA involvement, PASI ≥ 12; have received prior systemic therapy or were candidates for such therapy	Ustekinumab sc 45 mg**n=255 90 mg** n=256 Placebo n=225	PASI, PGA, DLQI, SF-36, Safety at 2, 4, 8, 12 wks
Papp (PHOENIX-2) 2008(41) Jadad Score = 5	12 wks	Adult patients with moderate to severe plaque psoriasis for ≥ 6 months; ≥ 10% BSA involvement, PASI ≥ 12; have received prior systemic therapy or were candidates for such therapy	Ustekinumab sc 45 mg**n=409 90 mg** n=411 Placebo n=410	PASI, PGA, DLQI, SF-36, Safety 2, 4, 8, 12 wks

Griffiths ACCEPT 2008(42)	12 wks	Adult patients with moderate to severe plaque psoriasis for ≥ 6 months; ≥ 10% BSA involvement, PASI ≥ 12; have received prior systemic therapy or were candidates for such therapy	Ustekinumab sc 45mg** n=209 90mg** n=347 Etanercept 50mg twice weekly n=347	PASI, PGA Safety

*0.7 mg/kg Efalizumab dose administrated on day 0
** Initial dose administrated at week 0 and 4, followed by q12 weeks maintenance dosing
N = number of patients randomised within treatment arm

Table 6.6.2a: Patient characteristics and main results

	Total no. of patients	**No. of males %**	**Age mean (range)**	**Caucasian %**	**Duration of psoriasis mean (range)**	**Previous therapies: %**	**% PASI response: PASI 50 PASI 75 PASI 90 (where reported)**	**PGA Cleared/ Minimal %**	**DLQI Mean value or change (range)**	**Safety n discontinued % due to adverse events (AE)**
Adalimumab										
Gordon 2006(50)	147 (140 at 12wks)	67%	44 yrs (20-86)	90%	19 yrs (1-58)	No data	40 mg (EOW) 76% 53% 24% 40 mg (QW) 88% 80% 48% Placebo 4% PASI-75	40 mg (EOW) 49% 40 mg (QW) 76% Placebo No data	No data	40 mg (EOW) n=3 of which n=2 AE 40 mg (QW) n=3 of which n=2 AE Placebo n=2 of which n=1 AE One death by end of study at 60 wks
Saurat 2007(56) & Revicki 2008 (57) (additional data)	271 (252 at 16 wks)	66%	4% ≥65yrs	95%	19 yrs	Previous systemic and or phototherapy 87%	PASI-75 & PASI-100 80mg-40mg 79.6% 16.7% Methotrexate	PGA data in graph form only	80mg-40mg 2.5±4.0 MTX 4.1±5.0 Placebo 7.6 ±6.4	80mg-40mg n=4 of which n=1 AE MTX n=6 of which n=6 AE

	Total no. of patients	No. of males %	Age mean (range)	Caucasian %	Duration of psoriasis mean (range)	Previous therapies: %	% PASI response: PASI 50 PASI 75 PASI 90 (where reported)	PGA Cleared/ Minimal %	DLQI Mean value or change (range)	Safety n discontinued % due to adverse events (AE)
							35.5% 7.3% Placebo 18.9% 1.9%			Placebo n=5 of which n=1 AE
Menter 2008(58)	1212 (1138 at 16wks)	66%	45 yrs	91%	18 yrs	Topical therapy 74.4% Phototherapy 15.9% Systematic non-biologic 22.6% Systemic biologic 12.6% Laser 0.5%	PASI -75 90 & 100 40mg (EOW) 71% 45% 20% Placebo 7% 2% 1%	No data at 16 weeks Week 12 data 40mg (EOW) 60% Placebo 4%	No data	40mg (EOW) n=31 of which n=10 AE Placebo n=43 of which n=4 AE
Efalizumab										
Dubertret 2006(54)	793 (723 at 12 wks)	67%	45 yrs	No data	20 yrs	Prior treatment of an least one systemic therapy and phototherapy 89%	PASI- 50 & 75 1mg/kg/wk 53.7% 31.4% Placebo 14.4% 4.2%	1mg/kg/wk 26.1% placebo 3.4%	No data	1mg/kg/wk n=53 of which n=29 AE placebo n= 17 of which n=7 AE
Lebwohl 2003(51)	597 (549 at 12 wks)	65%	46 yrs	No data	19 yrs	No data	1mg/kg/wk 52% 22% 4% 2mg/kg/wk 57%	No data	No data	1mg/kg/wk n=21 of which n=7 AE 2mg/kg/wk n=16 of which n=16 Placebo

	Total no. of patients	No. of males %	Age mean (range)	Caucasian %	Duration of psoriasis mean (range)	Previous therapies: %	% PASI response: PASI 50 PASI 75 PASI 90 (where reported)	PGA Cleared/ Minimal %	DLQI Mean value or change (range)	Safety n discontinued % due to adverse events (AE)
							28% 6% Placebo 16% 5% <1%			n=11 of which n=1 AE
Leonardi 2005(59)	498 (445 at 12 wks)	72%	44 yrs (18-75)	No data	18 yrs 91-60)	Previous systemic therapy 54.8%	1mg/kg/wk 61.1% 38.9% 12.3% 2mg/kg/wk 51.2% 26.5% 4.8% Placebo 14.7% 2.4% 1.2%	1mg/kg/wk 38.9% 2mg/kg/wk 30.1% Placebo 4.1%	No data	1mg/kg/wk n=13 of which n=5 AE 2mg/kg/wk n=21 of which n=8 AE Placebo n=19 of which n=5 AE
Menter 2005(60)	556 (520 at 12 wks)	69%	45 yrs (18-75)	90%	19 yrs (1-62)	Prior systemic therapy 75.5%	1mg/kg/wk 58.5% 26.6% 5.1% Placebo 13.9% 4.3% 0.5%	1mg/kg 25.7% Placebo No data	1mg/kg +5.6 Placebo +1.6	1mg/kg n=24 discontinued of which n=7 AE Placebo n=12 of which n=n=2 AE
Papp 2006(61)	686 (639 at 12 wks)	63.3%	46 yrs (18-77)	91%	18 yrs (0-68)	Prior systematic therapy 73.2% of which MTX 28.4% Systemic retinoids 13.4%	PASI-50 & 75 1mg/kg/wk 52% 23.6%	1mg/kg/wk 20.2% Placebo 4.2%	No data	1mg/kg/wk n=29 of which n=11 AE Placebo n=18 of which n=6

	Total no. of patients	No. of males %	Age mean (range)	Caucasian %	Duration of psoriasis mean (range)	Previous therapies: %	% PASI response: PASI 50 PASI 75 PASI 90 (where reported)	PGA Cleared/ Minimal %	DLQI Mean value or change (range)	Safety n discontinued % due to adverse events (AE)
						Unspecified 12.8% Systemic corticosteroids 10.3% Cyclosporine 8.7%	 Placebo 14% 3%			AE
Etanercept										
Gottlieb 2003(62)	112 (60at 24 wks)	63%	47yrs (18-77)	92%	22 yrs	MTX 37.5% Ciclosporin 11.5% Oral retinoids 24.5% Corticosteroids 11.5% Psoralen UVA 39.5% UVB 47%	25mg (BIW) 77% 56% 21% Placebo 13% 5% 0%	No data	No data	25mg (BIW) n=5 of which n=2 AE Placebo n=28 of which n=2 AE
Leonardi 2003(63)	672 (652 at12wks)	67%	45yrs	87%	19 yrs	Topical corticosteroids 88% Systemic or phototherapy 76%	25 mg (QW): 41% 14% 3% 25 mg (BIW): 58% 34% 12% 50 mg(BIW): 74% 49% 22% Placebo 14% 4% 1%	25 mg (QW): 2% 25 mg (BIW): 11% 50 mg(BIW): 20% Placebo 0%	25 mg (QW): 47.2± 2.9 25 mg (BIW): 50.8± 3.8 50mg(BIW): 61 ±4.3 Placebo 10.9 ±4.8	Over the whole study period (24wks) n=27 discontinued due to AE and n=16 due to lack of efficacy across the groups
Papp 2005(53)	583 (559 at 12 wks)	66%	45yrs (18-87)	91%	19 yrs (0.8- 64.6)	UVB 58% PUVA 34% MTX 37% Ciclosporin 16%	25mg BIW 64% 34% 11%	25mg BIW 39% 50mg BIW 57%	No data	25mg BIW n=5 of which n=3 AE 50mg BIW

	Total no. of patients	No. of males %	Age mean (range)	Caucasian %	Duration of psoriasis mean (range)	Previous therapies: %	% PASI response: PASI 50 PASI 75 PASI 90 (where reported)	PGA Cleared/ Minimal %	DLQI Mean value or change (range)	Safety n discontinued % due to adverse events (AE)
							50mg BIW 77% 49% 38% 21% Placebo 3% 1% 4%	Placebo 4%		n=4 of which n=2 AE Placebo n=15 of which n=2 AE
Tyring 2006(48)	620 (597 at 12 wks)	68%	8% ≥65yrs	89%	20 yrs	Patients were excluded if they had any other therapy within 4 wks but there were no details.	50mg BIW 74% 47% 21% Placebo 14% 5% 1%	No data	50mg BIW 69.1% Placebo 21.1%	50mg BIW n=6 of which n=4 AE Placebo n=15 of which n=3 AE
Van der Kerkhof 2008(64)	142 (126 at 12 wks)	58%	45yrs	No data	18 yrs	Failed ≥one systemic treatment 48% Failed ≥one phototherapy 69.8% No previous systemic/phototherapy 2.4%	50mg QW 68.8% 37.5% 13.5% Placebo 8.7% 2.2% 2.2 %	50mg QW 38.5% Placebo 4.3%	50mg QW 54.5% Placebo 5.2%	50mg QW n=6 of which n=3 AE Placebo n=10 of which n=3 AE
Infliximab										
Chaudhari 2001(49)	33 (30 at 10 wks)	70%	44yrs (21-69)	No data	'A minimum of 6 months'	Patients were excluded if they had a topical therapy in the past 14 days or a systemic therapy in the past 28 days but there were no details	PASI 75 only 2^{O}outcome 5mg/kg 82% 10mg/kg 73%	1^{0} outcome 5mg/kg 82% 10mg/kg 91%	No data	5mg/kg n=1 due to AE 10mg/kg n=1 worsening of psoriasis Placebo n=1 lack of efficacy

	Total no. of patients	No. of males %	Age mean (range)	Caucasian %	Duration of psoriasis mean (range)	Previous therapies: %	% PASI response: PASI 50 PASI 75 PASI 90 (where reported)	PGA Cleared/ Minimal %	DLQI Mean value or change (range)	Safety n discontinued % due to adverse events (AE)
							Placebo 18%	Placebo 18%		
Gottlieb 2004(65)	249 (199 at 30 wks)	70%	44 yrs median (35-53)	No data	17 yrs (median) (11-24)	No of topical agents 90.8% No of systemic agents 86.7% No of photo therapies 68.7% No. of biologics 32.5%	3mg/kg 83.8% 71.7% 45.5% 5mg/kg 97% 88% 58% Placebo 22% 6% 2%	3mg/kg 71.2% 5mg/kg 90% Placebo 9.8%	Mean change from baseline 3mg/kg -8 5mg/kg -10 Placebo 0	3mg/kg n=30 of which n=7 AE 5mg/kg n=18 of which n=5 AE Placebo n=37 of which n=1 AE
Menter 2007(66)	835 (773 at 10 wks)	67%	44 yrs	92%	18 yrs	Biologics 14.3% Topical 92.8% UVB 53% PUVA 28.5% MTX 33.7% Acitretin 15% Ciclosporin 12.7%	Results at wk 10 PASI-75 & 90 data 3mg/kg 70.3% 37.1 5mg/kg 75.5% 45.2 Placebo 1.9% 0.5%	3mg/kg 69.8% 5mg/kg 76% Placebo 0.5%	% achieving a total DLQI of 0 3mg/kg 28.3% 5mg/kg 39% Placebo 1%	3mg/kg n=21 of which n=13 AE 5mg/kg n=17 of which n=12 AE Placebo n=24 of which n=4 AE
Reich 2005(52)	378 (dis-continuation data unclear)	71%	43yrs SE 11.9	No data	19 yrs	UVB 66% PUVA 43% MTX 43% Ciclosporin30%	5mg/kg 90% 82% 58% Placebo 6%	5mg/kg 74% Placebo 3%	No data	5mg/kg n=32 of which n=20 AE Placebo n=9 of which n=3 AE

	Total no. of patients	No. of males %	Age mean (range)	Caucasian %	Duration of psoriasis mean (range)	Previous therapies: %	% PASI response: PASI 50 PASI 75 PASI 90 (where reported)	PGA Cleared/ Minimal %	DLQI Mean value or change (range)	Safety n discontinued % due to adverse events (AE)
							4% 1%			
Ustekinumab										
Leonardi 2008(40) ITT	766 (679 at 12wks)	69%	45yrs	No data	20 yrs	Previously treated with Topical agent 94.8% Phototherapy 64.2% Conventional systemics 55.4% Biologics 51.2%	Ustekinumab 45mg 83.5% 67.1% 41.6% Ustekinumab 90mg 85.9% 66.4% 36.7% Placebo 10.2% 3.1% 2.0%	Ustekinumab 45mg 60.4% Ustekinumab 90mg 61.7% Placebo 3.9%	Ustekinumab 45mg -8.0 Ustekinumab 90mg -8.7 Placebo -0.6	Ustekinumab 45mg n=1 of which n=0 AE Ustekinumab 90mg n=10 of which n=2 AE Placebo n=12 of which n=6 AE
PHOENIX 1 Weight based	Ustekinumab 45mg n=168 Ustekinumab 90mg n=92						Ustekinumab 45mg 85.1% 73.8% 47% Ustekinumab 90mg 85.9% 68.5% 30.4%			
Papp 2008(41) ITT	1230 (1197 at 12wks)	68%	46yrs	No data	20 yrs	Previously treated with Topical agent 95.4% Phototherapy 67.4%	Ustekinumab 45mg 83.6% 66.7% 42.3%	Ustekinumab 45mg 68% Ustekinumab	Ustekinumab 45mg -9.3 Ustekinumab	Ustekinumab 45mg n=6 of which n=2 AE

	Total no. of patients	No. of males %	Age mean (range)	Caucasian %	Duration of psoriasis mean (range)	Previous therapies: %	% PASI response: PASI 50 PASI 75 PASI 90 (where reported)	PGA Cleared/ Minimal %	DLQI Mean value or change (range)	Safety n discontinued % due to adverse events (AE)
						Conventional systemics 56% Biologics 38%	Ustekinumab 90mg 89.3% 75.7% 50.9% Placebo 10% 3.7% 0.7%	90mg 73.5% Placebo 4.9%	90mg -10.0 Placebo -0.5	Ustekinumab 90mg n=9 of which n=5 AE & one death Placebo n=18 of which n=8 AE
PHOENIX 2 Weight based	Ustekinumab 45mg n=297 Ustekinumab 90mg n=121						Ustekinumab 45mg 87.2% 73.4% 49.2% Ustekinumab 90mg 87.6% 71.1% 41.3%			
Griffiths 2008 (42) ITT	903	68%	45yrs (median)	No data	No data	Documented inadequate response to, intolerance of, or contraindication to ciclosporin, methotrexate, or PUVA therapy.	PASI-75 & 90 Ustekinumab 45mg 67.5% 36.4% Ustekinumab 90mg 73.8% 44.7% Etanercept	Ustekinumab (45mg and 90mg 65.1% & 70.6% Etanercept 50mg 49.0%	No data	No data

	Total no. of patients	No. of males %	Age mean (range)	Caucasian %	Duration of psoriasis mean (range)	Previous therapies: %	% PASI response: PASI 50 PASI 75 PASI 90 (where reported)	PGA Cleared/ Minimal %	DLQI Mean value or change (range)	Safety n discontinued % due to adverse events (AE)
							50mg 56.8% 23.1%			
ACCEPT Weight based	Ustekinumab 45mg n=151 Ustekinumab 90mg n=103						Ustekinumab 45mg 90.1% 72.2% 32.0% Ustekinumab 90mg 90.3% 65.0% 32.0%			

N = number of patients in treatment arms reporting this characteristic

Table 6.6.2b Patient characteristics and main results - baseline severity

	PASI (0-72)	PGA (0-5)	DLQI (0-30)
Adalimumab			
Gordon 2006	Mean (range) Placebo (n=52): 16 (5.5-40.4) Adalimumab 40mg EOW (n=45):16.7 (5.4-39) Adalimumab 40mg/wk (n=50):14.5 (2.3-42.4)	Moderate to severe psoriasis (%) Placebo (n=52): 29 Adalimumab 40mg EOW (n=45):56 Adalimumab 40mg/wk (n=50):42 Severe psoriasis (%) Placebo (n=52)= 8; adalimumab 40mg EOW(n=45)= 9; adalimumab 40mg/wk (n=50) = 8	NR
Saurat 2007 & Revicki 2008	Mean, SD (range) Placebo (n=53): 19.2, 6.9 (6.5-38.1) methotrexate (n=110): 19.4,7.4 (9.3-46.6)	Very severe psoriasis (%) Placebo (n=53): 3.8 methotrexate (n=110): 5.5	

	PASI (0-72)	PGA (0-5)	DLQI (0-30)
	adalimumab (n=108) : 20.2, 7.5 (10.4-52.9)	adalimumab (n=108):8.4 Moderate to severe psoriasis (%) Placebo (n=53): 58.5 Methotrexate (n=110): 41.8 adalimumab (n=108) :43 Moderate psoriasis (%) Placebo (n=53): 37.7 methotrexate (n=110): 52.7 adalimumab (n=108): 47.7	NR
Menter 2008	Mean (SD) Placebo (n=398): 18.8 (7.09) Adalimumab (n=814): 19 (7.08)	Moderate, n (%) Placebo (n=398): 220(55.3) Adalimumab (n=814): 417(51.2) Severe, n (%) Placebo (n=398): 155(38.9) Adalimumab (n=814): 346 (42.5) Very Severe, n (%) Placebo (n=398): 23(5.8) Adalimumab (n=814): 51(6.3)	NR
Efalizumab			
Dubertret 2006	Mean, SD Placebo (n=264): 23, 9.6 Efalizumab (n=529):23.6, 20.2	Mild, n (%) Placebo (n=264): 9 (3.4) Efalizumab (n=529):13 (2.5) Moderate, n (%) Placebo (n=264): 137 (51.9) Efalizumab (n=529): 275 (52) Severe, n (%) Placebo (n=264): 108 (40.9) Efalizumab (n=529): 221 (41.8) Very Severe, n (%) Placebo (n=264): 10 (3.8) Efalizumab (n=529)= 20 (3.8)	NR
Lebwohl 2003	Total study population n=597 The mean baseline psoriasis area and severity index was 20.	NR	NR
Leonardi 2005	Mean (range) Placebo (n=170): 19(9.6-57.6) Efalizumab 1mg/kg/wk (n=162):18.6 (11.9-50.1) Efalizumab 2mg/kg/wk (n=166):18.9 (10-55.6)	NR	NR
Menter 2005	Mean (range) Placebo (n=187): 19.4 (11.4-50.3) Efalizumab (n=369):19.4 (10.1-58.7)		
Papp 2006	Mean (SD)	Mild, n (%)	

	PASI (0-72)	PGA (0-5)	DLQI (0-30)
	Placebo (n=236): 18.69,7 (10.5-49.6) Efalizumab (n=450): 19.14,7.5 (10.2 – 54.6)	Placebo (n=236): 15 (6.4) Efalizumab (n=450): 20 (4.5) Moderate, n (%) Placebo (n=236): 131 (55.5); Efalizumab (n=450): 253 (56.3) Severe, n (%) Placebo (n=236): 82 (34.7); Efalizumab (n=450): 156 (34.7) Very Severe, n (%) Placebo (n=236): 8 (3.4); Efalizumab (n=450): 20 (4.5)	NR
Etanercept			
Gottlieb 2003	Mean (SE) Placebo (n=55): 19.5 (1.3) Etanercept 25mg BIW (n=57): 17.8 (1.1)	*NR*	NR
Leonardi 2003	Mean (SE) Placebo (n=166): 18.3 (0.6); Etanercept 25mg QW (n=160): 18.2 (0.7) Etanercept 25mg BIW (n=162): 18.5 (0.7) Etanercept 50mg BIW (n=164): 18.4 (0.7)	Marked or Severe (%) Placebo (n=166): 23 Etanercept 25mg QW (n=160): 21 Etanercept 25mg BIW (n=162): 23 Etanercept 50mg BIW (n=164): 21	Mean (SE) Placebo (n=166): 12.8 (0.6) Etanercept 25mg QW (n=160):12.2 (0.5) Etanercept 25mg BIW (n=162):12.7 (0.5) Etanercept 50mg BIW (n=164):11.3 (0.5)
Papp 2005	Median (range) Placebo (n=193): 16 (7-62.4) Etanercept 25mg BIW (n=196): 16.9 (4-51.2) Etanercept 50mg BIW (n=194): 16.1 (7-57.3)	NR	NR
Tying 2006	Mean (SD) Placebo (n=307): 18.1 (7.4) Etanercept 50mg BIW (n=311): 18.3 (7.6)	NR	Mean (SD) Placebo (n=307): 12.5 (6.7) Etanercept 50mg BIW (n=311):12.1(6.7)
Infliximab			
Chaudhari 2001	Mean (SD), range Placebo (n=11): 20.3 (5.5), 13.8-31.9 Infliximab 5mg/kg (n=11): 22.1(11.5),10-42.6 Infliximab 10mg/kg (n=11): 26.6 (10.3), 14.8-42	NR	NR
Gottlieb 2004	Median (IQR) Placebo (n=51): 18, (15,27) Infliximab 3mg/kg (n=99): 20 (15,26) Infliximab 5mg/kg (n=99): 20 (14,28)	NR	Median (IQR) Placebo (n=51): 14, (9,18) Infliximab 3mg/kg (n=99): 11 (6,17), Infliximab 5mg/kg (n=99): 12 (8,17)
Menter 2007	Mean (SD), median Placebo (n=208): 19.8 (7.7), 17.4	NR	Mean (SD), median Placebo (n=208): 13.4 (7.3), 13

	PASI (0-72)	PGA (0-5)	DLQI (0-30)
	Infliximab 3mg/kg (n=313): 20.1(7.9), 17.6 Infliximab 5mg/kg (n=314): 20.4 (7.5), 18.6		Infliximab 3mg/kg (n=313):12.8(6.9), 12 Infliximab 5mg/kg (n=314):13.1 (7.0), 12.5
Reich 2005	Mean (SD) Placebo (n=77): 22.8 (8.7) Infliximab (n=301): 22.9 (9.3)	NR	NR
Ustekinumab			
Leonardi 2008 ITT	Mean (SD) Placebo (n=255): 20.4 (8.6) Ustekinumab 45mg (n=255): 20.5 (8.6) Ustekinumab 90mg (n=256): 19.7 (7.6)	Marked or severe, n (%) Placebo (n=255):112 (43.9) Ustekinumab 45mg (n=255):114 (44.7) Ustekinumab 90mg (n=256):109 (42.6)	Mean (SD) Placebo (n=255) = 11.8 (7.4); Ustekinumab 45mg (n=255) = 11.1 (7.1) Ustekinumab 90mg (n=256) = 11.6 (6.9)
PHOENIX 1 Weight based	Mean (SD) Ustekinumab 45mg (n=168) 19.9 (8.3) Ustekinumab 90mg (n=92) 20.6 (7.9)		Mean (SD) Ustekinumab 45mg (n=168) 10.9 (6.9) Ustekinumab 90mg (n=92) 11.6 (7.2)
Papp 2008 ITT	Mean (SD) Placebo (n=410): 19.4 (7.5) Ustekinumab 45mg (n= 409):19.4 (6.8) Ustekinumab 90mg (n= 411):20.1 (7.5)	Marked or severe, n (%) Placebo (n=410): 160 (39) Ustekinumab 45mg (n= 409): 169 (41.3) Ustekinumab 90mg (n= 411): 159 (38.7)	Mean (SD) Placebo (n=410): 12.3 (6.9) Ustekinumab 45mg (n= 409):12.2 (7.1) Ustekinumab 90mg (n= 411): 12.6 (7.3)
PHOENIX 2 Weight based	Mean (SD) Ustekinumab 45mg (n=168) 19.6 (7.2) Ustekinumab 90mg (n=92) 21.2 (7.9)		Mean (SD) Ustekinumab 45mg (n=168) 12.4 (7.1) Ustekinumab 90mg (n=92) 13.4 (7.9)
Griffiths 2008 ITT	Mean, SD (range) Etanercept (n=347): 18.64 (6.1); Ustekinumab 45mg (n= 209): 20.49 (9.1) Ustekinumab 90mg (n= 347): 19.87 (8.3)	Moderate, n (%) Etanercept (n=347): 199 (57.3) Ustekinumab 45mg (n= 209) 111(53.1) Ustekinumab 90mg (n= 347): 201 (58.1) Marked, n (%) Etanercept (n=347): 135 (38.9) Ustekinumab 45mg (n= 209): 87 (41.6) Ustekinumab 90mg (n= 347): 135 (39) Severe, n (%) Etanercept (n=347): 13 (3.7) Ustekinumab 45mg (n= 209): 11 (5.3) Ustekinumab 90mg (n= 347): 9 (2.6)	NR
ACCEPT Weight based	Mean (SD) Ustekinumab 45mg (n=168) 20.5 (9.1) Ustekinumab 90mg (n=92) 21.4 (9.6)		Not applicable

Table 6.6.3: Weight based dosing for ustekinumab (45mg for patients ≤100kg and 90mg for patients >100kg) - Probability of Response

Treatment	PASI 50			PASI 75			PASI 90		
	Mean	2.5%	97.5%	Mean	2.5%	97.5%	Mean	2.5%	97.5%
Supportive care/Placebo	13%	12%	14%	**4%**	3%	4%	1%	0%	1%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50mg	77%	71%	81%	**52%**	46%	59%	24%	19%	30%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efalizumab	51%	45%	58%	**26%**	21%	32%	8%	6%	11%
Etanercept 25mg	64%	56%	71%	**38%**	30%	45%	14%	10%	19%
Infliximab	94%	90%	96%	**80%**	73%	86%	54%	44%	63%
Adalimumab	81%	75%	87%	**59%**	50%	68%	30%	22%	39%

Please note: All patient data were used for treatments other than ustekinumab. In addition, these results include those from the ACCEPT head to head trial

Table 6.6.4: Weight based dosing for ustekinumab (45mg for patients ≤100kg and 90mg for patients >100kg) - Relative Risk

Treatment	PASI 50			PASI 75			PASI 90		
	Mean	2.5%	97.5%	Mean	2.5%	97.5%	Mean	2.5%	97.5%
Supportive care/Placebo	1.0	1.0	1.0	**1.0**	1.0	1.0	1.0	1.0	1.0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50mg	6.0	5.4	6.6	**14.9**	12.7	17.5	47.8	37.2	60.0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efalizumab	4.0	3.5	4.5	**7.4**	6.1	9.0	15.9	11.9	21.0
Etanercept 25mg	5.0	4.4	5.7	**10.8**	8.6	13.1	28.4	19.9	37.7
Infliximab	7.3	6.6	8.1	**23.0**	19.6	26.7	107.4	82.8	135.4
Adalimumab	6.4	5.7	7.1	**16.8**	13.9	20.1	58.6	43.1	78.6

Please note: All patient data were used for treatments other than ustekinumab. In addition, these results include those from the ACCEPT head to head trial

Table 6.6.5: Probability of response for all patients

Treatment	PASI 50			PASI 75			PASI 90		
	Mean	2.5%	97.5%	Mean	2.5%	97.5%	Mean	2.5%	97.5%
Supportive care/Placebo	13%	12%	14%	**4%**	3%	4%	1%	0%	1%
Ustekinumab 45mg	88%	84%	91%	**69%**	62%	75%	40%	33%	48%
Etanercept 50mg	76%	71%	81%	**52%**	45%	59%	24%	19%	30%
Ustekinumab 90mg	90%	87%	93%	**74%**	68%	80%	46%	39%	54%
Efalizumab	51%	45%	58%	**26%**	21%	32%	8%	6%	11%
Etanercept 25mg	65%	56%	73%	**39%**	30%	48%	15%	10%	21%
Infliximab	93%	89%	96%	**80%**	70%	87%	54%	42%	64%
Adalimumab	81%	74%	87%	**58%**	49%	68%	30%	23%	39%

Table 6.6.6: Relative Risk for all patients

Treatment	PASI 50			PASI 75			PASI 90		
	Mean	2.5%	97.5%	Mean	2.5%	97.5%	Mean	2.5%	97.5%
Supportive care/Placebo	1.0	1.0	1.0	**1.0**	1.0	1.0	1.0	1.0	1.0
Ustekinumab 45mg	6.9	6.3	7.6	**19.5**	16.8	22.6	74.2	59.5	93.0
Etanercept 50mg	6.0	5.4	6.6	**14.7**	12.5	17.1	45.2	35.2	56.8
Ustekinumab 90mg	7.1	6.5	7.8	**20.9**	18.1	24.0	84.8	68.6	104.6
Efalizumab	4.0	3.5	4.5	**7.4**	6.1	8.9	15.5	11.7	20.3
Etanercept 25mg	5.1	4.4	5.8	**10.9**	8.6	13.7	28.1	19.3	39.8
Infliximab	7.3	6.6	8.1	**22.6**	19.3	26.5	100.2	76.0	126.9
Adalimumab	6.4	5.7	7.1	**16.5**	13.7	19.8	55.5	40.9	73.7

Figure 6.6.4: Relative risk of achieving a PASI 75 - Weight based dosing for ustekinumab (45mg for patients ≤100kg and 90mg for patients >100kg)

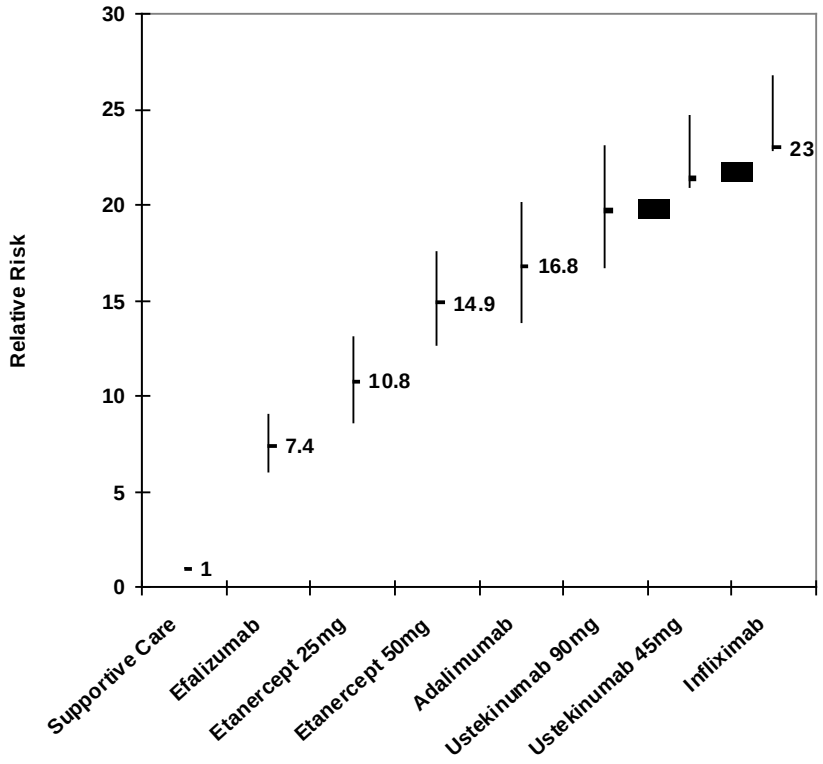
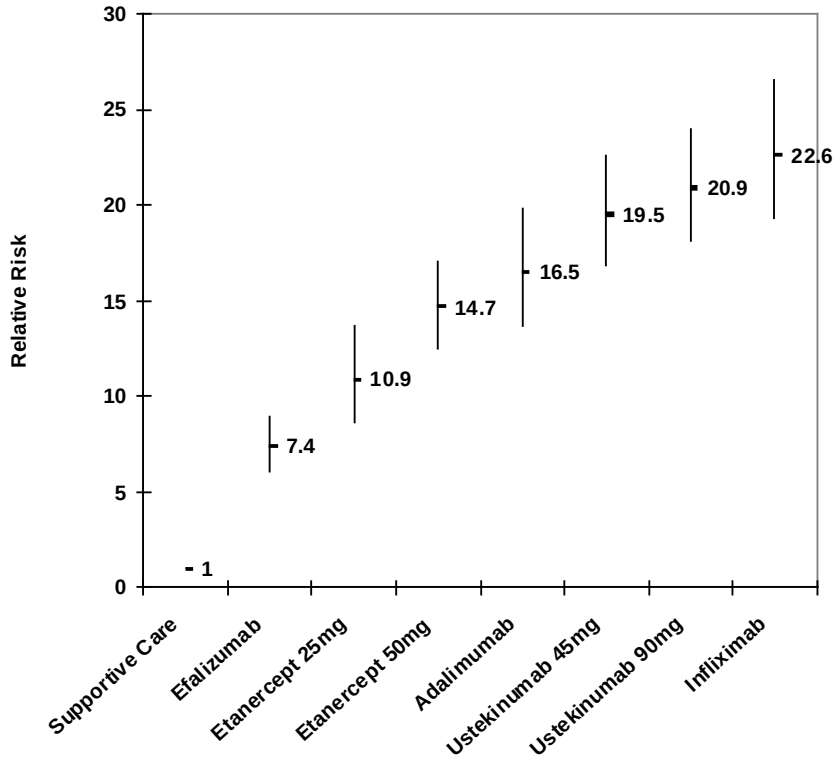


Figure 6.6.5: Relative risk of achieving a PASI 75 – for all patients



For the weight based dosing analysis, in terms of response rates (at PASI 75) infliximab is estimated to have the highest efficacy with ustekinumab 45mg and ustekinumab 90mg having the second and third highest efficacy respectively (see table 6.6.3). The same ordering also holds in terms of PASI 50 and PASI 90, with infliximab estimated to have the highest efficacy followed by ustekinumab 45mg and ustekinumab 90mg (again see table 6.6.3). The ordering of the three most efficacious biologics changes slightly when using the all-patient analysis with infliximab, ustekinumab 90mg and ustekinumab 45mg being first, second and third respectively (see table 6.6.5). This ordering holds true for all the three efficacy measures: PASI 50, PASI 75, and PASI 90. In both the weight-based and the all-patients analyses etanercept 25mg and efalizumab are the least efficacious.

It is important to note that the estimate of response rate for adalimumab is lower than reported in the manufacturers submission for TA146. This can be explained by the inappropriate WinBUGS code described earlier in section 6.6.

There is some uncertainty around the response rates demonstrated by the relatively wide Bayesian credible intervals.

The following figures present the results (PASI 50, 75 and 90) of individual trials, with a corresponding meta-analysis of the trial data for each product individually and the effect estimates from the mixed treatment comparison (here referred to as network meta-analysis). It should be noted that whilst the number of trials contributing to each PASI response category varies depending on the reporting of individual studies, the network meta-analysis uses the available data from all categories to estimate each individual category under an assumption of constant treatment effects on the probit scale.

Figure 6.6.6 Forest plots for PASI 50

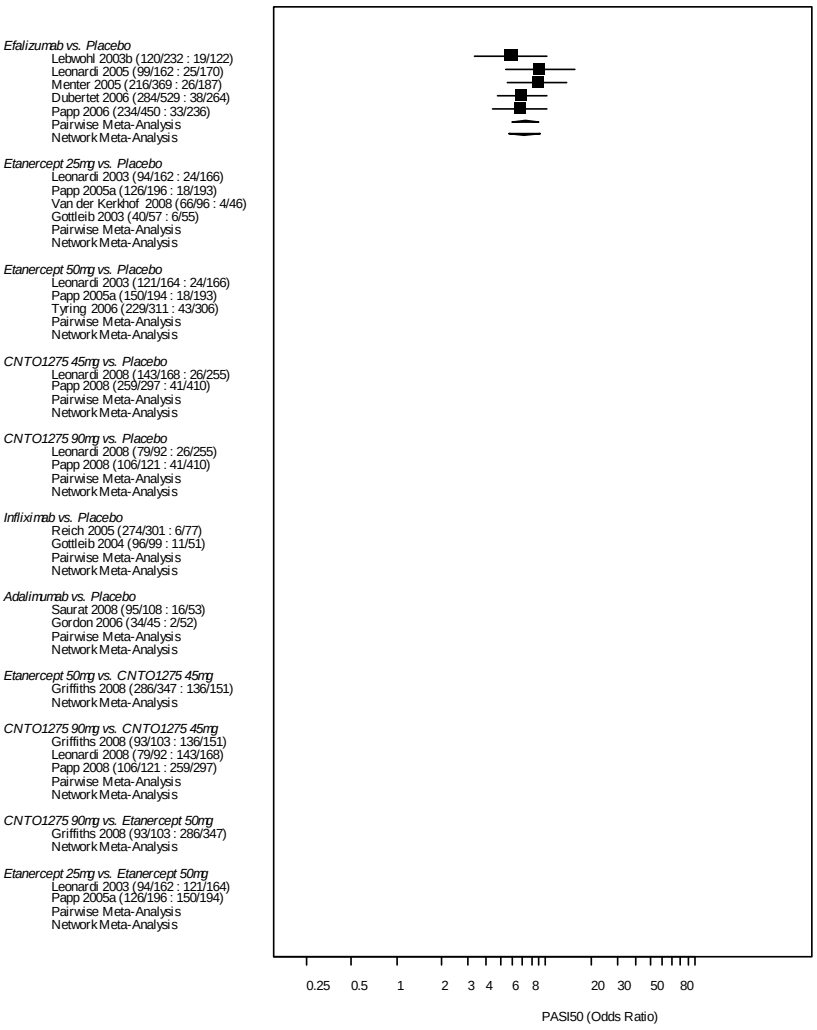


Figure 6.6.7 Forest plots for PASI 75

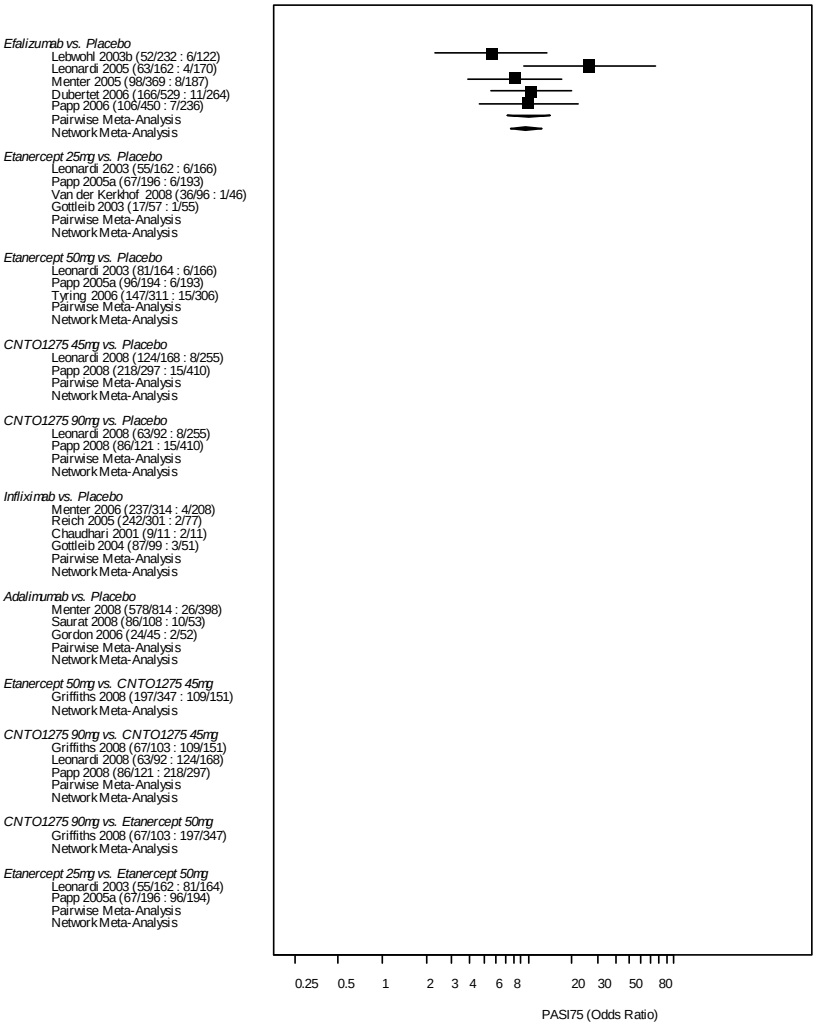
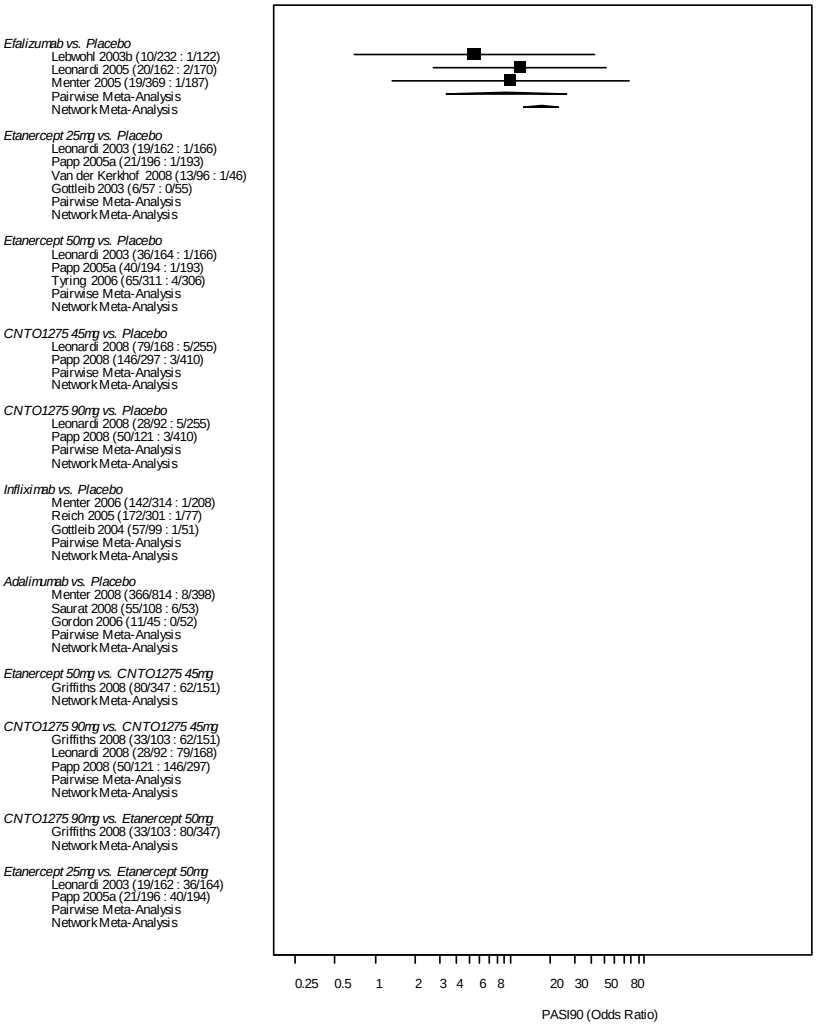


Figure 6.6.8 Forest plots for PASI 90



6.7 *Safety*

The safety profile of ustekinumab has been determined by analysis of adverse event rates reported in the published clinical trials referred to in this submission. Adverse events for studies T04(39), PHOENIX-1 (T08)(40;43) , PHOENIX-2 (T09)(41;44) , and ACCEPT (T12)(42;45) are summarised in Table 6.7.1 below.

Ustekinumab was well-tolerated in subjects with moderate to severe psoriasis in the Phase II and III clinical trials. In these studies, the safety profile was generally consistent and comparable across the placebo and ustekinumab groups during the placebo-controlled period of the studies (that is the first 12 weeks). There was generally no increase in safety events with 90mg compared with 45mg, and there was no increase in the frequency of events occurring over time with maintenance dosing. Overall, few patients discontinued treatment with ustekinumab with 13.1% of patients ending study participation by week 52 in PHOENIX 1 and 12.1% in PHOENIX 2.

Adverse events

Up to week 12, the overall proportions of subjects who experienced at least one adverse event was similar between the placebo, ustekinumab 45mg, and 90mg groups, and no dose-response was apparent. Adverse events that occurred with frequency ≥1% were also generally similar between the placebo, ustekinumab 45mg, and 90mg groups. The most frequently reported adverse events in all groups were nasopharyngitis and upper respiratory tract infection. Over the course of the trials, the overall pattern of adverse events was similar to that reported to week 12. When adverse event reporting rates were compared with those observed during the first 12 weeks of the study, the adverse events did not appear to increase over the course of the trials at a rate disproportionate to the additional follow up. Analyses of rates of adverse events adjusted for follow up (e.g., per 100 patient years of follow-up) led to similar conclusions.

Serious adverse event rates and discontinuation of study treatment due to an adverse event were low throughout the studies. Through week 12, serious adverse event rates were comparable across the three groups in the combined Phase III trials. One death resulting from sudden cardiac death was reported in a 33 year-old man with an underlying congestive cardiomyopathy treated with ustekinumab 90mg. Serious adverse event rates were comparable between the 45mg and 90mg groups. Serious adverse event reporting rates in the first 12 weeks did not appear to increase over the course of the trials at a rate disproportionate to the additional follow up. Three additional deaths occurred in ustekinumab-treated subjects that are not included in the clinical database for the reporting period (one subject from the phase 2 study (T04) died approximately 1 year after the study ended and two subjects from the ongoing PHOENIX 2 study (T09) died).

Specific analyses of important adverse events undertaken to evaluate potential risks

Specific analyses of targeted adverse events of malignancy (including non-melanoma skin cancer (NMSC)), serious infections, and cardiovascular events indicate no consistent pattern of these events in ustekinumab-treated subjects (Table 6.7.1). Exposure of large numbers of patients and follow-up for longer periods of time will be required to more carefully examine the potential impact of ustekinumab on these infrequent events.

Table 6.7.1: Summary of serious infections, serious cardiovascular events and cerebrovascular events, and neoplasm; treated subjects in psoriasis (phase 2 and 3 studies)

	12-week placebo-controlled period				Until end of follow up period			
	Placebo	Ustekinumab			Placebo	Ustekinumab		
		45mg	90mg	Combined		45mg	90mg	Combined
Subjects treated	732	790	792	1582	732	1110	1156	2266
Total subject years of follow-up	177	203	203	407	182	725	742	1467
Event rate per hundred subject-years								
Serious infections	1.70	0.49	1.97	1.23	1.65	0.83	1.21	1.02
Serious myocardial infarction	0.00	0.00	0.98	0.49	0.55	0.28	0.40	0.34
Serious stroke	0.00	0.98	0.00	0.49	0.00	0.41	0.00	0.20
Incidence per 100 subject years								
Neoplasms (malignant)	1.70	0.99	0.98	0.99	1.65	1.52	1.08	1.30
NMSC	1.13	0.49	0.98	0.74	1.10	0.83	1.08	0.96
Non-cutaneous malignancy	0.57	0.49	0.00	0.25	0.55	0.69	0.00	0.34
Lymphoma	0	0	0	0	0	0	0	0

The total subject years of follow-up for malignancy is slightly lower since only the first event is counted in the calculation of incidence per 100 subject-years.
NMSC = non-melanoma skin cancer

Immune reactions

No cases of anaphylaxis or serum sickness reaction were detected in the phase 2 and 3 studies. Allergic reactions (e.g., drug eruption, urticaria) were reported in less than 1% of subjects.

Ustekinumab injections were generally well tolerated. The proportions of subjects who reported injection-site reactions and the proportions of injections complicated by an injection-site reaction were low in all groups. Injection site reactions were generally mild. Injection-site erythema was the only specific injection-site reaction that occurred in 1% or more of ustekinumab-treated subjects. It occurred more frequently in subjects treated with ustekinumab (1.6%) than placebo (0.9%). No injection site reactions resulted in study agent discontinuation.

Table 6.7.2: Summary of key safety findings in PHOENIX 1 (T08) (to Week 12)

	Placebo	Ustekinumab		
		45mg	90mg	Combined
Subjects treated	255	255	255	510
Average duration of follow-up (weeks)	12.1	12.2	12.1	12.2
Average exposure (weeks)	4.1	4.2	4.1	4.2
Subjects with ≥1 AE, *n* (%)	122 (47.8%)	146 (57.3%)	131 (51.4%)	277 (54.3%)
Subjects with ≥1 SAE, *n* (%)	2 (0.8%)	2 (0.8%)	4 (1.6%)	6 (1.2%)
Subjects with ≥1 infection, *n* (%)	68 (26.7%)	80 (31.4%)	66 (25.9%)	146 (28.6%)
Subjects with ≥1 serious infection, *n* (%)	1 (0.4%)	0 (0%)	2 (0.8%)	2 (0.4%)
Subjects with ≥1 malignancy, *n*	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	Placebo	Ustekinumab		
		45mg	90mg	Combined
(%)				
Subjects with ≥1 MI/stroke, *n* (%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.2%)

AE = adverse event; SAE = serious adverse event; MI = myocardial infarction

Table 6.7.3: Summary of key safety findings in PHOENIX 2 (T09) (to Week 12)

	Placebo	Ustekinumab		
		45mg	90mg	Combined
Subjects Treated	410	409	411	820
Average duration of follow-up (weeks)	12.0	12.1	12.2	12.2
Average exposure (weeks)	4.1	4.1	4.2	4.2
Subjects with ≥1 AE, *n* (%)	202 (49.3%)	215 (52.6%)	197 (47.9%)	412 (50.2%)
Subjects with ≥1 SAE, *n* (%)	8 (2.0%)	8 (2.0%)	5 (1.2%)	13 (1.6%)
Subjects with ≥1 infection, *n* (%)	82 (20.0%)	88 (21.5%)	88 (21.4%)	176 (21.5%)
Subjects with ≥1 serious infection, *n* (%)	2 (0.5%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Subjects with ≥1 malignancy, *n* (%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
NMSC	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Non-cutaneous malignancies	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with ≥ 1 MI/stroke, *n* (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

AE = adverse event; SAE = serious adverse event; NMSC = non melanoma skin cancer; MI = myocardial infarction

Table 6.7.4: Summary of key safety findings in ACCEPT (T12)(to Week 12)

	Etanercept 50mg twice weekly	Ustekinumab		
		45mg	90mg	Combined
Subjects Treated	347	209	347	556
Average duration of follow-up (weeks)	12.1	12.1	12.2	12.2
Average exposure (weeks)	23.1	2.0	2.0	2.0
Subjects with ≥1 AE, *n* (%)	241 (69.5%)	138 (66.0%)	237 (68.3%)	375 (67.4%)
Subjects with ≥1 SAE, *n* (%)	4 (1.2%)	4 (1.9%)	4 (1.2%)	8 (1.4%)
Subjects with ≥1 infection, *n* (%)	93 (26.8%)	59 (28.2%)	93 (26.8%)	152 (27.3%)
Subjects with ≥1 serious infection, *n* (%)	1 (0.3%)	0 (0.0%)	4 (1.2%)	4 (0.7%)
Subjects with ≥1 malignancy, *n* (%)	0 (0%)	3 (1.4%)	1 (0.3%)	4 (0.7%)
NMSC	0 (0%)	2 (1.0%)	1 (0.3%)	3 (0.5%)
Non-cutaneous malignancies	0 (0%)	1 (0.5%)	0 (0%)	1 (0.2%)
Subjects with ≥ 1 MI/stroke, *n* (%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)

AE = adverse event; SAE = serious adverse event; NMSC = non melanoma skin cancer; MI = myocardial infarction

Serious infections, including tuberculosis

Rates of serious infections were low in all treatment groups and remained low throughout the treatment and follow up period. Serious infections per hundred subject years of follow-up were generally comparable between the combined ustekinumab group (1.23 (95% CI: 0.40, 2.87)) and the placebo group (1.70 (95% CI: 0.35, 4.96)) during the placebo-controlled portions of the studies). The only serious infection reported in more than one subject in any treatment group, cellulitis, was reported in

two (0.4%) subjects in the placebo group and two (0.1%) subjects in the combined ustekinumab group. Rates of serious infections through the end of the treatment and follow-up period remained low and were comparable between the combined ustekinumab and placebo groups. No cases of active tuberculosis were observed. One potential opportunistic infection was observed, a 54-year-old woman receiving ustekinumab 90mg thought to have possible disseminated cutaneous herpes zoster based on the presence of 19 vesicles identified outside the primary affected dermatomes (20 vesicles is defined as a diagnosis for disseminated zoster[227]). This subject had no visceral involvement.

Of note, subjects with newly diagnosed latent tuberculosis were eligible for study participation if appropriate treatment for latent tuberculosis was initiated either prior to or simultaneously with the first administration of study agent. A total of 68 subjects were treated with isoniazid (INH), none of whom developed active tuberculosis. One subject was exposed to tuberculosis during the trial, developed a positive purified protein derivative (PPD) and initiated INH treatment, but did not develop active tuberculosis.

Malignancies

Across the Phase II and III studies, 7 subjects (3 placebo-treated and 4 ustekinumab-treated) reported at least one malignancy during the placebo-controlled period. After the placebo-crossover, an additional 15 subjects treated with ustekinumab reported at least one malignancy. During the controlled period, rates of Non-Melanoma Skin Cancer (NMSC), non-cutaneous malignancies, and all malignancies were each low and similar between treatment groups. The overall incidence of malignancy per 100 subject-years of follow-up was 0.99 (95% CI: 0.27, 2.52) in the combined ustekinumab group and 1.70 (95% CI: 0.35, 4.98) in the placebo group during the controlled period and 1.30 (95% CI: 0.78, 2.03) and 1.10 (95% CI: 0.13, 3.98), respectively, through the treatment and follow up period.

The rates of non-cutaneous malignancies were consistent with rates expected based on rates observed in the National Institutes of Health (NIH) Surveillance Epidemiology and End Results (SEER) database (2004) (standardised incidence ratio [SIR] = 0.71 [95% CI: 0.23, 1.65] for ustekinumab-treated subjects versus SIR = 1.12 [95% CI: 0.03, 6.24] for placebo-treated subjects). Rates of NMSC were consistent with rates observed in psoriasis clinical trials of other biologic agents, including trials of infliximab, efalizumab, and etanercept.

The malignancies observed in the ustekinumab psoriasis clinical studies did not reveal a pattern that was suggestive of immunosuppression. In particular, the non-cutaneous malignancies were common types of malignancies in the general population (prostate, breast, kidney, thyroid) of varied histogenesis not suggesting a mechanistic link, and no lymphomas were reported. Moreover, among NMSC, the observed 6:1 ratio of basal:squamous cell cancers was consistent with the ratio observed in immunocompetent patients in the general population (4:1), and does not reflect the reversal of this ratio seen in immunosuppressed patients (e.g., with immunosuppression post-organ transplant[228]). Combined, these observations do not suggest a significant impact of ustekinumab on malignancies.

Asthma or seasonal allergies

The impact of ustekinumab on asthma was evaluated because of the drug's theoretical potential to block differentiation of Th1 cells towards a Th2 phenotype. This differentiation can exacerbate atopic types of diseases like asthma. While subjects with asthma were excluded from the ustekinumab Phase II trial in psoriasis, subjects with non-severe asthma were eligible to participate in the two phase III studies. Approximately 8% of subjects in the phase 3 trials reported a medical history of asthma. In general, adverse event rates of asthma were low; subjects responded appropriately to therapy and showed no clear relationship to drug exposure. One serious adverse event of worsening asthma was reported in the placebo group, but no serious adverse events of asthma were reported in ustekinumab-treated subjects. No subjects discontinued study agent due to asthma. By medical history, 22.5% of subjects enrolled in the phase 3 studies reported seasonal allergies, and 1.2% of subjects reported atopic dermatitis, other diseases considered to be Th2-mediated. As with asthma, adverse event rates of seasonal allergies were low and showed no clear relationship to drug, and only one adverse event of atopic dermatitis was reported (in a subject receiving placebo). Combined, these observations do not suggest a detrimental effect of ustekinumab on asthma or other diseases with putative Th2-mediated pathophysiology.

Cardiovascular disease

The prevalence of cardiovascular risk factors including diabetes, obesity, overweight, hyperlipidaemia, hypertension, and smoking was higher in the subjects with psoriasis enrolled in the phase 2 and 3 clinical trials than in the general US population. The rates of these baseline comorbidities were comparable in each of the clinical studies and were generally comparable to rates reported in the psoriasis population.

Rates of serious myocardial infarction and stroke in the phase 2 and 3 studies were low (occurring at a rate of less than one event per hundred subject-years) in all ustekinumab dose groups. The rates for ustekinumab were comparable to placebo through the controlled period and follow-up period of the clinical trials. For myocardial infarction, the rates were 0.34 (95% CI: 0.11, 0.80) and 0.55 (95% CI: 0.01, 3.06) in the combined ustekinumab and placebo groups, respectively. For stroke, the rates were 0.20 (95% CI: 0.04, 0.60) and 0.00 (95% CI: 0.00, 1.64) in the combined ustekinumab and placebo groups, respectively. The event rates did not appear to increase over time.

The event rate for serious myocardial infarction in the ustekinumab psoriasis Phase II and III studies was higher than expected compared to the general US population utilizing the CDC (Centers for Disease Control and Prevention) database (rate ratios of 1.35 and 2.07 in the combined ustekinumab and placebo groups, respectively). However, this elevation did not appear to be due to ustekinumab since rate ratios greater than one were observed in both the ustekinumab group and the placebo group, and both groups showed a similar magnitude of increased relative risk. This observation suggests that those with psoriasis have underlying risk factors for myocardial infarction, an observation that is supported by research.

When myocardial infarction event rates were compared with rates expected in a psoriasis population, adjusted for underlying cardiovascular risk factors using the General Practice Research Database (GPRD), no events in the ustekinumab psoriasis studies occurred at a rate that was higher than expected. In both

ustekinumab-treated and placebo-treated subjects, the standardized incidence rates (SIRs) for myocardial infarction and stroke were less than one.

Combined, these analyses do not demonstrate an impact of ustekinumab on cardiovascular risk during the period of the trials.

Immunogenicity

In PHOENIX 1, the overall incidence of development of antibodies to ustekinumab was low with 5.1% (n=38) developing an immune response to ustekinumab by week 76. This result is similar in the PHOENIX 2 trial, with 5.4% (n=65) developing an immune response to ustekinumab by week 52.

Laboratory parameters

Similar to the approach with adverse events, safety analyses evaluated the frequency of potentially clinically significant laboratory abnormalities (e.g., pre-specified markedly abnormal laboratory values). Safety analyses also examined whether rates of laboratory abnormalities in drug-treated subjects exceeded the placebo rates, and the extent of dose-response. Rates of markedly abnormal haematologic and chemistry values were generally low in ustekinumab-treated subjects. The only clinical chemistry and haematology values in which markedly abnormal changes were observed in more than 1% of the study population during the controlled portions of the studies were elevated non-fasting glucose and overall lymphocytes, which occurred in comparable or lower proportions of ustekinumab-treated subjects *vs.* placebo-treated subjects.

Longer-term safety data

To date safety has been established in 1,285 patients treated for at least one year within the PHOENIX trials, and 373 patients for at least 18 months. Analysis shows that there were no increased risks identified with rates of serious infection, malignancy and major cardiovascular events. These were all consistent with expected rates as observed in external databases such as SEER.

6.8 *Non-RCT evidence*

6.8.1 Details of how the relevant non-RCTs have been identified and selected

No non-RCT evidence is included in this submission.

6.8.2 Summary of methodology of relevant non-RCTs

No non-RCT evidence is included in this submission.

6.8.3 Critical appraisal of relevant non-RCTs

No non-RCT evidence is included in this submission.

6.8.4 Results of the relevant non- RCTs

No non-RCT evidence is included in this submission.

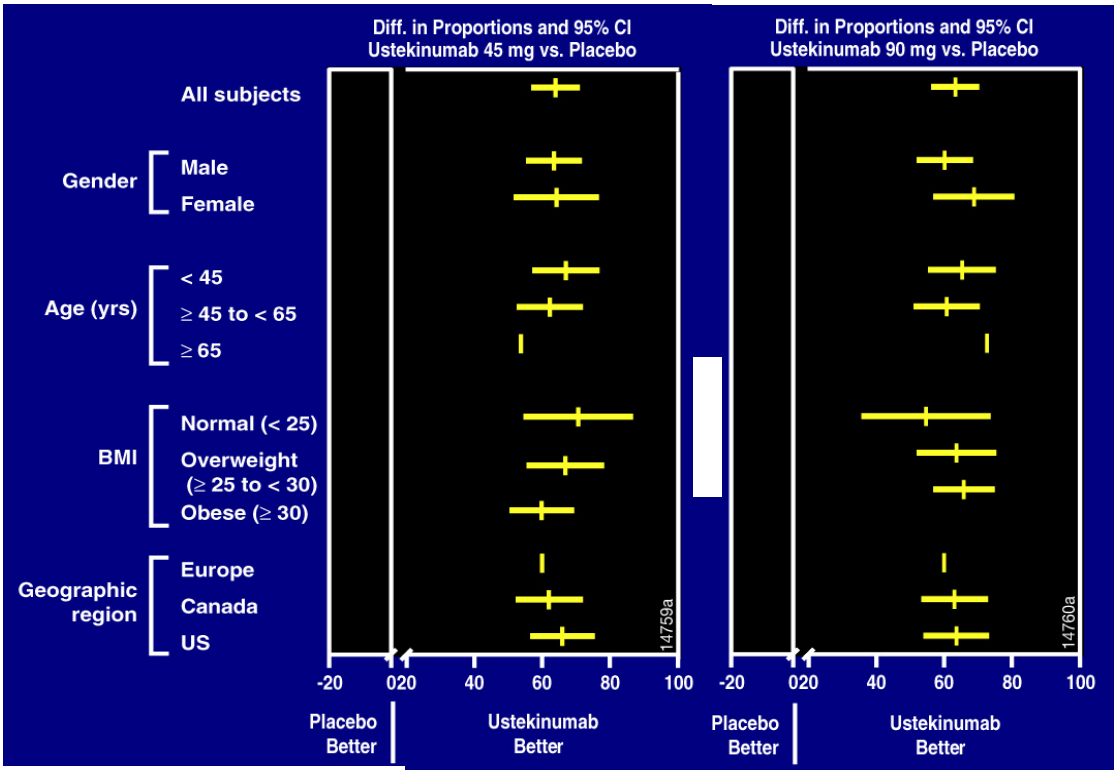
6.9 *Interpretation of clinical evidence*

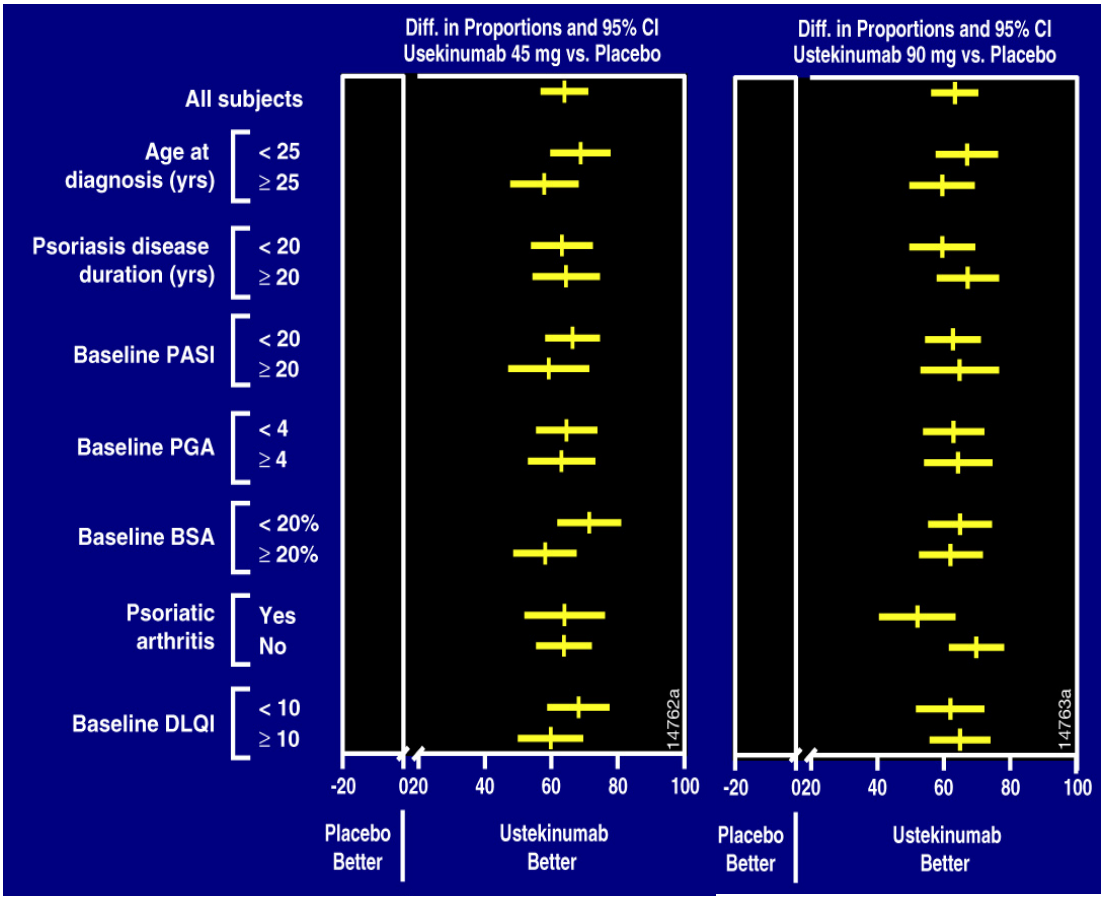
6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

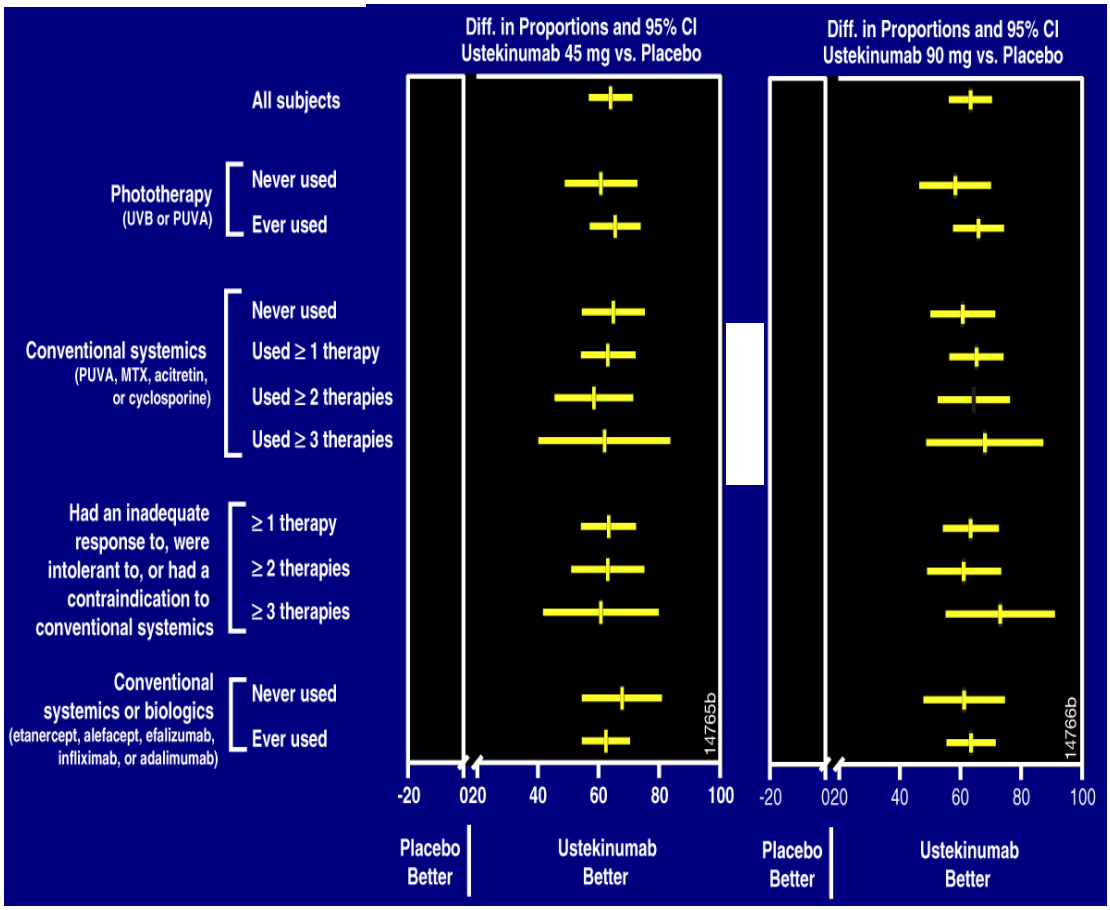
Overall, we believe that the clinical evidence base is broadly appropriate and relevant to the decision problem. The supporting evidence for this is detailed below.

The PHOENIX and ACCEPT trials consistently demonstrated that ustekinumab is a highly effective treatment for in patients who have moderate to severe psoriasis. The patient population involved in the clinical trials are broadly representative of the severe psoriasis patient population in England & Wales. European patients were enrolled in all three studies and the UK patients in two of the three. Extensive analyses of various subgroups within the PHOENIX trials, including gender, age, BMI, geographic location, age at diagnosis, disease duration, baseline measurements i.e. PASI, PGA, BSA, DLQI and finally previous experience of other treatments for psoriasis, have shown that the response to ustekinumab does not vary significantly regardless of subgroup (see figure 6.9.1).

Figure 6.9.1 PASI 75 response by subgroup




Diff. in Proportions and 95% CI
Usekinumab 45 mg vs. Placebo
Diff. in Proportions and 95% CI
Ustekinumab 90 mg vs. Placebo
All subjects
Age at diagnosis (yrs)
< 25
≥ 25
Psoriasis disease duration (yrs)
< 20
≥ 20
Baseline PASI
< 20
≥ 20
Baseline PGA
< 4
≥ 4
Baseline BSA
< 20%
≥ 20%
Psoriatic arthritis
Yes
No
Baseline DLQI
< 10
≥ 10
14762a
14763a
-20
020
40
60
80
100
Placebo Better
Ustekinumab Better


Diff. in Proportions and 95% CI
Ustekinumab 45 mg vs. Placebo
Diff. in Proportions and 95% CI
Ustekinumab 90 mg vs. Placebo
All subjects
Phototherapy (UVB or PUVA)
Never used
Ever used
Conventional systemics (PUVA, MTX, acitretin, or cyclosporine)
Never used
Used ≥ 1 therapy
Used ≥ 2 therapies
Used ≥ 3 therapies
Had an inadequate response to, were intolerant to, or had a contraindication to conventional systemics
≥ 1 therapy
≥ 2 therapies
≥ 3 therapies
Conventional systemics or biologics (etanercept, alefacept, efalizumab, infliximab, or adalimumab)
Never used
Ever used
14765b
14766b
-20
020
40
60
80
100
Placebo Better
Ustekinumab Better

Etanercept 50mg twice weekly

Twice-weekly doses of etanercept 50mg were used as the active control in the head to head ACCEPT trial of ustekinumab versus etanercept. Although this etanercept dosing regimen has not received a positive recommendation from NICE (TA103)(22) (because, although more effective than 25mg dosing it was not considered to be cost-effective), it is licensed in England & Wales for the treatment of moderate to severe psoriasis. Etanercept 50mg twice weekly dosing for the first 12 weeks is the maximum approved dose and schedule for the drug, and provides a reasonable timeframe for comparison of the initial efficacy of ustekinumab versus etanercept. To evaluate whether ustekinumab represented a significant therapeutic advance in the treatment of patients with moderate to severe plaque psoriasis, comparing the ustekinumab benefit-risk profile against the highest approved dose and schedule of etanercept was thought to provide the fairest basis of comparison. Additionally, there is current evidence from database studies that demonstrates that this higher dose is still being used in the UK(67) (see Appendix 6). Therefore, this is an appropriate comparator for ustekinumab in relation to the decision problem.

Importantly, there is strong evidence to suggest that etanercept 50mg twice weekly is significantly more efficacious than the 25mg twice weekly dose. This evidence comes from randomised, controlled trials of etanercept where the PASI 75 response rate at week 12 for etanercept 50mg twice weekly was 49%, 49%, and 47% across three separate studies(48;53;63). For the etanercept 25mg twice-weekly regimen, PASI 75 response rates at week 12 have been reported as 34%, 34%, and 30%(53;62;63). These results suggest that the superior efficacy of ustekinumab versus etanercept observed in the ACCEPT trial are a conservative estimate of the efficacy difference between the ustekinumab and the NICE recommended dose of etanercept, and this is supported by the results of the mixed treatment comparison presented earlier.

Relevance of outcome measures

Outcome measures such as PASI and DLQI used within the clinical trials are used within clinical practice and also feature in both national guidelines from the British Association of Dermatology as well as guidance from NICE and the SMC. Therefore, the outcomes measured within the trials are relevant to clinical practice.

The primary outcome measure of the proportion of patients who achieve a greater than or equal to 75% improvement in their PASI score was assessed at 12 weeks and due to the study design this was the last point at which a placebo controlled comparison could be made. In practice, this is unlikely to be the time point for assessment of clinical response to ustekinumab. An advisory board including dermatologists agreed this assessment of response would take place just prior to the third dose at week 16. Although the response rates improve slightly between week 12 and week 16, this is not dramatic and any bias would likely be conservative to ustekinumab. This assumption was also discussed during the decision problem step and this proposal was felt to be acceptable in discussions with the NICE technical team.

Summary

- The safety and efficacy of ustekinumab has been evaluated in three phase III trials involving approximately 3,000 patients. Of these participants, around 1,700 have been randomised to treatment with ustekinumab.

- In all three studies, clinical assessments at week 12 have demonstrated that after only two initial doses, ustekinumab is highly effective in improving psoriasis across multiple clinically relevant outcome measures including PASI, PGA and patient reported outcomes.
- In both studies, there were statistically significant and clinically meaningful improvements in patients' quality of life as measured by the DLQI with both doses of ustekinumab. The benefits of ustekinumab on patients' quality of life are stated in section 5.1 of the SmPC.
- The PHOENIX 1 and 2 studies demonstrate that the high PASI response rates observed during the double-blind, randomised phases of the studies are maintained longer term (up to and over one year) with 12 weekly maintenance injections.
- The ACCEPT trial is the first randomised, comparative trial of two biologic agents to have been conducted in psoriasis and is of particular relevance to this appraisal as it compares ustekinumab to the most commonly used agent in UK clinical practice
- In the ACCEPT trial, which evaluated over 900 patients with moderate to severe psoriasis, ustekinumab 45mg and ustekinumab 90mg were both significantly more effective than etanercept 50mg twice weekly at week 12.
    - 68% and 74% of patients treated with ustekinumab 45mg and ustekinumab 90mg respectively achieved PASI 75 response compared to 57% treated with etanercept 50mg twice weekly ($p<0.001$)
    - A significantly higher proportion of patients treated with ustekinumab 45mg and ustekinumab 90mg also achieved a PGA of cleared or minimal (65% and 71% respectively) compared with etanercept 50mg twice weekly (49%).
    - Significantly more patients also achieved the more stringent response criteria of PASI 90 at week 12 for both ustekinumab groups versus etanercept 50mg twice weekly ($p<0.001$).
- Efficacy appears consistent across all identified sub-populations including demography, disease characteristics, previous treatment and self-administration
- Ustekinumab 90mg is a more effective dose than the 45mg for patients who weight more than 100kg
- Ustekinumab is well tolerated and across studies to date, the safety profile comparable is comparable to placebo to week 12.
- To date safety has been assessed in 1,285 patients treated for at least one year and 373 patients for at least 18 months.
- In these three studies ustekinumab was well tolerated. Rates of serious infections, malignancies and cardiovascular events were low and comparable to placebo and etanercept 50mg twice weekly.
- To compare the effectiveness of ustekinumab to other treatment options for moderate to severe psoriasis, a mixed treatment comparison was undertaken following a comprehensive systematic review of the literature. The mixed treatment comparison followed the methodology employed by the assessment group in the original Multiple Technology Appraisal of efalizumab and etanercept.
- Results from this analysis suggest that ustekinumab has the highest mean PASI 75 response rates after infliximab. In the weight-based mixed treatment comparison, mean PASI 75 response rates were 75% and 69% for ustekinumab 45mg and ustekinumab 90mg groups, compared to mean response rates of 59%, 26%, 38%, and 52% for adalimumab, efalizumab, etanercept 25mg and etanercept 50mg respectively.
- In summary, in the first head to head trial of biologic agents for the treatment of psoriasis, both doses of ustekinumab were more effective than the most effective licensed dose of etanercept. In a mixed treatment comparison, which built upon

the methodology developed by the University of York in the original Multiple Technology Appraisal, ustekinumab resulted in higher PASI 75 responses than adalimumab, efalizumab and etanercept.

6.9.2 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?

Based on the evidence from the clinical trials, the criteria that should be applied to psoriasis patients to identify eligibility for treatment with ustekinumab are a PASI ≥10 and DLQI >10.

7 Cost effectiveness

7.1 *Published cost-effectiveness evaluations*

7.1.1 Identification of studies

The searches for the relevant economic literature were designed and conducted to replicate those performed in the review carried out by Woolacott et al (2006)(46). Searches took place in November 2008 and where possible searches were limited to retrieve articles published from 2004-2008. Articles and abstracts were identified through searches on the following databases:

- MEDLINE and In-Process Citations (OVID Online)
- EMBASE (www.embase.com)
- NHS Economic Evaluation Database (NHS EED) (CRD administration database)
- Cochrane Library.

No language or other restrictions were applied. Full details of the search strategies are reported in Appendix 3.

Two reviewers selected the studies for inclusion. All titles and abstracts were screened and any references that were considered relevant by either of these two reviewers were obtained. There were no discrepancies in decisions and therefore a third reviewer was not required. Economic evaluations reported as full publications or unpublished full reports were included in the review. Abstracts were only included if adequate information was provided. Economic evaluations reported as full publications or unpublished full reports were included in the review. Any duplicate records were excluded and abstracts were only included if adequate information was provided based on the criteria below. The quality of the studies was appraised using an updated version of a checklist developed by Drummond et al. 1997.

Inclusion criteria

Studies were eligible for inclusion if they assessed both the costs and benefits of adalimumab, efalizumab, etanercept, infliximab or ustekinumab and compared findings with an appropriate comparator treatment. Full details of the inclusion criteria are reported in Table 7.1.1 below.

Table 7.1.1 Inclusion criteria for the review on cost-effectiveness

Study design	Cost-consequence analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis
Setting	Any
Population	Adult patients with psoriasis
Intervention	Adalimumab (Humira) or Etanercept (Enbrel) or efalizumab (Raptiva) or infliximab (Remicade) or ustekinumab (Stelara) compared with each other or to conventional treatments
Comparator	Any
Primary outcome	PASI response
Time period	2004-2008

Overview of literature review results

Overall, six references were identified for potential inclusion into the review (Woolacott et al. 2006(46), Pearce et al. 2006(68), CADTH 2007(69), Nelson et al, 2008(70), Menter & Baker 2005(71) and Hankin et al. 2005(72)). Of these four were deemed to be appropriate for data extraction and full appraisal(69); Woolacott et al. 2006(46) and Pearce et al. 2006(68)). The remaining three studies were considered to not be of high quality based on their basic methodological flaws and simple modelling approach and were not deemed useful enough from a methodological and outcome point of view to warrant full critical appraisal.

7.1.2 Description of identified studies

The cost-effectiveness evidence on this clinical area is scarce. The HTA report(46) which includes the economic model developed by the Technology Assessment Review team at the University of York (referred to hereafter as the 'York model') will be of special attention as this forms the basis for the economic evaluation presented in this submission. The second study compares etanercept, efalizumab, infliximab and alefacept with each other and five alternative treatments (Pearce et al. 2006(68)).

Two other studies were identified for mention in the narrative review (Menter & Baker 2005(71), Hankin et al. 2005(72)) but given their basic methodological flaws (e.g. both reported average cost-effectiveness ratios instead of incremental cost-effectiveness ratios, ICERs) and simple modelling approach they were not deemed to be appropriate from a methodological and outcomes point of view to warrant full critical appraisal.

The York model(46)

The objective of this model was to assess the cost-effectiveness of etanercept and efalizumab for the treatment of moderate to severe chronic plaque psoriasis. This project, published as a HTA monograph, was commissioned by the National Coordinating Centre of Health Technology Assessment (NCCHTA) on behalf of NICE. The following table summarises the study methodology.

Table 7.1.2 Summary of the York model

Study design	Cost-effectiveness based on a Markov model - Short-term trial data is used to model the response of patients to initial treatment, using the combined probabilities of achieving a 50, 75 or 90% reduction in the PASI score. Beyond this period, the underlying Markov structure allows the extrapolation of results up to 10 years.
Population	Moderate to severe psoriasis
Intervention	Efalizumab, etanercept (25mg intermittent, 25mg continuous and 50mg intermittent)
Comparator(s)	Placebo (regarded as supportive care)
Outcome	Cost-utility
Time horizon	10 years
Resource use	Resource utilisation was derived from several sources, such as the SmPCs of the included treatments, BAD guidelines for the treatment of psoriasis, published literature, UK national databases and clinical expert opinion. All relevant resource use (drug acquisition, administration and monitoring costs; hospital-related costs) were included. Resource use associated with the treatment of adverse events was not included.

	The prices of drugs were taken, where available, from the BNF No. 48. The price of efalizumab was based on information provided by the manufacturer. Prices of monitoring tests were obtained from the York NHS Trust. The rest of costs were obtained from the latest available NHS Reference Costs and PSSRU databases. All costs were estimated from UK sources and updated using latest available PSSRU Hospital and Community Health Services (HCHS) prices index when needed.
Results	Costs of treatment per patient are detailed for both the short-term trial period and the annual maintenance period at 2004-05 prices. Etanercept 50mg as intermittent use is the most expensive therapy option (£14,102 annual cost per patient), with infliximab 5mg ranking second (£12,304), followed by etanercept 25mg continuous use (£9,562) and efalizumab (£9,070). These differences were primarily due to drug acquisition cost. Biological therapies (efalizumab and etanercept) would only be cost-effective in a treatment sequence for all patients with moderate to severe psoriasis if the NHS were willing to pay over £60,000 per QALY gained. Intermittent use of etanercept 25mg would only be a cost-effective option in a treatment sequence for patients with poor baseline DLQI (fourth quartile) if the NHS were willing to pay up to £35,000 per QALY gained. This threshold reaches £45,000 per QALY gained for the same patient group in the case of efalizumab. For patients with a poor baseline DLQI who are also at a high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment (assumed to be equivalent to 21 inpatient days per year), intermittent use of etanercept 25mg could be a cost-effective option if the NHS were willing to pay up to £20,000 per QALY gained. The threshold increases to £35,000 per QALY gained for the same patient group under the same hospitalisation costs assumption in the case of efalizumab.
Sensitivity analyses	A probabilistic sensitivity analysis was conducted as well as a number of scenario analyses, such as severity level in terms of baseline DLQI and the risk of hospitalisation for non-responding patients.

Critical appraisal

This study is based on a systematic and comprehensive approach to identifying evidence relevant to informing a decision model comparing different biological and systemic therapies in the treatment of moderate to severe psoriasis. On this basis, a number of assumptions and parameters are subsequently utilised in the decision analytic model known as the 'York model'. Clinical evidence was obtained from a Bayesian meta-analysis of RCTs. The design of the studies included and the statistical techniques used to synthesise the efficacy data, as well as the comprehensive and transparent description of the methods used, enhance the internal validity of the analysis.

The model structure comprises two main elements. The first short-term 'trial period' component, which resembles a basic decision-analytic tree up to 3 months, evaluates costs and effects over this period which matches the period of follow-up reported in most of the RCTs and used in the Bayesian evidence synthesis for the base-case analysis. The second element involves a long-term extrapolation using a Markov model, which extends the analysis from 3 months up to 10 years time-horizon, with yearly cycles. The results of the short-term model inform the proportion

of non-responding and responding patients after the initial 'trial period' which will enter the long-term model. However, the Markov model time-horizon has not been adjusted for this initial short-term period, so in consequence the overall time-horizon of the analysis is 10 years and 3 months.

A discussion of the specific challenges associated with modelling treatment sequences for chronic diseases is provided in the form of a technical appendix. The analytical structure of the York model is explained and justified under this framework. The cost-effectiveness analysis compares estimates of expected costs and health benefits per unit time (per year) per each treatment, incorporating both patients who respond and continue treatment after a 'trial' period and those who do not respond and stop treatment. The key assumptions and parameters needed to estimate the net-benefit for a treatment are detailed and justified, including the equations that inform the cost-effectiveness model.

Key parameters were varied in the probabilistic sensitivity analysis, with the exception of the annual withdrawal rate for responding patients based on expert opinion and entered into the model as a fixed parameter. Although the authors state that a sensitivity analysis was conducted on this parameter, results are not reported. The frequency of annual laboratory tests and outpatient visits associated with the different treatment strategies was mainly based on expert opinion due to the lack of published evidence or patient level data. Some assumptions are likely to have a relatively small impact on final results, such as the number of laboratory tests, but the number of outpatient visits seems a more important element. The authors stated that parametric uncertainty in drug costs was reflected in terms of a gamma distribution, but it is not clear how the uncertainty around the number of outpatient visits and laboratory tests was incorporated into the model.

The costs associated with treating serious adverse effects were excluded from the analysis. The authors stated that it was not possible to include this cost category given the uncertainty about the incidence of such events. Unit costs were reported separately from resource use. An annual discount rate of 1.5% for benefits and 6% for costs were applied, according to NICE methodological guidelines at the time. Costs and benefits were discounted incorporating separate discounted 'treatment' durations for the estimation of total costs and effects.

The authors discuss many limitations of the study. They acknowledge that some parameters in the modelling are highly uncertain, and in particular they highlight the limitations in the efficacy evidence. In this sense, conclusions from the mixed treatment comparisons (MTC) are limited by the data available and restricted to those relating to short-term use. However, this lack of information reflected the evidence base for all treatments at the time the model was developed, including the lack of long-term clinical experience with new biological treatments, so results should be interpreted with caution.

The authors present a methodological approach, which identified the optimum treatment sequences based on the expected net monetary benefit (NMB) per unit time, under the assumptions that effectiveness is independent of the position in the treatment sequence and that patients benefit only while receiving treatment. This approach allows consideration of the use of treatments in sequence instead of restricting the analysis to individual treatments as mutually exclusive options, from which inappropriate treatment recommendations may result.

Pearce et al. 2006(68)

The objective of this study is to assess the cost-effectiveness of nine treatments for moderate to severe psoriasis: PUVA, narrowband UVB phototherapy, acitretin, ciclosporin, methotrexate, alefacept, efalizumab, etanercept and infliximab. The following table describes the study in more detail.

Table 7.1.3 Summary of the methodology used in Pearce et al, 2006

Study design	Cost-effectiveness model – cost per PASI 75 responder
Population	Moderate to severe psoriasis
Intervention	PUVA, narrowband UVB phototherapy, acitretin, ciclosporin, methotrexate, alefacept, efalizumab, etanercept and infliximab
Outcome	The primary outcome of interest to the authors was the percentage of patients achieving a 75% improvement in their PASI score (PASI75) from baseline following approximately 12 weeks of treatment
Time horizon	Approximately 12 weeks dependent upon the treatment
Resource use	All relevant direct costs were included in the analysis including drug acquisition costs, drug monitoring, physician visits, nurse visits, laboratory tests, and hospitalisation for liver biopsy. The costs of managing adverse events are not included. All assumptions are clearly stated together with the relevant Medicare reimbursement code
Results	The cost per PASI 75 responder for the biologics is reported to be $1,926 for infliximab, $8,319 for etanercept, $12,897 for efalizumab and $50,383 for alefacept. For conventional systemic treatments, the cost per PASI 75 responder is reported to be $187 for methotrexate, $505 for ciclosporin and $767 for PUVA.
Sensitivity analyses	Univariate sensitivity analysis was conducted for the average cost-effectiveness ratios, but it was focused only on efficacy values

Critical appraisal

The authors discuss many limitations of the study including the use of a short term time horizon for the evaluation of a chronic disease, the use of PASI 75 as a surrogate marker for success as opposed to patient reported outcomes, and lack of consideration for combination and rotational treatments. The authors also stress the potential limitation of not including adverse events in the evaluation as many biologics were developed in response to the limiting toxicity associated with traditional treatments. In addition, they highlight the fact that performing the analysis at approximately 12 weeks may bias against some of the biologics as many of the treatment costs associated with biologics occur in the first 12 weeks, but the results can last for longer than conventional treatments. The widespread use of Medicare reimbursement codes makes it difficult to assess the generalisability of results to other settings, including the NHS in the UK.

The authors explain that their choice of comparators is based on treatments most commonly used in US clinical practice, though no evidence is given to support of this statement. The authors use non-standard indirect comparison methods, using a 'weighted average' approach to estimate the relative PASI 75 response for the nine treatments evaluated, hence breaking randomisation. This is indirectly discussed by the authors as one of the main limitations of this study in the discussion section, when they recognize that trial patient population heterogeneity has not been taken into account in the estimation of the 'relative efficacy' estimates, confounding the comparison of true efficacies.

The method for calculating the cost of treatment failure should incorporate a series of costs associated with the treatment of a flare up of psoriasis, and not just the cost of failed treatment. Weaknesses in the evidence base are identified and explored to some extent in a univariate sensitivity analysis (efficacy data only), but no attempt is made to interpret the findings. A major limitation of the analysis is the 12-week period of treatment, during which it is very unlikely that all costs and consequences associated with all the therapies selected for evaluation can be realised, especially taking into account the chronic nature of this condition.

A valuable element of this study is that the authors recognise the need to account for the cost of treatment failure when estimating the cost-effectiveness of different treatments for psoriasis, and they make an attempt of doing so. Secondly, they also highlight that given the different adverse event profiles of the available systemic therapies, the importance of appropriate patient selection is a key factor in the estimation of cost-effectiveness, recognizing the importance of modelling sequences in the treatment of psoriasis.

Overall, this study did not rate well in terms of quality according to the criteria set out by Drummond et al. 1997. For instance, the method used for pooling trial results was not methodologically sound, no modelling was undertaken to investigate outcomes beyond the trial horizons, and the reporting of the sensitivity analysis was inadequate.

Canadian Agency for Drugs and Technologies in Health, 2007(69)

This health technology assessment was carried out to answer several research questions, one of which is 'What is the comparative cost-effectiveness of adalimumab, alefacept, efalizumab, etanercept and infliximab for the treatment of adult patients with severe plaque psoriasis?' This report is a review of all available cost-effectiveness papers including those described in this section. The overall conclusions of this report were that various methodological issues were identified including few of the studies conducted a proper multi-comparator cost-effectiveness analysis, proper conclusions relating to the cost-effectiveness cannot be made using average ratios as was done in the those studies being reviewed, only one study used utility measures which limits the comparability of cost per QALY results to common cost per QALY benchmarks and finally, all cost-effectiveness studies were limited to one year despite psoriasis being a chronic condition which has a significant negative impact on quality of life.

Nelson et al., 2008(70)

The objective of this study is to determine the cost-effectiveness of biologic agents (that is adalimumab, alefacept, efalizumab, etanercept, infliximab) and placebo in cost per patient achieving a minimally important difference in the DLQI and cost per patient achieving a 75% improvement in PASI score assessed over 12 weeks. The authors discuss the main limitation of this study, which is the short time horizon of 12 weeks. There is acknowledgement that this time horizon may not be appropriate and suitable for real-world outcomes as well as the results may not reflect the true cost-effectiveness of these agents. Other limitations discussed are that the literature review carried out did not identify any studies relating to conventional systemic therapies and also the lack of inclusion of costs associated with potential adverse events, tachyphylaxis and other indirect costs. The authors did carry out some univariate sensitivity analyses and found that multiple agents had overlapping cost-

effectiveness ratios at relatively low levels of variance; thus it may not be accurate to differentiate the cost-effectiveness of these agents. The authors do state that further research is required, particularly head to head studies including phototherapy and conventional systemic treatments over a longer period, to help ascertain the most cost effective and ideal treatment regimen for moderate to severe psoriasis. Similarly, with Pearce et al, 2006(68), this study did not obtain a high quality rating based on the criteria set out by Drummond et al. 1997.

Menter & Baker, 2005(71)

Menter & Baker, 2005(71) compared the cost-efficacy over 18 months of the following biological treatments for moderate to severe plaque psoriasis: alefacept 15 mg intramuscularly weekly for two 12-week courses; efalizumab 1 mg/kg subcutaneously (SC) weekly; and etanercept 50 mg SC twice weekly for 12 weeks followed by a maintenance dose of 50 mg weekly. The study only considered direct costs and used efficacy data from large-scale trials. Cost-effectiveness was expressed in terms of total annualised costs of treatment divided by the percentage of patients achieving a PASI 75 response. No modelling technique is described, and standard decision rules for cost-effectiveness analysis were not used (Johannesson & Weinstein 1993) as results were presented in the form of average cost-effectiveness ratios ($66,669, $75,828 and $61,041 respectively). In short, the study methodology would not add any value to the economic evaluation presented in this submission.

Hankin et al, 2005(72)

Hankin et al. 2005(72) compared the cost-effectiveness of UVB, PUVA, acitretin, ciclosporin, methotrexate, alefacept, efalizumab, etanercept and infliximab, and combined regimens of acitretin with PUVA or UVB for moderate to severe psoriasis. The perspective adopted was that of the US health care system. The efficacy data were derived from 16 trials identified through a systematic review of relevant articles in Medline. Costs included drug acquisition, treatment administration and adverse events. The annual costs to achieve PASI 75 ranged (depending on dose) from $2,290-2,491 for methotrexate, $3,111-4,731 for PUVA, $4,149 for broadband UVB plus acitretin, $4,233-7,472 for broadband UVB, $4,811 for narrowband UVB, $5,735 for PUVA plus acitretin, $10,025-10,600 for ciclosporin, $16,217 for acitretin, and $23,946 for infliximab. The authors did not use sensitivity analysis in any form to examine the robustness of their findings. The findings suggested that the most cost-effective treatment is methotrexate, but the long-term risks are not known. Again, no modelling technique is described and standard decision rules for cost-effectiveness analysis were not used as results were presented in the form of average cost-effectiveness ratios, expressed as average cost per 1% patients achieving PASI 75.

7.2 *De novo economic evaluation(s)*

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of evidence on outcomes	Bases in a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

The most recent NICE methods guide(73) states that head to head RCTs should be presented in the reference case analysis. Whilst the results from the head to head trial are presented in section 6, these have been incorporated into a mixed treatment comparison and this forms the basis of the cost-effectiveness analysis presented in this section. We have not used the data from the head to head comparison as our base case analysis primarily because etanercept 50mg twice weekly is not the most relevant comparator with respect to the decision problem as it has not been recommended by NICE. We have however included this study in the mixed treatment meta-analysis and do present an economic comparison to etanercept 50mg twice weekly, the conclusions of this analysis would not change dependent on the use of the trial evidence compared to the mixed treatment comparison and as such is not presented separately. Furthermore, ustekinumab delivers better outcomes at a similar cost to etanercept 50mg twice weekly (£9,336 per year for ustekinumab compared to £9,327 with etanercept 50mg twice weekly).

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

In the cost-effectiveness model, ustekinumab is modelled as per its licensed indication 'for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to, or have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA'. As per previous NICE guidance(22-24), moderate to severe psoriasis is defined as a PASI ≥10 and DLQI>10.

The SmPC states that the recommended posology of ustekinumab is an initial dose of 45mg administered subcutaneously at week 0, followed by a 45mg dose at week 4, then every 12 weeks thereafter. For patients with a body weight >100kg the dose is 90mg administered subcutaneously at week 0, followed by a 90mg dose at week 4, then every 12 weeks thereafter (see section 5.1 of the SmPC). In patients >100kg, 45mg was also shown to be efficacious. However, 90mg resulted in greater efficacy in these patients.

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

Within the cost-effectiveness model patients who do not respond to ustekinumab (i.e. do not achieve ≥PASI 75) at either dose should stop treatment at week 16, just prior to the third dose. It is anticipated that this is how ustekinumab response will be assessed in clinical practice (this has been supported by expert opinion (See Appendix 11).

The SmPC states that 'Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment'. We have assumed a more stringent stopping rule of 16 weeks.

Patients treated with ustekinumab in the model can be treated for up to a maximum of ten years with an average annual drop out rate of 20% being applied over this time as per the 'York model' described above(22-24). This assumption has also been supported by dermatological experts (See Appendix 11).

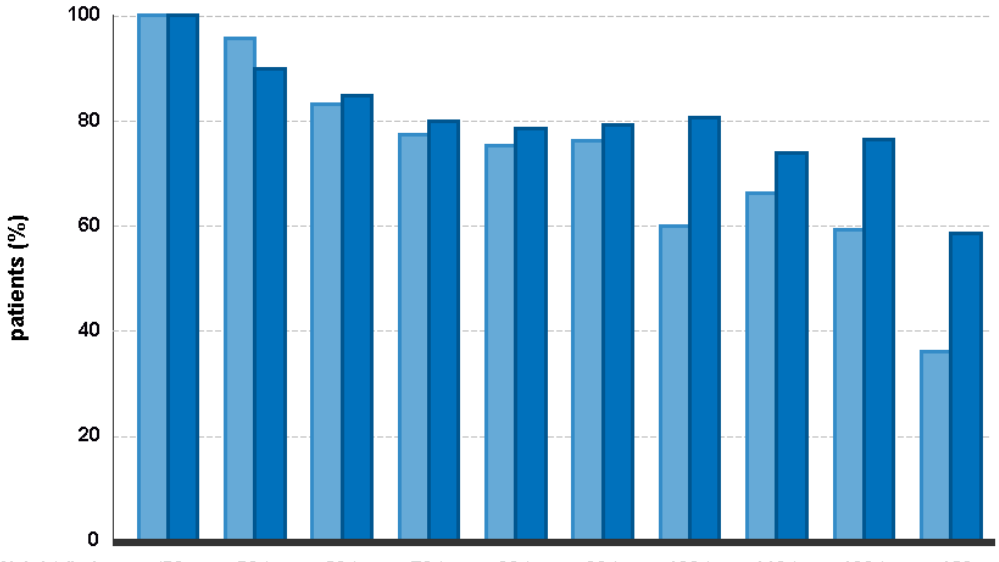
7.2.2 Patients

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

The group of patients included in the economic evaluation are those with moderate to severe psoriasis. For the purposes of this submission moderate to severe psoriasis is defined as a PASI ≥10 and DLQI>10.

The base case analysis presented in section 7.3.1 includes a sub-group of patients included in the clinical trials. The ustekinumab Phase III clinical trials investigated both the 45mg and 90mg doses of ustekinumab in patients with moderate to severe psoriasis. These trials contained patients of all weights in both the 45mg and 90mg treatment arms. The primary outcome results from the all-patient analyses for the PHOENIX trials have recently been published(40;41). The design of the phase III studies and the planned statistical analyses recognised the need to assess efficacy by dose and patient weight, and as such randomisation was stratified by a patient weight at above and below 90kg (so as to include 40-60% of patients in each stratification level). The statistical analysis plan specified a sub-group analysis by dose and 90kg weight stratification, and additionally summary tables by dose and 10kg weight increments. Weight quartiles were also specified. These data suggested a degree of heterogeneity of response for the 45mg strength by weight, and a patient weight of above 100kg was identified as optimising the risk-benefit ratio for the use of the higher dose of ustekinumab (Figure 7.2.1).

Figure 7.2.1 PASI 75 Response at week 28 by 10kg increments from PHOENIX 1 and PHOENIX 2



The CHMP has provided a positive opinion with a recommended posology of 90mg at week 0, 4 and every 12 weeks thereafter for patients >100kg. As a result, the SmPC for ustekinumab recommends that 90mg be administered for patients with a weight >100kg with the 45mg dose being recommended for all other patients. The results from the weight based analysis from the ACCEPT trial feature in this recommendation(1).

Base case

In summary, the base case weight-based dosing analysis is presented for ustekinumab as a weighted average of the 45mg and 90mg doses where 80% receive ustekinumab 45mg (≤100kg) and 20% receive ustekinumab 90mg (>100kg) as estimated by the proportion of patients >100kg (See Appendix 6). This analysis provides estimates of the cost-effectiveness of ustekinumab and not by dose specifically.

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

Scenario analyses are presented in section 7.3.2 for the weight based dosing (ustekinumab 45mg for ≤100kg and ustekinumab 90mg for >100kg) analysis which provides estimates of the cost-effectiveness of each dose of ustekinumab, as well as the all-patient analysis, aimed to allow the investigation of consistency of cost-effectiveness by weight in the light of the SmPC recommendation and pricing arrangements.

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

The sub-groups of patients detailed in section 6.9.1 were considered for inclusion but as the results show there are no statistical differences in response rates these have not been included in the economic evaluation. However, these data are not currently available for the other biologics. Therefore, a mixed treatment comparison was not possible.

7.2.2.4 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 cost-effectiveness model following treatment initiation. The model is split into two treatment stages: a 'trial' or induction period and a 'treatment' period. The 'trial' period varies by treatment and is detailed in section 7.2.6.1. If a patient has responded on treatment at the end of the 'trial' period they will then continue on treatment for a maximum of ten years ('treatment' period). An annual drop-out rate of 20% is applied to all treatments over the time horizon of the model, following the

"York Model". In addition, the patient 'exits' the evaluation during the treatment period if a PASI75 response is not achieved during a cycle in the Markov model.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The comparators included in the economic evaluation are other biologics currently licensed for use in the treatment of psoriasis in the UK. These are as follows:

- Adalimumab: 80mg initially, then 40mg at week 1, and every two weeks thereafter
- Efalizumab: 0.7mg/kg initially then 1 mg/kg every week
- Etanercept: 25mg twice weekly administered continuously and intermittently*; 50mg twice weekly administered continuously for the first 12 weeks**, then 25mg twice weekly thereafter
- Infliximab: 5mg/kg infused initially, repeated 2 and 6 weeks following initial infusion and then every 8 weeks

In addition, comparisons against supportive care are also presented.

* Although approved by NICE, intermittent etanercept is used infrequently (67) (see Appendix 6)

** The higher dose of etanercept has not been recommended by NICE (TA103)(22). However, as it is a licensed dose and because a recent treatment pathways and resource use study (See Appendix 6) demonstrates that the higher dose is being used in clinical practice in the UK, we have included this as a comparator.

7.2.4 Study perspective

The perspective of the economic evaluation is that of the NHS and Personal Social Services (PSS) in England and Wales.

7.2.5 Time horizon

The time horizon incorporated in the model is ten years as previously used in the original York model developed for the Multiple Technology Appraisal for etanercept and efalizumab in 2006(22). The subsequent Single Technology Appraisals for infliximab(23) and adalimumab(24) have utilised the same time horizon. The choice of ten years is appropriate as nearly all costs and effects are accrued by this point due to the 20% drop out applied.

7.2.6 Framework

a) Model-based evaluations

7.2.6.1 Please provide the following.

A description of the model type

A schematic of the model.

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

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

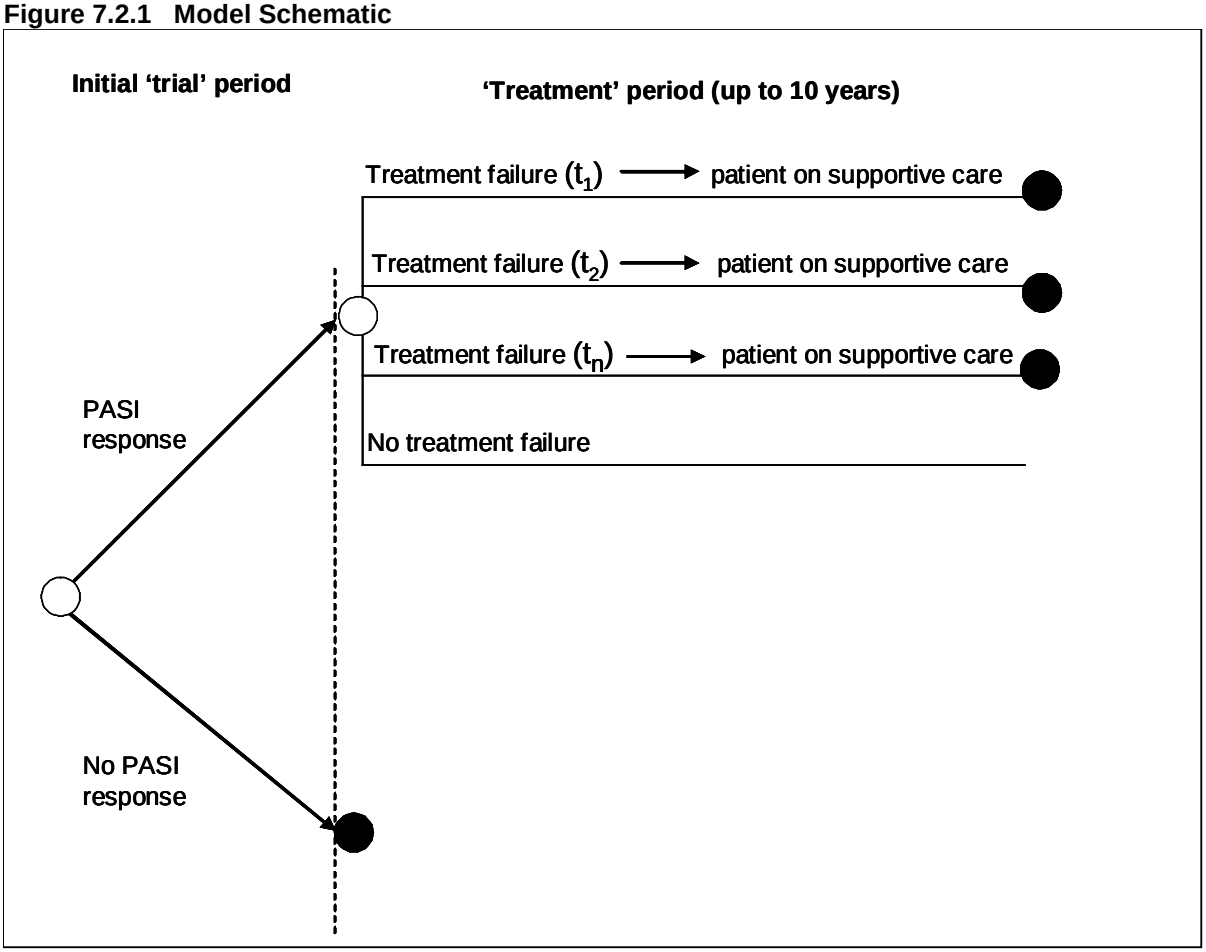
Model type

A probabilistic decision analytic model has been developed to compare the cost-effectiveness of ustekinumab to all relevant treatment options for the treatment of severe psoriasis in the context of their licensed indications. This cost-effectiveness model follows the same structure and methods used in the York model developed for NICE TA103(22). It compares estimates of expected costs and health effects per unit of time for each treatment considered, incorporating both patients who respond and continue treatment after an initial 'trial' period and those who do not respond and stop treatment.

A schematic of the model

Patients enter the model on treatment initiation and undergo an initial 'trial' period. Estimation of the response to treatment, that is the achievement of a PASI 75 response, is made at the end of this 'trial' period. Those patients who have achieved this level of response will remain on treatment and those who have not will discontinue biologic treatment and revert back to supportive care. Discontinuations of responders are estimated at an annual rate of 20% over the remainder of the time horizon.

Figure 7.2.1 Model Schematic



The measure of treatment success following the initial 'trial period' is assumed to be a PASI 75 response. This was the primary outcome measure in the ustekinumab clinical trials programme and it is the same endpoint that was used in the York model, and probabilities of response are based on the results of a mixed treatment comparison as reported in section 6.4. For those who respond to treatment, there is an ongoing risk of withdrawal at any time period (t_1 to t_n and the model incorporates an annual drop-out rate common to all treatments, $p_t^{annFail}$).

For those who drop-out at any time after the initial 'trial period' it is assumed that costs associated with one hospitalisation and two outpatient visits would take place annually for the treatment of a flare up of psoriasis (see $c_{Supp}^{treatment}$ equation below). Accordingly, mean QALYs for each treatment are also netted out of 'supportive care' (i.e. placebo effect, see u_{Supp}^{all} equation below).

In order to incorporate time preference, both discounted mean costs and QALYs are presented per unit of time a patient spends on treatment (divided by the total duration of treatment, $d_t^{trial} + p_t^{pasi75} \times d_t^{treatment}$). The mean treatment response period per each treatment and the mean discounted duration of the 'treatment' period are both estimated (in years) from the Markov model, based on: a treatment specific response after initial 'trial' period (PASI 75); a maximum treatment period of ten years and a constant annual withdrawal rate of 20% for all treatments. All assumptions are taken from Woolacott et al. 2006(46) and are detailed in this section).

Following the York model, our model is specified based on the equations below:

(1) **Mean utilities during the trial and treatment periods** by each treatment were estimated by weighting utility estimates for each PASI level by the probability of achieving the respective PASI response. Utility gains associated with response represent a weighted average relative to PASI 75 as a minimum response.

$$u_t^{all} = u_{oo} \times (1 - p_t^{pasi50}) + u_{50} \times (p_t^{pasi50} - p_t^{pasi75}) + u_{75} \times (p_t^{pasi75} - p_t^{pasi90}) + u_{90} \times (p_t^{pasi90})$$

$$u_t^{responders} = (u_{75} \times (p_t^{pasi75} - p_t^{pasi90}) + u_{90} \times (p_t^{pasi90})) / p_t^{pasi75}$$

Mean utilities during the initial trial period account for the utility associated with no response ($u_{oo} \times (1 - p_t^{pasi50})$). Both the utilities associated with the initial trial period and for responders during the ongoing treatment period are adjusted for the placebo effect (assumed to be equivalent to *supportive care*).

$$u_{Supp}^{all} = u_{oo} \times (1 - p_{placebo}^{pasi50}) + u_{50} \times (p_{placebo}^{pasi50} - p_{placebo}^{pasi75}) + u_{75} \times (p_{placebo}^{pasi75} - p_{placebo}^{pasi90}) + u_{90} \times (p_{placebo}^{pasi90})$$

(2) **Mean costs during the trial and treatment periods by each treatment**. This is calculated as a fixed initial trial cost (c_t^{trial}) and the associated inpatient hospitalisation cost for those who do not respond during the trial period ($(1 - p_t^{pasi75}) \times c^{hospital} \times d_{t,disc}^{trial}$). The treatment costs are calculated as the treatment specific annual costs multiplied by the duration of the treatment ($p_t^{pasi75} \times d_{t,disc}^{treatment} \times c_t^{treatment}$), netted out of the cost of 'supportive care' for the same period of time.

$$c_{Supp}^{treatment} = (c^{hospital} + c^{outpatient}) \times (1 - p_{placebo}^{pasi75})$$

The final model outputs are:

Mean QALY gained per year per each treatment, netted out of 'supportive care':

$$QALY_t = \frac{d_{t,disc}^{trial} \times (u_t^{all} - u_{Supp}^{all}) + p_t^{pasi75} \times d_{t,disc}^{treatment} \times (u_t^{responders} - u_{Supp}^{all})}{d_t^{trial} + p_t^{pasi75} \times d_t^{treatment}}$$

Mean costs per year per each treatment, netted out of the cost of 'supportive care':

$$Cost_t = \frac{\begin{array}{c} c_t^{trial} + (1 - p_t^{pasi75}) \times c^{hospital} \times d_{t,disc}^{trial} + p_t^{pasi75} \times d_{t,disc}^{treatment} \times c_t^{treatment} \\ -(p_t^{pasi75} \times d_{t,disc}^{treatment}) \times c_{Supp}^{treatment} \end{array}}{d_t^{trial} + p_t^{pasi75} \times d_t^{treatment}}$$

Table 7.2.1 List of parameters used in the model equations

Parameter	Description	Uncertainty	Source
c_t^{trial}	Cost of treatment with the t[th] treatment during the 'trial' period	Fixed	
c_t^{treat}	Annual cost of ongoing treatment with the t[th] treatment	Gamma distribution	
$c^{hospital}$	Annual cost of hospitalisation for non-responding patients	Fixed	NHS Reference Costs (2006/07)
$c^{outpatient}$	Annual cost of two outpatient visits for non-responding patients	Fixed	NHS Reference Costs (2006/07)
p_t^{pasi50}	Probability of PASI 50 response for the t[th] treatment	Simulated posterior distribution from MCMC analysis	Mixed treatment comparison results based on clinical trial data (see section 6.4)
p_t^{pasi75}	Probability of PASI 75 response for the t[th] treatment	Simulated posterior distribution from MCMC analysis	Mixed treatment comparison results based on clinical trial data (see section 6.4)
p_t^{pasi90}	Probability of PASI 90 response for the t[th] treatment	Simulated posterior distribution from MCMC analysis	Mixed treatment comparison results based on clinical trial data (see section 6.4)
$p_t^{annFail}$	Annual probability of treatment failure for the t[th] treatment	Fixed	Woolacott et al. 2006(46)
d_t^{trial}	Duration (in years) of the 'trial' period	Fixed	Based on clinical trial follow-up
$d_{t,disc}^{trial}$	Discounted duration (in years) of the 'trial' period	Fixed	Based on clinical trial follow-up. Discount rate from NICE methods guidelines
$d_t^{treatment}$	Duration (in years) of the 'treatment' period	Fixed	Woolacott et al. 2006(46)
$d_{t,disc}^{treatment}$	Discounted duration (in years) of the 'treatment' period	Fixed	Woolacott et al. 2006(46). Discount rate from NICE methods guidelines
u_{00}	Utility associated with < PASI50 response	Normal distribution	Woolacott 2006(46)
u_{50}	Utility associated with a PASI50 response	Normal distribution	Woolacott 2006(46)
u_{75}	Utility associated with a PASI75 response	Normal distribution	Woolacott 2006(46)
u_{90}	Utility associated with a PASI90 response	Normal distribution	Woolacott 2006(46)

MCMC= Markov Chain Monte Carlo

Parameters

Mean costs and QALYs are presented per unit time a patient spends on treatment. The model requires estimates, for each of the treatments compared, of the following parameters:

- PASI response rates (50, 75 and 90)
- 'Trial' period and 'treatment' duration for responders
- Initial trial period costs and annual treatment costs
- Utility gain associated with the various PASI response categories

The sources for these parameter estimates are discussed below:

Response rates

Treatment response was measured in terms of the probability of achieving at least a 75% reduction in the PASI score. For each treatment these were estimated directly from the mixed treatment comparison analysis as reported in section 5. The model uses the PASI 50, 75 and 90 response rates to define utility in the trial period, then PASI 75 for continuation into maintenance.

Trial period and treatment duration for responders

The initial 'trial' period was estimated based on the time frame of the included RCTs for each treatment option and clinical expert opinion, following the methods used in the York model(46). In short, for the base-case analysis the trial period used was 12 weeks by default, with the exception of infliximab (10 weeks), adalimumab and ustekinumab (16 weeks). The mean 'treatment' duration for responding patients was estimated based on a number of assumptions: a fixed annual withdrawal rate of 20% for all treatments and a maximum treatment period based on published guidelines for the treatment of psoriasis(6;20;74).

The trial period of 16 weeks has been set for ustekinumab as the duration of effect from doses administered at week 0 and week 4 is until 16 weeks. It is at this point that an assessment of response is expected to take place, just prior to the third injection. This assumption has been supported by a panel of dermatology experts, (see Appendix 11). The efficacy for ustekinumab at 16 weeks is assumed to be the same as at 12 weeks as per the primary outcome measure in the trials. We applied the 12-week efficacy in the analysis to accurately reflect the costs associated with the first two injections.

Even though we have applied 12-week efficacy, longer-term data exists from the PHOENIX trials which show that ustekinumab response rate continues to rise based on the four week dosing beyond the time of the 12 week assessment, however this is the last placebo controlled trial assessment and therefore forms the basis for the analysis. Therefore, the use of 12-week efficacy may therefore be considered conservative.

The estimated 'trial' and 'treatment' periods are shown in Table 7.2.2 below. As already mentioned, the mean treatment response period for each treatment is estimated from the 10-year Markov model. The annual 3.5% discount rate used to discount both costs and effects was incorporated into the model by estimating a discounted 'treatment' duration. The model assumes no differential mortality risk

between therapies based on available evidence, so mortality was not considered a relevant parameter.

Table 7.2.2 Estimated duration of the 'trial' and 'treatment' periods in the model

Treatment	'Trial' period in weeks	Maximum 'treatment' period in years	Mean 'treatment period for responders in years (weeks)*
Adalimumab	16	10	3.653 (189)
Efalizumab	12	10	3.653 (189)
Etanercept	12	10	3.653 (189)
Infliximab	10	10	3.653 (189)
Ustekinumab	16	10	3.653 (189)

* Based on an annual treatment failure rate of 20% common to all treatments, as assumed in the York model

Initial trial period costs and annual treatment costs

See section 7.2.9.1.

Efficacy for each treatment during the 'treatment' period

Patients who respond (i.e. PASI 75) at the end of the initial 'trial' period are assumed to retain this level of efficacy until they drop out. This applies for all treatments with the exception of etanercept 25mg intermittent, which is assumed to have reduced efficacy due to disease recurrence between treatment courses.

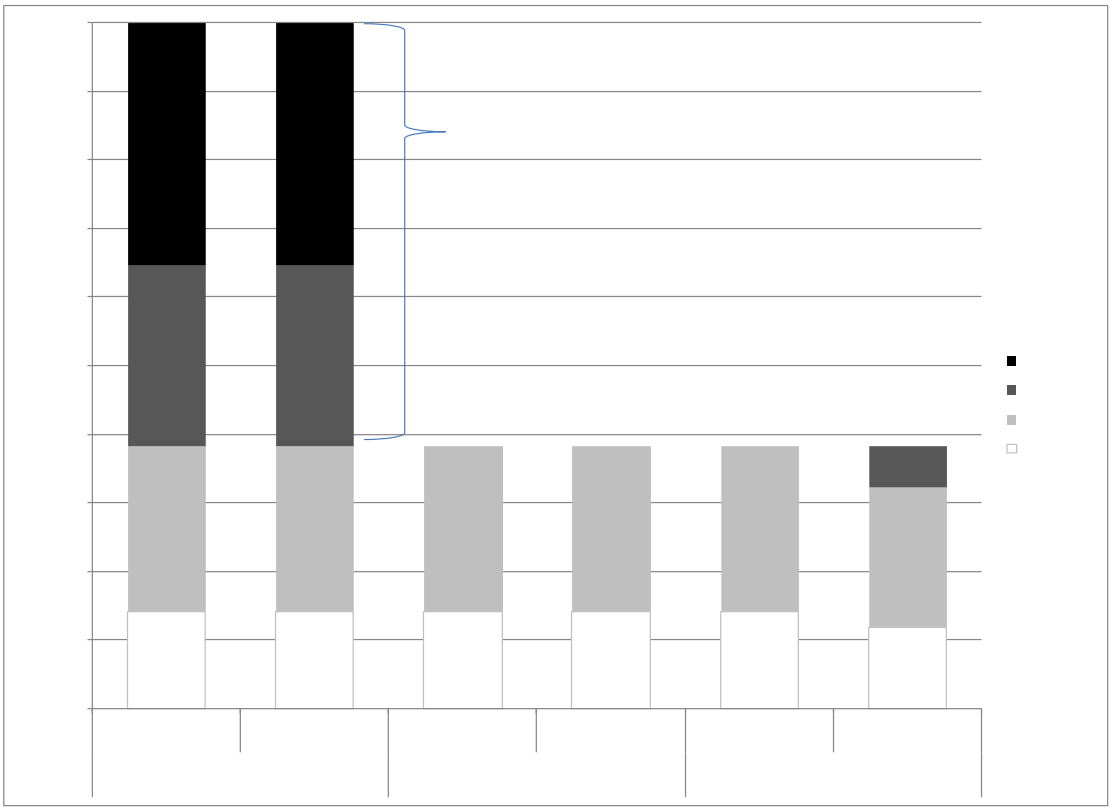
The previously referenced report by Woolacott et al, 2006(46) assumed that in the assessment of the cost effectiveness of etanercept, costs would be reduced (by less frequent dosing), but there would be no adjustment to the effectiveness of treatment. The logic of the assumption rests on the ability of patient to manipulate the dosing interval, such that those fairing well would continue without treatment, whilst those whose condition deteriorates could reintroduce dosing before any significant loss of effect has occurred. Such an assumption of exquisite fine tuning of the dosing interval and clinical effect however may not accord with standard clinical practice and would not be appropriate in the presence of an insidious recurrence of the disease process nor an extended period of treatment required to regain response.

A recent large randomised open label clinical trial has attempted to address the clinical implications of intermittent dosing when compared to continuous dosing(2). This study concluded that those patients who received intermittent etanercept following the initial 'trial' period had a reduced response compared to those who received continuous etanercept at 24 weeks (59.5% vs 71.0% respectively, $p<0.0001$). In addition, this study concluded that there was indeed a delay in regaining response on re-dosing for those patients. Within this submission we have therefore attempted to account for this loss of effectiveness in our economic modelling. We have done this by assuming a reduction in PASI response for a proportion of patients from week 24 onwards in the model and the associated effect of this loss of response on utility.

As described in section 7.2.7.3 of this report, utility for patients who reach a PASI 75 during the 'trial' period and continue into long term dosing is estimated from the proportion of patients at a PASI 90 and the proportion between PASI 75 and 90 after the initial 'trial' period (estimated from the mixed treatment meta-analysis), applied to the utility values associated with each of these PASI response levels. That is to say

that on continuous dosing those who achieve PASI 75 in the 'trial' period, and do not drop out subsequently, are assumed to maintain the clinical response they achieved during the 'trial' period. To allow for a reduction in efficacy on intermittent dosing we have relaxed that assumption and assumed that a proportion of those achieving a PASI 90 will have their response fall to PASI 75-90, whilst a proportion of those achieving a PASI 75-90 will fall to a PASI 50-75 (see Figure 7.2.2). No data was available to provide direct evidence of those proportions, however the study by Moore *et al* referenced above does provide data that we have used as a proxy. In that study after 12 weeks of intermittent dosing 69% of those patients who had originally responded to an induction course of etanercept continued to respond (as measured by a PGA of $\leq$2), compared to 85% amongst those dosing continuously. We therefore used the ratio of these two values as our adjustment factor for the proportion of patients failing to maintain their original PASI response, that is to say we that in the base case we assumed that 80.6% of patients would maintain their original response whilst 19.4% would fall by one level. This estimate has been subjected to sensitivity analyses.

Figure 7.2.2 Illustrative changes in PASI response over time



7.2.6.2 Why was this particular type of model used?

The model presented here is an adaptation of the York model, which has been utilised in all other NICE appraisals for biologics in psoriasis (TA103(22), TA134(23) and TA146(24)). The combination of a decision tree and Markov model appropriately reflects the treatment paradigm of psoriasis with an initial decision based on the response during the induction period followed by long term treatment if appropriate. This coupled with the York model having been validated and accepted by previous appraisal committees, we considered that a strong rationale would be required to justify deviating from this approach and it would be appropriate to present a consistent approach to estimate the cost-effectiveness of ustekinumab. This model also allows for simultaneous comparisons against multiple biologics. This is appropriate as several other biologics are currently available and being used in clinical practice in England & Wales.

7.2.6.3 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.

Other potential structures were feasible, for example attempting to model the full sequence of consequences of treatment failure for all patients or allowing for treatment sequences. However, these alternatives would have faced greater data demands and would not have provided significant advantages with respect to the decision problem, whilst forfeiting consistency with previous appraisals.

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

The sources of information used within the model are based on a mixture of the sources utilised in the original York model(46) developed for TA103 as well as published literature and expert opinion. Unit costs have been estimated from publicly available information and these along with the resource use can be seen in section 7.2.9.1.

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

The model does reflect all of the essential features of psoriasis that relate directly to the decision problem.

7.2.6.6 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?

Following the initial 'trial' period, the model cycle length is every three months up to a maximum of 10 years. A 3-month cycle length is appropriate to the clinical course of and also the time frame used for clinical decision-making. In addition it closely reflects the dosing frequency of ustekinumab every twelve weeks following the trial period.

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

A half-cycle correction was not required in the model due to the Markov model not following a cyclical structure.

7.2.6.8 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 in the York model, both costs and outcomes are extrapolated beyond the initial 'trial' period for all treatments. If patients respond to treatment during the initial' trial' period they will be assumed to remain on treatment beyond this period and retain the PASI response (PASI 75-90, PASI 90) until drop-out occurs at a rate of 20% as mentioned earlier. In this way only continued responders are assumed to continue on treatment in both the ustekinumab and comparator groups.

b) Non-model-based economic evaluations

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

No non-model-based economic evaluations are being presented within this submission.

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

Not applicable

7.2.6.11 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

7.2.6.12 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

7.2.6.13 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

7.2.7 Clinical evidence

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

There is currently no data mapping out the progression of severe psoriasis over time. Therefore in this model it is assumed that severe psoriasis is not progressive.

7.2.7.2 How were the relative risks of disease progression estimated?

Not applicable – see 7.2.7.1.

7.2.7.3 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?

Following the methodology from the York model and used in TA103(22) and TA134(23), the utilities associated with treatment were based on the proportion of patients in the different PASI categories and the change in utility from baseline associated with these PASI response categories (< PASI 50, PASI 50-PASI 75, PASI 75-PASI 90, >PASI 90), adjusted for baseline DLQI. These were estimated from an original analysis of patient-level data from two ustekinumab Phase III trials (PHOENIX 1 and PHOENIX 2) and a replica of the EQ5D – DLQI regression based on the scatter-plot as published in the HTA report, originally estimated using the HODaR database(46). The estimation process consisted of the following two stages:

In the first stage, the mean change in the DLQI score between baseline and week 12 was estimated for patients from the PHOENIX trials, with different levels of PASI response. In contrast to the York model, we used only patients with a baseline DLQI ≥10 in line with the eligible population for biologics(6) and that a baseline DLQI≥10 matches the patient population characteristics for most of the included trials. Based on patient level data from the PHOENIX trials(43;44) (n=1,996). The results can be seen in Table 7.2.3.

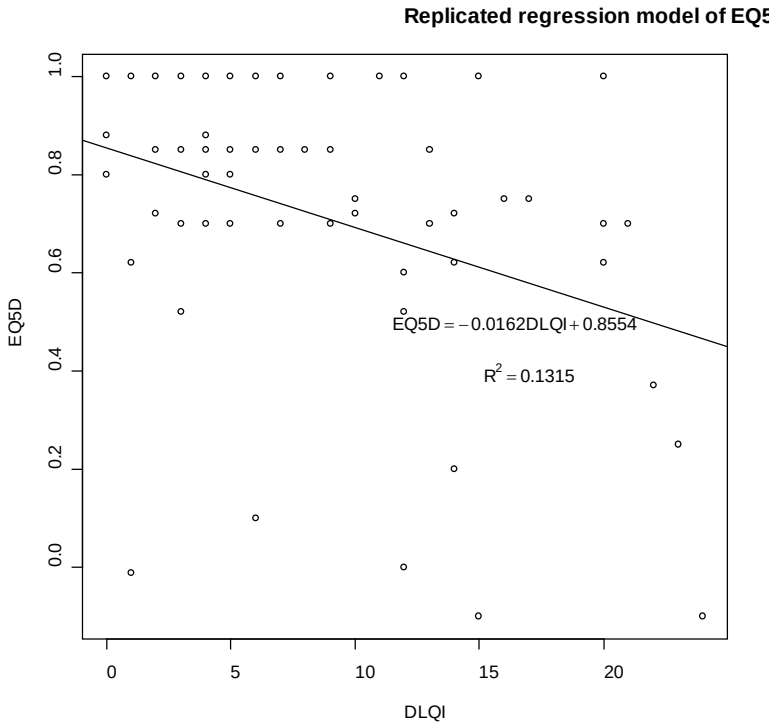
Table 7.2.3 Mean change in DLQI between baseline and week 12 by PASI response and baseline DLQI

PASI Response	n	Mean change in DLQI (SD)
< 50	430	-2.5 (6.7)
≥ 50 and < 75	160	-10.3 (6.1)
≥ 75 and < 90	207	-13.4 (5.8)
≥ 90	318	-15.3 (5.6)
All	1,115*	-9.3 (8.3)

* Patients with a baseline DLQI ≥10

In the second stage, an ordinary least squares (OLS) linear regression analysis of the DLQI-EQ5D data from the HODaR database was undertaken in order to estimate the mean gain in utility for the various PASI response categories. Although results were deemed as confidential and not reported in the HTA report(46), we estimated the coordinates in the published scatter-plot in order to replicate the regression and predict the relationship between DLQI and EQ-5D. The results of the OLS linear regression can be seen in Figure 7.2.3. The regression equation obtained was: EQ-5D = (-0.0162)DLQI + 0.8554.

Figure 7.2.3 Linear regression of EQ5D and DLQI using coordinates estimated from scatter-plot as published in Woolacott et al. 2006(46)



Estimated mean utility gains associated with PASI response categories, conditional on baseline DLQI severity, are reported in Table 7.2.4 below.

Table 7.2.4 Estimated utility gains for the different PASI response categories

PASI response	All patients
<50	0.04
≥50-<75	0.17
≥75-<90	0.22
≥90	0.25

In addition, we have carried out a replicate mapping study to validate the methodology of mapping from DLQI onto the EQ-5D. This study was carried out in Germany and involved more than 3,500 psoriasis patients and resulted in a similar simple linear regression equation (EQ-5D=0.908 – 0.016(DLQI)). See Appendix 12 for the study report). The results from this study support the methodology that was applied in the Evidence Review Group's report for TA103(69) and is subject to sensitivity analysis (see section 7.2.11.2 and 7.3.3.1).

7.2.7.4 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?

The health effects associated with ustekinumab were included in the economic evaluation. However, adverse effects were not directly included in the economic evaluation presented in this submission. These have been considered indirectly by

response rates and the estimation of annual drop-out. This is due to a lack of long-term data for all treatments included in the model in psoriasis. However, direct inclusion of these adverse effects would be unlikely to affect the estimated cost effectiveness of ustekinumab, since adverse effects are infrequent and similar to the control groups in the Phase III trials (placebo and etanercept 50mg twice weekly).

7.2.7.5 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?

An advisory board was held on 15th October 2008 (See Appendix 11), including dermatologists, where the following clinical assumptions were agreed:

- It was agreed that intermittent etanercept would be less effective than maintenance treatment based on the findings of a study by Moore et al, 2008(2).
- The annual drop-out rate of 20% is a reasonable assumption that is consistent with previous NICE submission assumptions
- The use of an initial 'trial' period of 16 weeks for ustekinumab as this is the time point where response will be assessed just prior to the third dose
- It was agreed that non-responders would require one hospitalisation per year
- In common with previous NICE appraisals, the length of inpatients stay for a non-responder is assumed to be 21 days.

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

No further assumptions were made regarding the clinical evidence.

7.2.8 Measurement and valuation of health effects

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

Not applicable

7.2.8.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

Health effects were measured by the level of improvement in the PASI score.

7.2.8.3 How were health effects measured and valued? Consideration should be given to all of the following:

The valuation and measurement of health effects has been described in section 7.2.7.3. In the base case the DLQI scores have been mapped directly to the EQ-5D as described in section 7.2.7.3.

7.2.8.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data

below. The results should be considered in a sensitivity analysis (see Section 6.2.11).

The generic quality of life measurement SF-36 was also collected in the PHOENIX 1 trial to evaluate the impact of ustekinumab on patients' overall quality of life. The change from baseline to week 12 in both the Mental Component Summary (MCS) score and the Physical Component Summary (PCS) score of the SF-36 were statistically significantly greater than placebo for both 45mg and 90mg doses(43). Improvements in the SF-36 MCS and PCS for ustekinumab at week 12 were maintained to week 40(43). There were significant improvements from baseline in SF-36 domain scores at week 12 for ustekinumab 45mg and 90mg *vs.* placebo ($p<0.05$ in both groups *vs.* placebo), with the greatest improvements observed in the 'bodily pain' and 'social functioning' domains(43). Patient level SF-36 responses were also converted to SF-6D utility scores, and changes in this utility measure for PASI response levels were estimated as described above for the DLQI. This SF-6D based utility algorithm has the advantage of being directly estimated from longitudinal changes in utility without the need for a secondary mapping exercise. However, this methodology has three important limitations, which have led us to prefer the mapping methodology and maintain consistency with previous appraisals.

- Firstly, in the presence of EQ-5D data (albeit from a mapping exercise) it is not clear that the SF-6D provides additional value in covering important psoriasis disease concepts, and as such there is no justification for overriding NICE's preference for EQ-5D in the reference case.
- Secondly, the SF-6D has a well reported limitation in range with a lower limit of 0.3 on the utility scale. In both the HoDAR study and the replicate German study EQ-5D utilities ranged beyond this level. This has clear implications for the possible gradient of any regression line to be drawn and hence the validity of a mapping exercise.
- In addition, the SF-36 was included in PHOENIX 1 only whereas the DLQI was included in both of the PHOENIX trials.

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

As mentioned previously, the health effects associated with adverse events have not directly been included in the modelling, in line with York model(47) and previous appraisals(22-24). In addition, mortality has also not been included in the modelling.

Other health effects collected within the clinical trials have been excluded from the analysis and these are that patients receiving ustekinumab showed significant improvements in co-morbidities such as depression and anxiety as measured by the Hospital and Anxiety Score (HADS). In addition, significant improvement in the Nail Psoriasis Severity Index, the Nail Physicians Global Assessment and the Itch VAS have been shown when using ustekinumab. It is not clear to what extent these effects may have been captured within utility measurements. In addition, no health benefits accruing to carers have been incorporated.

7.2.9 Resource identification, measurement and valuation

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

Costs were analysed from the perspective of the NHS in England & Wales. Apart from the cost of the biologic therapies (including drug acquisition, administration and monitoring), the direct medical costs associated with ongoing treatment (outpatient visits) and inpatient hospital stays for patients not responding to therapy were estimated. Resource utilisation was based on the respective SmPCs, current BAD guidelines for the treatment of psoriasis, published literature, UK national databases and clinical expert opinion.

Drug costs

Drug dosage and costs were based on the September 2008 edition of the British National Formulary (56)(75) and the published BAD guidelines for the treatment of psoriasis(6;8). The dose of ustekinumab was as studied in the Phase III clinical trials (PHOENIX 1, PHOENIX 2 and ACCEPT) and specified in the SmPC with dosing at week 0 and 4 for the 16-week initial 'trial' period. Following the licensed dose for infliximab we assumed that infusions would take place at 0, 2 and 6 weeks for the 12-week initial 'trial period'. An assumption of 4 vials for infliximab has been applied as per previous appraisals.

Table 7.2.5 Drug unit costs

Treatment	Price per vial	Notes
Adalimumab	£357.50	40mg prefilled syringe
Efalizumab	£169.20	125mg vial
Etanercept 25mg	£89.38	25mg prefilled syringe
Etanercept 50mg	£178.75	50mg prefilled syringe
Infliximab	£419.62	100mg vial
Ustekinumab 45mg	£2,147	45mg vial
Ustekinumab 90mg*	[redacted]	2 x 45mg vial

Source: BNF 56 (excluding ustekinumab)

[redacted]

Drug administration

The administration method for ustekinumab is by subcutaneous (SC) self-administered injection, as for adalimumab, efalizumab and etanercept. Following the latest BAD guidelines for the use of biological interventions in psoriasis(8) we assumed that: treatment should be initiated and monitored by a consultant dermatologist experienced in psoriasis (i.e. the first visit is costed as an "Outpatient visit – Dermatology total attendances", NHS Reference Costs)(76). In addition, to educate patients to self-inject, three 1-hour sessions of staff nurse time were costed during the initial trial period. The above assumptions, also used in the York HTA report(46), are common to all biologics included in the analysis.

All drugs are assumed to be administered on a continuous basis with the exception of etanercept 25mg, which can also be administered intermittently. The cost of etanercept intermittent is assumed to be 88% of the continuous dose. This estimate has been ratified by clinical experts and was also utilised in TA146(24) (See Appendix 11).

Monitoring and assessment

Regarding monitoring and assessment of disease response, the following types and frequency of laboratory tests were assumed, following the latest BAD guidelines for the use of biological interventions in psoriasis(8):

- Full blood count (FBC; at week 0, at 3 months, then every 6 months)
- Urea and electrolytes (U&E; at week 0, at 3 months, then every 6 months)
- Liver function tests (LFT; at week 0, at 3 months, then every 6 months)
- Creatinine serum (at week 0, at 3 months, then every 6 months).

In order to avoid potential double-counting of costs, clinician and nurse time for initial screening tests (e.g. X-rays, HEAF tests for tuberculosis etc), routine clinical examinations (e.g. blood pressure) and administration of laboratory tests were assumed to be included in the care covered by a standard outpatient visit to the dermatology department. See Tables 7.2.7 and 7.2.8 for full details of the different types and frequency of laboratory tests for all therapies during the initial trial and treatment periods.

The following outpatient visits for patient monitoring and nurse training sessions have been costed, according to the assumptions stated in the York HTA report(46): three outpatient visits to the dermatology department during the initial trial period to determine whether therapy should be continued; and one visit at 3-month intervals thereafter (i.e. four annual visits). These assumptions were based on clinical expert opinion and are in accordance with the latest BAD guidelines(6;8). Our estimates for infliximab infusions were based on the SmPC (i.e. two hours of monitoring during the first four infusions, reduced to one hour thereafter)(77). After the initial visit, the number of outpatient visits was adjusted by the number of infliximab infusions to avoid double-counting. See Table 7.2.6 for full details of the frequency of outpatient visits for all therapies during the initial trial and treatment periods.

Table 7.2.6 Resource use: frequency of outpatient visits

Treatment	Type of treatment	Initial 'trial' period	Annual maintenance
Supportive care*	-	-	2
Adalimumab**	Continuous	3	4
Efalizumab*	Continuous	3	4
Etanercept 25mg*	Intermittent	3	4
Etanercept 25mg*	Continuous	3	4
Etanercept 50mg*	Intermittent	3	4
Infliximab*	Continuous	4-5	5-6
Ustekinumab 45mg***	Continuous	3	4
Ustekinumab 90mg***	Continuous	3	4

* - Woolacott et al, 2006(46); ** - BAD guidelines(6); *** - expert opinion

Table 7.2.7 Resource use frequency of laboratory tests during the initial 'trial' period

Treatment	Type of treatment	FBC	LFT	U+E	Total protein	Serum creatinine
Supportive care*	-	-	-	-	-	-
Adalimumab**	Continuous	2	2	2	-	1
Efalizumab*	Continuous	4	-	4	4	1
Etanercept 25mg*	Intermittent	2	2	2	-	1
Etanercept 25mg*	Continuous	2	2	2	-	1
Etanercept 50mg*	Intermittent	2	2	2	-	1
Infliximab*	Continuous	2	2	2	-	1
Ustekinumab 45mg***	Continuous	2	2	2	-	1
Ustekinumab 90mg***	Continuous	2	2	2	-	1

* - Woolacott et al, 2006(46); ** - BAD guidelines(6); *** - expert opinion

Table 7.2.8 Resource use frequency of laboratory tests during the annual 'treatment' period

Treatment	Type of treatment	FBC	LFT	U+E	Total protein	Serum creatinine
Supportive care*	-	-	-	-	-	-
Adalimumab**	Continuous	2	2	2	-	2
Efalizumab*	Continuous	4	-	4	4	2
Etanercept 25mg*	Intermittent	2	2	2	-	2
Etanercept 25mg*	Continuous	2	2	2	-	2
Etanercept 50mg*	Intermittent	2	2	2	-	2
Infliximab*	Continuous	2	2	2	-	2
Ustekinumab 45mg***	Continuous	2	2	2	-	2
Ustekinumab 90mg***	Continuous	2	2	2	-	2

* - Woolacott et al, 2006(46); ** - BAD guidelines(6); *** - expert opinion

Following the methods of the York model, we did not estimate the costs of treating adverse events.

An additional cost associated with 'supportive care' in the model was assumed regarding an estimate of the increased rate of hospitalisation for non-responding patients. At the time of the development of the York model, no data were available to inform an estimate of the rate of hospitalisation, however in line with previous NICE appraisals of biologics in psoriasis we have assumed that there will be one hospitalisation per year for non-responding patients. This estimate has been agreed with clinical experts (See Appendix 11) and also supported by an analysis of the SLIM database which showed that primary admissions for psoriasis resulted in 90.5 admissions per 1,000 patient years, which is approximately one per year (See Appendix 5) Length of stay for this inpatient admission is estimated at 21 days as used in the York model (46). This assumption has also been agreed by dermatological experts (See Appendix 11).

Table 7.2.9 Laboratory tests unit costs

Test	Cost per test
Full blood count with differential (FBC)	£2.52
Liver biopsy with overnight stay	£514.88
Liver function test (LFT)	£0.63
Serum creatinine	£0.32

Total protein	£0.45
Urea & electrolytes	£1.16

Source: Woolacott et al 2006(46) inflated to 2006(78)

Table 7.2.10 Unit costs for hospital visits

Category	Description	£	Source
Inpatient day*	Elective inpatient, major dermatological conditions	£288.74	NHS Reference Costs 2006-2007(76)
Outpatient - Dermatology Total Attendances	NHS Trusts Consultant Led Follow up Attendance Multiprofessional Face to Face	£73.00	National Schedule of Reference Costs 2006-07(76)
Staff nurse, patient educational hour	Cost per hour of patient-contact	£40.00	PSSRU Unit Costs of Health and Social Care 2007(78)

*Weighted average of cases with and without complications by number of FCEs.

Table 7.2.11 Total costs for the initial 'trial' period

Treatment	Duration	Drug cost	Administration cost	Monitoring costs	Outpatient costs	Total costs
Supportive care*	12	0	0	0	0	£0
Adalimumab	16	£3,396.25	£120	£8.96	£219	£3,744.21
Efalizumab	12	£2,199.60	£120	£16.84	£219	£2,555.44
Etanercept 25mg intermittent	12	£2,145.12	£120	£8.96	£219	£2,493.08
Etanercept 25mg continuous	12	£2,145.12	£120	£8.96	£219	£2,493.08
Etanercept 50mg continuous	12	£4,290.00	£120	£8.96	£219	£4,637.96
Infliximab	10	£5,035	£219	£8.96	£73	£5,336.40
Ustekinumab 45mg	16	£4,294.00	£120	£8.96	£219	£4,641.96
Ustekinumab 90mg	16	£4,294.00	£120	£8.96	£219	£4,641.96

Table 7.2.12 Total annual costs for the 'treatment' period

Treatment	Drug cost	Administration cost	Monitoring costs	Outpatient costs	Total costs
Supportive care	£0	£0	£0	£146	£146
Adalimumab	£9,326.92	£0	£9.28	£292	£9,628.20
Efalizumab	£8,828.61	£0	£17.16	£292	£9,137,78
Etanercept 25mg intermittent	£8,208.15	£0	£9.28	£292	£8,509.43
Etanercept 25mg* continuous	£9,327.44	£0	£9.28	£292	£9,628.72
Etanercept 50mg* continuous	£9,327.44	£0	£9.28	£292	£9,628.72

Infliximab	£10,947.59	£476.13	£9.28	£0	£11,432.99
Ustekinumab 45mg	£9,335.62	£0	£9.28	£292	£9,636.89
Ustekinumab 90mg	£9,335.62	£0	£9.28	£292	£9,636.89

* The average annual cost in the etanercept 50mg twice weekly group is identical to the 25mg dose following the initial period to reflect the current licence for etanercept which states patients should only receive 50mg twice weekly for the first 12 weeks and then 25mg twice weekly thereafter. This varies from the 'York' model which included etanercept 50mg twice weekly on a continuous basis.

7.2.9.2 How were the resources measured?

See section 7.2.9.3.

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

This model assumes that there is no progression of severe psoriasis.

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

See section 7.2.9.1

7.2.9.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

See section 7.2.9.1

7.2.9.6 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? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

The list price of an ustekinumab 45mg vial is £2,147 with the list price of 90mg (2x45mg) being £4,294. [redacted]

7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

No additional infrastructure is required to be in place to use ustekinumab.

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

Yes

7.2.9.9 Were resource values indexed to the current price year?

The PSSRU inflation index was used to inflate costs to 2006 levels where necessary(78). Drug costs were estimated from the latest version of the British National Formulary (56) September 2008(75).

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

See section 7.2.9.3.

7.2.10 Time preferences

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

Costs and outcomes have been discounted at a 3.5% rate as specified in the NICE reference case.

7.2.11 Sensitivity analysis

7.2.11.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

A scenario analysis which utilises data from all the patients from the ustekinumab trials regardless of weight has been carried out and is presented in section 7.3.2.

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

The variables have been subjected to sensitivity analysis. The ranges tested in the univariate sensitivity analysis are show in table 7.2.13 below:

Table 7.2.13 Univariate Sensitivity analyses

Variable	Base case estimate	Ranges or estimates tested	Source
Length of stay for a hospitalisation	21 days	17.5 days 27.5 days	SLIM database (see Appendix 5) St John's Institute Resource Use Study (See Appendix 6)
Drop-out rate	20%	10% 30%	PHOENIX trials(43;79)
Duration of initial period for ustekinumab	16 weeks	12 weeks	Primary outcome in clinical trials(40;41)
Estimate of dose for etanercept intermittent	88% of continuous dose	74% of continuous dose 98% of continuous dose	TA103 (22) St John's Institute Resource Use Study (See Appendix 6)
SF-36 (SF-6D)	-	***PASI response for patients with a DLQI>10*** / **Mean change in SF-6D** <50 / 0.0016 ≥50 and <75 / 0.0424 ≥75 and <90 / 0.0970 >=90 / 0.1276	PHOENIX 1 trial(43)
EQ-5D estimates based on mapping from PASI	-	***PASI response*** / **Mean change in EQ-5D** All patients, <50 / 0.0630 All patients, ≥50 and <75 / 0.1780 All patients, ≥75 and <90 / 0.1780 All patients, ≥90 / 0.3080	Abbott submission for TA146(80)
DLQI-EQ-5D	TA103 based on HoDAR	***PASI response*** / **Mean change in EQ-5D** All patients, <50 / [redacted] All patients, ≥50 and <75 / [redacted] All patients, ≥75 and <90 / [redacted] All patients, ≥90 / [redacted]	German Utility Study (See Appendix 12)
Percentage of patients >100kg	20%	6% 17%	Market Research (See Appendix 13) HoDAR database (See Appendix 5)
Discount rate for costs and benefits	3.5%	0% 6%	NICE Guide to the methods of technology appraisal June 2008(73)
Efficacy of intermittent etanercept (% of continuous)	81%	71% 91%	

7.2.11.3 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'.

The uncertainty in the individual parameters has been tested with probabilistic sensitivity analysis using Monte Carlo simulation with 10,000 iterations (see table 7.2.1 for the distributions applied).

7.2.12 Statistical analysis

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

Not applicable

7.2.12.2 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 currently no evidence suggesting that severe psoriasis progresses over time.

7.2.13 Validity

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

The cost-effectiveness model presented in this submission was originally developed by [redacted] Subsequently, the cost-effectiveness model has been independently reviewed by [redacted] have thoroughly QC'd all aspects of the model data, code and the MTC. They have confirmed that it follows the same structure as the other models submitted as part of previous NICE appraisals on biologics in psoriasis, including the York model.

7.3 *Results*

7.3.1 Base-case analysis

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

Deterministic analysis

Weight by dose for ustekinumab - weighted average analysis

The results from the base case analysis are shown in table 7.3.1. Overall, the weighted average estimate for ustekinumab generates more QALYs than all other treatment options with the exception of infliximab. The weighted average has been estimated as 80% of patients receive ustekinumab 45mg (patients ≤100kg) and 20% receive ustekinumab 90mg (patients >100kg) (See Appendix 6). Apart from supportive care, etanercept 25mg intermittent produces the lowest QALY gains. In terms of cost, etanercept 25mg intermittent has the lowest mean costs. Ustekinumab is cheaper on average than adalimumab, efalizumab, etanercept 25mg and 50mg continuous and infliximab. The ICER for ustekinumab versus supportive care is estimated to be £29,587. Furthermore the ICER is estimated to be £26,637 for ustekinumab versus etanercept 25mg intermittent, whereas ustekinumab dominates all other treatments with the exception of infliximab.

Table 7.3.1 Base case results (weighted average - weight by dose for ustekinumab) - deterministic

Treatment	Mean QALYs	Mean costs	ICER ustekinumab vs other treatments	ICER vs supportive care
Supportive care	0	£0	£29,587	-
Efalizumab	0.1308	£5,264	Dominant	£40,250
Etanercept 25mg intermittent	0.1325	£3,989	£26,637	£30,111
Etanercept 25mg continuous	0.1409	£4,829	Dominant	£34,281
Etanercept 50mg continuous	0.1483	£5,333	Dominant	£35,964
Adalimumab	0.1502	£4,660	Dominant	£31,022
Ustekinumab	**0.1560**	**£4,615**	**-**	**£29,587**
Infliximab	0.1616	£6,327	£304,566*	£39,153

* this ICER compares infliximab to ustekinumab. Therefore, for willingness to pay thresholds up to £30,000 ustekinumab is the favoured option over infliximab

Based on the results presented in table 7.3.1, comparing against the current standard of care which is etanercept 25mg intermittent results in ustekinumab dominating all other biologic interventions with infliximab being rendered not cost-effective compared with ustekinumab (see table 7.3.2 and figure 7.3.2).

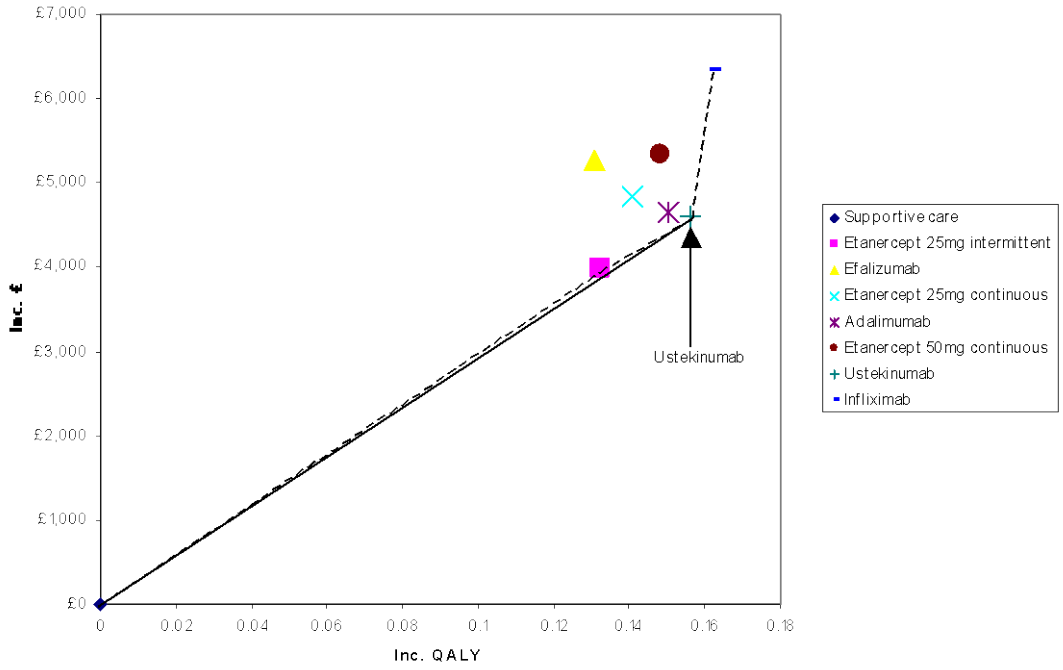
Table 7.3.2 Analysis comparing against the current standard of care etanercept 25mg intermittent

Treatment	Mean QALYs	Mean costs	ICER ustekinumab vs other treatments	
Supportive care	0.0000	£0	-	
Efalizumab	0.1308	£5,264	£40,250	
Etanercept 25mg intermittent	0.1325	£3,989	£30,111	*Extended dominated by ustekinumab*
Etanercept 25mg continuous	0.1409	£4,829	£100,014	Dominated by ustekinumab
Etanercept 50mg continuous	0.1483	£5,333	£67,865	Dominated by ustekinumab
Adalimumab	0.1502	£4,660	£37,821	Dominated by ustekinumab
Ustekinumab	0.1560	£4,615	£26,637	
Infliximab	0.1616	£6,327	£304,566	

In table 7.3.2 each comparator is presented in successive rows ordered by the number of QALYs generated. Each option is then compared to the next best option with lower cost. Options shown in italics are considered dominated by a subsequent option and hence may be excluded from decision-making. In addition etanercept intermittent is seen to be extended dominated by ustekinumab and is thus also excluded from the decision.

These results are also displayed in figure 7.3.2 below from which we can see that ustekinumab dominates all treatment options except etanercept 25mg intermittent versus which it displays extended dominance (ustekinumab has higher effectiveness and costs).

Figure 7.3.2 Cost-effectiveness plane



Probabilistic analysis

The table 7.3.3 below presents the same information as in table 7.3.1, derived from the mean costs and effects across 10,000 Monte Carlo simulations conducted for the probabilistic sensitivity analysis.

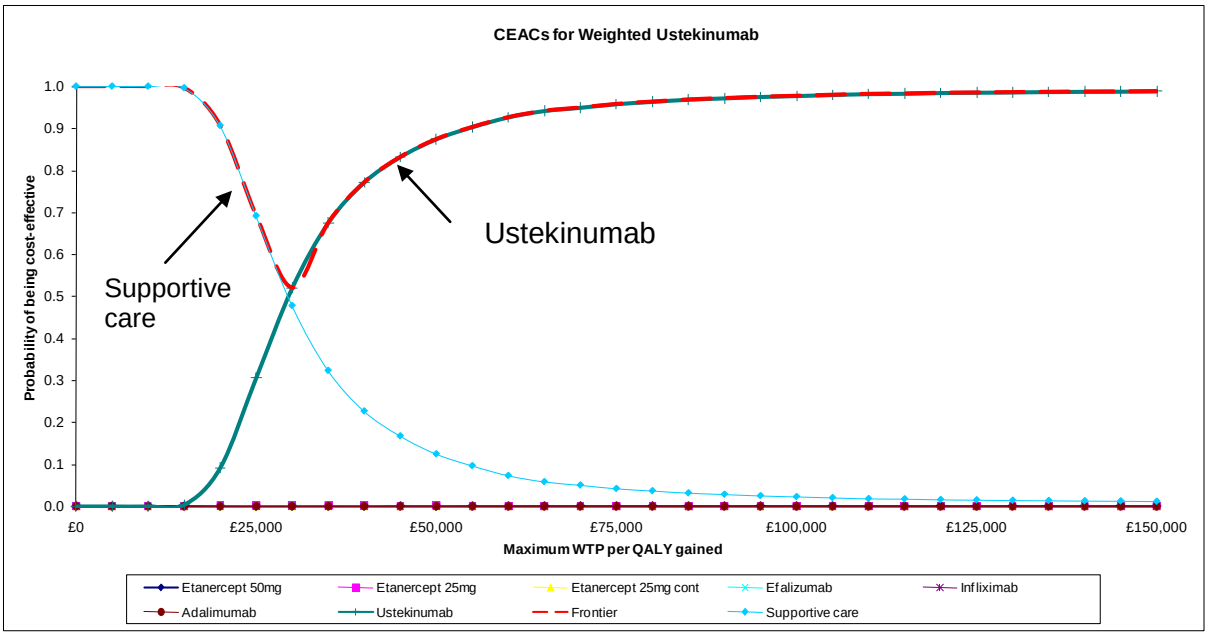
Table 7.3.3 Base case results (weighted average - weight by dose for ustekinumab) - probalistic

Treatment	Mean QALYs	Mean costs	ICER ustekinumab vs other treatments	ICER vs supportive care
Supportive care	0	£0	£29,382	-
Efalizumab	0.1296	£5,299	Dominant	£40,884
Etanercept 25mg intermittent	0.1320	£3,968	£25,610	£30,063
Etanercept 25mg continuous	0.1404	£4,810	Dominant	£34,269
Etanercept 50mg continuous	0.1459	£5,495	Dominant	£37,653
Adalimumab	0.1513	£4,536	£9,274	£29,990
Ustekinumab	**0.1558**	**£4,579**	**-**	**£29,382**
Infliximab	0.1602	£6,363	£405,622*	£39,713

* this ICER compares infliximab to ustekinumab. Therefore, for all willingness to pay thresholds of less than this would result in the favouring of ustekinumab over infliximab

Figure 7.3.2 shows the cost-effectiveness acceptability curve resulting from the probabilistic sensitivity analysis. Of the biologic agents, ustekinumab has the highest probability of being cost-effective at conventional NICE thresholds.

Figure 7.3.2 Cost-effectiveness acceptability curves for biologics in the base case (weighted average - weight by dose for ustekinumab)



At the £20,000 and £30,000 willingness to pay thresholds, ustekinumab is the only biologic that is likely to be cost-effective. All other biologics have a zero probability of being cost-effective.

7.3.2 Subgroup analysis

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

Scenario one: Weight based dosing for ustekinumab (ustekinumab 45mg for ≤100kg and ustekinumab 90mg for >100kg)

The results for the weight based dosing analysis are shown in Figure 7.3.5. Overall, when applying weight based dosing ustekinumab when compared to supportive care results in an incremental cost-effectiveness ratio of £29,334 for ustekinumab 45mg and £30,693 for ustekinumab 90mg.

When compared to the other biologic agents, ustekinumab 45mg dominates all other treatment options, apart from etanercept 25mg intermittent where the ICER is estimated to be £25,035 and infliximab. Ustekinumab 90mg has an ICER of £34,244 when compared to etanercept 25mg intermittent and it dominates all other biologic agents with the exception of adalimumab, infliximab and ustekinumab 45mg, however clearly these are two doses of ustekinumab are not alternatives for the same patients.

Table 7.3.5 Weight based dosing for ustekinumab - deterministic

Treatment	Mean QALYs	Mean costs	ICER ustekinumab 45mg vs other treatments	ICER ustekinumab 90mg vs other treatments	ICER vs supportive care
Supportive care	0	£0	£29,334	£30,693	-
Efalizumab	0.1308	£5,264	Dominant	Dominant	£40,250
Etanercept 25mg intermittent	0.1325	£3,989	£25,035	£34,244	£30,111
Etanercept 25mg continuous	0.1409	£4,829	Dominant	Dominant	£4,281
Etanercept 50mg continuous	0.1483	£5,333	Dominant	Dominant	£35,964
Adalimumab	0.1502	£4,660	Dominant	£18,204	£31,022
Ustekinumab 90mg	**0.1542**	**£4,732**	**Dominant**		**£30,693**
Ustekinumab 45mg	**0.1564**	**£4,588**		**Dominated**	**£29,334**
Infliximab	0.1616	£6,327	£334,423*	£216,081*	£39,153

* this ICER compares infliximab to ustekinumab. Therefore, for conventional willingness to pay thresholds,ustekinumab is favoured over infliximab

Scenario two: All patients analysis

The cost-effectiveness results for the all patients analysis (i.e. no weight based dosing for ustekinumab) are shown in table 7.3.6 below.

Table 7.3.6 All patients analysis for ustekinumab - deterministic

Treatment	Mean QALYs	Mean costs	ICER ustekinumab 45mg vs other treatments	ICER ustekinumab 90mg vs other treatments	ICER vs supportive care
Supportive care	0	£0	£30,664	£29,520	-
Etanercept 25mg intermittent	0.1330	£3,960	£36,272	£28,126	£29,763
Efalizumab	0.1311	£5,252	Dominant	Dominant	£40,052
Etanercept 25mg continuous	0.1415	£4,802	Dominant	Dominant	£33,930
Etanercept 50mg continuous	0.1484	£5,352	Dominant	Dominant	£36,061
Adalimumab	0.1504	£4,669	£16,400	Dominant	£31,046
Ustekinumab 45mg	**0.1544**	**£4,735**	**-**	**Dominant**	**£30,664**
Ustekinumab 90mg	**0.1563**	**£4,613**	**Dominated**	**-**	**£29,520**
Infliximab	0.1617	£6,342	£220,137*	£320,185*	£39,227

* this ICER compares infliximab to ustekinumab. Therefore, for conventional willingness to pay thresholds,ustekinumab is favoured over infliximab

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

Extensive sensitivity analyses have been carried out on the base case and the results from the univariate sensitivity analysis for both 45mg and 95mg can be seen in Table 7.3.6 below.

Overall, the model is sensitive to the following:

The number of hospital days associated with supportive care - with ICERs versus etanercept 25mg intermittent ranging from ustekinumab £20,672 to £34,387 when 27.5 and 17.5 days hospitalisation are assumed respectively. Overall, ustekinumab dominates all other biologics other than etanercept 25mg intermittent and infliximab, and the latter is rendered not to be cost-effective in the presence of ustekinumab.

Estimate of the cost of dosing for intermittent etanercept 25mg – the ICERs range from ustekinumab dominating etanercept 25mg intermittent at the 98% level to £68,339 when using the 74% as was used in TA103. Database evidence suggests now that there is only one day between use of intermittent etanercept per year or 98% of the continuous cost (See Appendix 6).

Use of SF-6D utility scores – The ICERs versus supportive care of £49,371 compared the base case of £29,587. However, this is not entirely unexpected based on the concerns raised earlier about the sensitivity of this instrument across the range of utility values seen in this condition. Further support is given to the inappropriateness of this approach by the values generated by the direct mapping from PASI undertaken by the manufacturer of adalimumab for their successful submission TA146. This mapping also suggests a stronger gradient between PASI response and utility than suggested by the SF-6D mapping.

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Table 7.3.6 Results from the univariate sensitivity analysis for ustekinumab

Ustekinumab versus	Value	Supportive care	Adalimumab	Efalizumab	Etanercept 25mg intermittent	Etanercept 25mg cont	Etanercept 50mg cont	Infliximab
Length of stay	17.5	£34,387	Dominant	Dominant	£31,394	Dominant	Dominant	-
	27.5	£20,672	Dominant	Dominant	£17,801	Dominant	Dominant	-
Drop-out rate	10%	£26,552	Dominant	Dominant	£34,087	Dominant	Dominant	-
	30%	£33,488	Dominant	Dominant	£20,284	Dominant	Dominant	-
Duration of initial period	12 weeks	£29,919	Dominant	Dominant	£28,846	Dominant	Dominant	-
Estimate of cost dose for etanercept intermittent	74% of cont dose	£29,587	Dominant	Dominant	£68,339	Dominant	Dominant	-
	98% of cont dose	£29,587	Dominant	Dominant	Dominant	Dominant	Dominant	-
SF-36-SF6D	See table 7.2.13	£49,371	Dominant	Dominant	£29,923	Dominant	Dominant	-
EQ-5D based on mapping from PASI	See table 7.2.13	£29,302	Dominant	Dominant	£15,390	Dominant	Dominant	-
EQ-5D based on mapping from DLQI – German utility study	See table 7.2.13	£29,637	Dominant	Dominant	£26,600	Dominant	Dominant	-
Percentage of patients >100kg	6%	£29,409	Dominant	Dominant	£25,505	Dominant	Dominant	-
	17%	£29,549	Dominant	Dominant	£26,390	Dominant	Dominant	-
Discount rate	0%	£28,634	Dominant	Dominant	£28,491	Dominant	Dominant	-
	6%	£30,272	Dominant	Dominant	£25,313	Dominant	Dominant	-
Efficacy of intermittent etanercept 25mg (% of continuous use)	71%	£29,587	Dominant	Dominant	£22,634	Dominant	Dominant	-
	91%	£29,587	Dominant	Dominant	£32,949	Dominant	Dominant	-

- refers to a comparison where the comparator has greater benefits but also at a greater cost
Dominant refers to ustekinumab dominating the specified treatment option

7.3.3.2 What are the key drivers of the cost effectiveness results?

See section 7.3.3.1.

7.3.4 Interpretation of economic evidence

Summary of economic evidence

- The annual cost of ustekinumab is very similar to the currently available NICE approved biologics in psoriasis. Average annual cost of ustekinumab is estimated to be £9,336 compared to £9,327 for etanercept 25mg (continuous) and £9,327 for adalimumab.
- Ustekinumab has lower acquisition costs than etanercept 50mg twice weekly dosing and infliximab.
- The ACCEPT trial demonstrates the clinical superiority of ustekinumab versus etanercept 50mg twice weekly dosing.
- The mixed treatment comparison suggests higher efficacy with ustekinumab than etanercept, adalimumab and efalizumab. These additional benefits are achieved at a similar annual acquisition cost.
- An economic evaluation was undertaken to evaluate the cost-effectiveness of ustekinumab compared to alternative biologic treatments and best supportive care in line with the NICE reference case.
- The model followed the same structure as that developed by the assessment group in the Multiple Technology Assessment, and was updated with the results from the mixed treatment comparison described above.
- The following base case modelling assumptions were agreed with the NICE technical team prior to the submission:
    - A trial period of 16 weeks will be used for ustekinumab
    - It is plausible that etanercept 25 mg intermittent is less effective than continuous treatment based on the findings of a recently published comparative clinical trial(2)
    - Weight based efficacy (45mg for patients ≤100kg and 90mg for patients >100kg) for ustekinumab used in the base case.
- Base case results from the model demonstrated that ustekinumab dominates adalimumab, efalizumab, etanercept 25mg and 50mg twice-weekly continuous treatment. The ICER for ustekinumab versus best supportive care was £29,587.
- When compared directly to etanercept 25mg intermittent, the ICER for ustekinumab was £26,637. In this analysis etanercept was extended dominated by ustekinumab and best supportive care.

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

The cost effectiveness model follows the same structure and the method used in the York model developed for NICE guidance TA103, which has subsequently been adapted for other NICE appraisals for biologics in psoriasis (TA134(23) and TA146(24)).

In contrast to previous appraisals for adalimumab, efalizumab, and etanercept where both biologics and conventional systemic therapies were included in the comparisons, only biologics along with supportive care were included in the model presented in this submission. This deviation is appropriate, because the labels of biologics recommend biologics use after patients failing conventional systemics and reflects the appraisal scope. This decision was made at the NICE scoping meeting.

Data on utilities (for example EQ-5D) are not directly collected from the clinical trials of all biologics. In order to derive utilities, we estimated the coordinates in the published scatter-plot in the Assessment Group report(47) developed for the Multiple Technology Appraisal of efalizumab and etanercept, so as to replicate the regression and predict the relationship between DLQI and EQ-5D. In addition, we carried out a study of more than 3,500 psoriasis patients in Germany and this study resulted in a similar algorithm for conversion of DLQI and EQ-5D, which along with a mapping from PASI (TA146) provides supporting evidence of the validity of the algorithm in the submission.

We have identified an inconsistency in the code used in the WinBUGS programming in the Assessment group report(47) (please see section 6.6, mixed treatment comparison for meta analysis). In the analysis presented in this submission, the fixed effect baseline has been used in preference as it does not require the strong assumption of exchangeability of baseline rates between studies required by the random effects baseline model. As a result of this change, in combination with the inclusion of additional studies in the mixed treatment comparison, the estimated efficacy rates among the comparators differ from those estimated in previous mixed treatment comparison analyses. Most notably, the estimated PASI 75 for adalimumab decreased from 67% in the adalimumab submission(80) to 59% in this submission.

In the base case model, a reduced utility is assumed with intermittent etanercept compared to continuous use. This assumption has been included following the publication of results from a recent large randomised controlled open label trial, which supports this approach. The results of this study demonstrated that maintenance therapy was associated with higher response rates than intermittent use(2).

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

The results are expected to be relevant to the intended population. The analysis performed is intended for patients with moderate to severe psoriasis, based on the anticipated label.

7.3.4.3 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 follows the structure of the York model. In addition, the evaluation is limited to all biologics in the comparisons, a scenario more accurately reflecting real practice. Furthermore, this evaluation is the first to include a head to head trial, potentially enhancing the robustness of the results.

As it has been done in previous submissions, disutility from adverse events is not directly incorporated as part of the evaluation. Based on the clinical trials, the rates of adverse events are generally low and comparable among the biologics approved for psoriasis. This omission is unlikely to have material impact on the results.

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

Short-term efficacy data from the clinical trials, resulted from the mixed treatment comparison, are applied to the Markov model. In this model, long-term efficacy is assumed to be the same as the short-term efficacy. However, there is a lack of long-term efficacy data from all the comparators.

As identified in sensitivity analyses, hospital length of stay, the efficacy and cost of intermittent etanercept and the utility algorithm used are important parameters in the cost-effectiveness assessment. We have undertaken additional studies, which support our base case assumptions for two of these parameters, however the parameters for intermittent etanercept are currently based on indirect evidence. Further information on the real world usage and outcomes of this strategy would allow greater robustness for this comparison.

8 Assessment of factors relevant to the NHS and other parties

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

The annual budget impact of ustekinumab on the NHS in England & Wales is estimated based on various sources of information and is presented in the following tables:

Table 8.1 – presents the estimates of the number of patients receiving a biologic for the next five years
Table 8.2 – presents the estimated uptake of ustekinumab for the first five years following introduction and the incremental cost associated with ustekinumab
Table 8.3 – presents the overall budgetary impact of ustekinumab compared to other available biologics including drug costs, administration, monitoring, outpatient costs for responders (i.e. achieving a PASI 75) and inpatient cost for those patients who do not respond.

Table 8.1 The number of patients receiving a biologic for the next five years

	%	2009	2010	2011	2012	2013
Estimated population*		54,895,969	55,319,249	55,744,028	56,166,122	56,582,165
Adults**	78.19%	42,925,539	43,256,520	43,588,673	43,918,727	44,244,049
Patients with psoriasis **	1.63%	699,686	705,081	710,495	715,875	721,178
Patients with severe psoriasis eligible for a biologic**	1.10%	7,697	7,756	7,815	7,875	7,933
Percentage of patients receiving a biologic		60.19%**	65.48%	70.77%	76.07%	81.36%**
Number of patients receiving a biologic		4,632	5,079	5,531	5,990	6,454

*Population projections obtained from the Government Actuary Statistics 2006; ** NICE costing template for Adalimumab June 2008

Table 8.2 Estimated uptake of ustekinumab over the five years following its introduction and incremental cost associated with ustekinumab

	2009	2010	2011	2012	2013
Patients receiving a biologic**	4,632	5,079	5,531	5,990	6,454
Uptake of ustekinumab	1.4%	6.7%	20.1%	33.7%	40.5%
	65	341	1,110	2,019	2,615
Drug costs if treating with ustekinumab	£606,815	£3,183,446	£10,362,538	£18,848,617	£24,412,646
Drug cost if treating with another biologic*	£585,403	£3,087,040	£10,100,564	£118,466,39	£24,039,728
Incremental cost	**£21,412**	**£96,406**	**£261,974**	**£382,217**	**£372,919**

* Weighted average based on market share data see section 8.3

Table 8.3 Overall incremental budgetary impact of ustekinumab - cost of administration, monitoring and outpatient costs for responders and hospitalisations for non-responders

	2009	2010	2011	2012	2013
Uptake of ustekinumab	65	341	1,110	2,019	2,615
Administration, monitoring and outpatient costs					
RESPONDERS*					
Other biologics	£10,333,31	£54,975.39	£181,443.08	£334,561.07	£439,190.34
Ustekinumab	£12,330,21	£64,686.17	£210,562.03	£382,995.25	£496,053.78
NON-RESPONDERS					
Other biologics	£230,306.27	£1,168,254.49	£3,672,722.66	£6,443,743.60	£8,039,421.07
Ustekinumab	£118,078.68	£619,458.90	£2,016,420.45	£3,667,705.31	£4,750,395.93
Incremental non-drug cost for responders and non-responders	-£112,227.59	-£548,795.60	-£1,656,302.21	-£2,776,038.30	-£3,289,016.14
Incremental drug costs	£21,412	£96,406	£261,974	£382,217	£372,919
Total budgetary impact	**-£90,815.40**	**-£452,389.56**	**-£1,394,327.84**	**-£2,393,820.89**	**-£2,916,097.36**

* includes administration, monitoring and outpatient costs
** assumes one inpatient stay for 21 days per year

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

Overall, population projections estimate there to be 54,895,969 people living in England & Wales in 2009(81). Of these 78.2% are adults (18 years or older). This equates to 42,928,648 adults and a further 1.63% or 699,686 are estimated to have psoriasis(82).

Of these, 1.1%, or 7,697, are estimated to have moderate to severe psoriasis and also be eligible for a biologic(82). However, it is likely that not all eligible patients will receive a biologic, therefore an assumption is made that 60.2% will receive a biologic in 2009 (n=4,632) rising to 81.4% by 2013 (n=6,454) (based on the future treatment rate estimated in the NICE costing template for adalimumab June 2008(82)). This

rise has been assumed to be linear. Table 8.1 applies these estimates to the adult population of England & Wales.

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

Treatment options included in the model are limited to those biologics currently recommended by NICE, namely adalimumab, efalizumab, etanercept, and infliximab.

Uptake of ustekinumab

Not all patients who are estimated to receive a biologic will receive ustekinumab. Overall, we estimate that of these patients 1.4% or 65 patients will receive ustekinumab in England & Wales in 2009 rising to 40.5% (n=2,615) in 2013 (see table 8.2).

Uptake of other biologics

Market research has been used to estimate the uptake of other biologics in 2009 (see Appendix 13). Future uptake has been estimated for 2013 from the NICE costing template for adalimumab(82). These are shown in table 8.4.

Table 8.4 Uptake of biologics

	2009	2010	2011	2012	2013
Adalimumab	16.7%	25.6%	34.6%	43.6%	52.6%
Efalizumab	25%	21.0%	17.0%	13.0%	9%
Etanercept	41.7%	37.8%	33.8%	29.9%	26%
Infliximab	16.7%	15.6%	14.6%	13.5%	12.5%

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

Market share data are not available for biologics between 2009 and 2013, therefore we have assumed that a linear relationship exists between the estimates in 2009 and 2013(see table 8.4).

The market shares presented in table 8.4 assume that ustekinumab is not available, since the budget impact analysis presented here is intended to compare a world with and without ustekinumab, for example, if the patients estimated to receive ustekinumab were treated with any of the other biologics.

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

Drug acquisition costs are estimated based on the average annual cost estimated by the cost-effectiveness model as detailed in table 7.2.12. The average annual costs are shown in table 8.5.

Table 8.5. Calculation of drug acquisition costs

	Adalimumab	Efalizumab	Etanercept	Infliximab	Ustekinumab
Average annual cost	£9,327	£8,827	£8,208	£10,948	£9,336

This estimated uptake for all biologics has been estimated in 2009 based on market research and the NICE costing template for adalimumab for 2013. A linear relationship has been applied to estimate this for 2010-2012. Overall, this estimation generates a weighted average annual cost of using another biologic, which starts at £9,756 in 2009, rising slowly to £9,848 in 2013. The incremental budgetary impact based on drug acquisition cost alone is presented in table 8.2 where ustekinumab is estimated to result in costs during the five years following its introduction ranging from £21,412 to £372,919 by 2013.

8.6 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?

When treating patients with any biologic a certain percentage of patients are likely to respond. The level of this treatment response varies and has been estimated via the mixed treatment comparison reported in section 6.6. The weighted average response rate for ustekinumab is 74% (weighted by the percentage of patients >100kg estimated at 20% (see Appendix 6). The response rates for the other biologics can be seen in table 6.6.3. Excluding drug costs the other resources and associated costs assumed for responders include administration, monitoring and outpatient costs as detailed in table 7.2.6, 7.2.8, 7.2.10 and 7.2.12.

Patients who are estimated not to respond are assumed to have one inpatient stay for an average of 21 days plus two outpatient visits at £73 per visit. This is assumed to cost £6,209.54 per patient per year based on £288.73 for an inpatient day and £73 for an outpatient visit.

Etanercept 50mg twice weekly is not currently recommended by NICE in England & Wales, however, there is evidence to suggest that this dose is being used(67) See Appendix 6). Therefore the estimates for the cost of etanercept presented in this section are likely to be underestimates.

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

Ustekinumab has a higher response rate overall (74%) compared to all other biologics with the exception of infliximab as estimated from the mixed treatment comparison in section 6.6. Based on the assumption that non-responders have one inpatient stay and two outpatient visits per year this would result in a saving of £6,209.54 per non-responder. For example, if all 65 patients eligible for ustekinumab received ustekinumab, a total of 48 are expected to respond compared to a total of 34, 17 and 25 patients who would respond on adalimumab, efalizumab and etanercept 25mg continuous respectively.

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

Indirect costs associated with psoriasis are work time lost and lost productivity. There are currently no UK specific studies, which investigate the extent of this. However,

one study carried out in Germany estimated that the absence of work, unemployment and occupational retraining resulted in a loss of productivity in 31% of patients with severe psoriasis for an average of 46.4 days. The average cost of this loss of productivity was €1,310 with this figure rising to €1,408 in psoriasis patients who are employed(83).

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