Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Ustekinumab for the treatment of moderate to severe psoriasis

Produced by [redacted]

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LIST OF ABBREVIATIONS

AAD	American Academy of Dermatology
AE	Adverse event
BAD	British Association of Dermatologists
BEE	Blinded efficacy evaluator
BIW	Twice weekly
BNF	British National Formulary
BSA	Body surface area
BSE	Blinded safety evaluator
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CIC	Commercial in confidence
CNTO-1275	Centocor 1275 - ustekinumab
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
DLQI	Dermatology life quality index
EADV	European Academy of Dermatology and Venerology
eCRF	Electronic case report form
EMEA	European Medicines Agency
EOW	Every other week
EQ-5D	Euro quality of life questionnaire
ERG	Evidence review group
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HTA	Health technology assessment
IHCIS	Integrated healthcare information services
ICER	Incremental cost-effectiveness ratio
ICP	International Congress of Psoriasis
ITT	Intention to treat
kg	kilogram
MEIP	Medline in process
mg	milligram
MS	Manufacturer’s submission
MTC	Mixed Treatment comparison
N or n	Number
N/A	Not applicable

NHS	National Health Service
NHS EED	NHS economic evaluation database
NICE	National Institute for Health and Clinical Excellence
OLS	Ordinary least squares
PAS	Patient access scheme
PASI	Psoriasis area and severity index
PGA	Physician's global assessment
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PUVA	Psoralen ultraviolet (light) A
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SC	Subcutaneous
SE	Standard error
SD	Standard deviation
SF-36	Short form (version) 36
SG	Standard gamble
SID	Society for Investigative Dermatology
SmPC	Summary of product characteristics
STA	Single technology appraisal
TAR	Technology assessment report
TTO	Time trade off
UK	United Kingdom
UKCRN	UK Clinical Research Network
USA	United States of America
VS	Versus
WLQ	Work limitations questionnaire

Please note: During the production of the Evidence Review Group report the European Medicines Agency (EMEA), recommended that marketing authorisation be suspended for Merck KGaA/Genentech's psoriasis drug efalizumab (raptiva). As a result of this decision, NICE guidance on the use of efalizumab has been temporarily withdrawn and will be reviewed in light of any further changes to efalizumab's marketing authorisation. Any references to efalizumab in the present report were made prior to this decision and as such do not reflect this change.

SUMMARY

Scope of the submission

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE), and is appropriate to the National Health Service (NHS). The intervention described in the Single Technology Appraisal (STA) scope is ustekinumab 45mg solution for injection which is proposed as a treatment for adults with moderate to severe chronic plaque psoriasis who have had an inadequate response to, or who have a contraindication to, or are intolerant to other systemic therapies. The decision problem defines the population as those considered to have moderate to severe psoriasis. The criteria of having previously had an inadequate response to, a contraindication to, or an intolerance of other systemic therapies, are not explicitly defined but are likely to be covered by the statement 'within licensed indication'. The manufacturer's decision problem states a dose of 45mg, but scope for a 90mg dose if patients have a body weight over 100kg is noted under 'special considerations'. The comparators and outcomes are as appropriate and clinically meaningful as possible.

Summary of submitted clinical effectiveness evidence

- The main evidence on efficacy in the submission comes from three randomised controlled trials (RCTs), two comparing ustekinumab with placebo, and one comparing ustekinumab with etanercept. One further RCT contributes to the evidence on adverse events.
- Higher proportions of participants treated with ustekinumab (at both the 45mg and 90mg doses) achieved an improvement on the Psoriasis Area and Severity Index (PASI) of at least 75% (PASI 75) when compared to placebo groups after 12 weeks (two trials), or after 12 weeks when compared to etanercept (one trial). No statistical comparisons between the two ustekinumab doses were presented for any of the trials. There were also statistically significant differences in favour of ustekinumab (at both the 45mg and 90mg doses) in comparison to placebo for the proportion of participants achieving a PASI 50 and a PASI 90 (two trials) but again no statistical comparisons were presented for the comparison between the two ustekinumab doses. In the trial comparing ustekinumab to etanercept, PASI 50 results appeared to be similar across the three treatment groups (45mg ustekinumab, 90mg ustekinumab, and etanercept) but no statistical comparison of these data was presented. In contrast, both doses of

ustekinumab led to statistically significantly higher proportions of participants achieving a PASI 90 than was observed in the etanercept group.

- The MS also presented PASI 75 data from a weight based sub-group dosing analysis for each of the three included trials but the methodological description of these analyses was limited and no statistical analysis to support the chosen weight threshold was presented.
- The MS did not present a narrative or quantitative synthesis of the data from the three included ustekinumab trials, except as part of a mixed treatment comparison (MTC). The MTC was conducted using data from the ustekinumab trials in two ways, either all participants as randomised, or subgroups of participants from the dose by weight analysis noted above. The MTC result from the all participant analysis for treatment with ustekinumab 45mg was a mean probability of achieving a PASI 75 response to treatment of 69% with a different result obtained from the weight based ustekinumab analysis MTC of [redacted]. For the ustekinumab 90mg dose the all participant analysis MTC resulted in a mean probability of achieving a PASI 75 response to treatment of 74%, and again a different result was obtained from the weight-based ustekinumab analysis MTC of [redacted]. For the PASI 75 MTC outcome the probability of response was greatest for infliximab (mean PASI 75 response of 80%) and the ustekinumab probability of responses were greater than those of the other comparators.
- For the reported secondary outcomes, there were statistically significant differences in favour of ustekinumab over placebo and etanercept in the Physician's Global Assessment (PGA) score, and in favour of ustekinumab over placebo in the Dermatology Life Quality Index (DLQI). The DLQI outcome was not reported for the ustekinumab versus etanercept trial. The incidence of adverse events appeared to be similar in treatment and placebo arms at 12 weeks although this was not statistically tested. Withdrawals due to adverse events were low and appeared to occur less often in the ustekinumab groups than in either the placebo or etanercept groups although a statistical comparison is not reported in the MS.

Summary of submitted cost effectiveness evidence

- The manufacturer's economic evaluation includes a review of the published economic literature on therapies used for psoriasis, and a report of an economic evaluation undertaken for the NICE STA process which includes a cost-effectiveness model of treatments for psoriasis comparing ustekinumab with other biological therapies. The

analysis estimates the number of individuals who respond to treatment at each time interval, the mean length of time that an individual would respond to treatment, and the utility gains associated with this response. The model is based closely on the model reported in Woolacott and colleagues.[1]

- The model is generally internally consistent and appropriate to psoriasis, in terms of structural assumptions. The cost-effectiveness analysis generally conforms to the NICE Reference Case, the scope and the decision problem.
- The evidence-based treatment effectiveness is reported in terms of the probability of achieving a specified PASI response with each of the treatment alternatives and supportive care by the end of the trial period. Evidence was synthesised from a variety of trials for ustekinumab and the comparators using an MTC model. In the base case analysis it was assumed that those under a weight of 100 kg (80% of patients in base case) receive ustekinumab 45mg, whilst those over 100 kg (20% of patients) receive ustekinumab 90mg.
- Patients who achieve improvements in PASI score were assigned an associated improvement in quality of life (a utility gain) with higher responses associated with larger improvements in quality of life. Two approaches were used to achieve this task. In the first the observed patient-level changes in DLQI were used as surrogate outcomes in the statistical modelling that related the PASI scores to utility gains assessed in EQ-5D. The EQ-5D utility values derived from the DLQI were used in the base case analysis. In the second approach the observed patient-level SF-36 scores were converted into the SF-6D utility values and aggregated according to the PASI response categories. The SF-6D utility estimates were used in the sensitivity analysis.
- The base case incremental cost-effectiveness ratio (ICER) for ustekinumab compared to supportive care, for patients with severe psoriasis was £29,587 per Quality Adjusted Life Year (QALY).
- The one-way sensitivity analysis reported in the MS shows the model was most sensitive to the number of hospital days associated with supportive care, the estimate of the cost of dosing for intermittent etanercept 25mg, and the use of SF-6D utility scores instead of the EQ-5D utility scores (with SF-6D utility scores associated with much higher cost-effectiveness ratio for ustekinumab in comparison to supportive care then the cost-effectiveness ratio estimated in the base case analysis).
- Scenario analyses are presented in the MS that compare outcomes from the model when the efficacy estimates come from a) the MTC subgroup data where the

ustekinumab dose regimen depends on the baseline weight and b) the all patients according to their randomisation outcome.

- Scenario analysis conducted by the Evidence Review Group (ERG) shows the model was most sensitive to the assumption about the price of ustekinumab 90mg; the proportion of patients with baseline weight >100kg and the assumptions about the relative risk of intermittent etanercept 25mg in comparison to continuous etanercept 25mg.

Commentary on the robustness of submitted evidence

Strengths

- The MS conducted a systematic search for clinical- and cost-effectiveness studies of ustekinumab. It appears unlikely that the searches missed any additional trials that would have met the inclusion criteria.
- The three key ustekinumab trials identified and systematically reviewed were of reasonable methodological quality, and measured a range of outcomes that are as appropriate and clinically relevant as possible.
- Overall, the MS presents an unbiased estimate of treatment efficacy for ustekinumab at 12 weeks based on the results of two placebo-controlled trials and one trial comparing ustekinumab with etanercept.
- The economic model presented with the MS used a reasonable approach.

Weaknesses

- There is a lack of information regarding the methodology used for the subgroup analysis and it was therefore difficult for the ERG to determine whether the methods used were appropriate and whether the subgroup analysis supports the weight-base categorisation presented. These clinical effectiveness estimates of the subgroup data were used in the base case analysis of the modelled economic evaluation of ustekinumab presented in the MS.

Areas of uncertainty

- The reliability of the estimates of clinical effectiveness derived from sub-groups of participants receiving differential weight based dosing is uncertain.

- The impact on MTC outcomes of using a fixed-effect model rather than a random-effects model (which was used by the assessment group who developed the original MTC) is unclear.
- The clinical effectiveness and cost-effectiveness of ustekinumab in relation to other drugs in the class is uncertain. A number of factors contribute to this uncertainty, including the two points above, but also the assumption about the proportion of patients with baseline weight >100kg and the assumptions about the relative risk of intermittent etanercept 25mg in comparison to continuous etanercept 25mg.
- It is not clear whether the estimates from the subgroup analysis, which were used in the MS base case analysis, were methodologically appropriate.
- The choice of utility estimates used for the cost-effectiveness analysis has a major impact on the estimated cost-effectiveness of ustekinumab. The cost-effectiveness of ustekinumab in relation to other drugs of this type is therefore also unclear.

Key issues

- Two of the trials of ustekinumab efficacy presented by the MS were placebo-controlled trials. There is also one head-to-head RCT that directly compares ustekinumab with etanercept 50mg. No studies were identified that directly compared ustekinumab to the other possible comparators included within the STA.
- The MS does not present the results of the subgroup analysis according to NICE methodological guidance and therefore the ERG was unable to determine whether the weight-based categorisation used in the cost-effectiveness analysis is justified.
- Although the manufacturers carried out an MTC, the effectiveness of ustekinumab in relation to other drugs of this type remains unclear due to uncertainties about the appropriateness of some of the methodological aspects of the MTC.
- All the economic outcomes in the MS are conditional on the price of ustekinumab 90mg as indicated in the Patient Access Scheme (PAS). Doubling the price of ustekinumab 90mg resulted in ustekinumab no longer dominating the comparators for a cost effectiveness threshold of £20,000 to £30,000 per QALY.

1 Introduction to ERG Report

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

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 23rd January 2008. A response from the manufacturer via NICE was received by the ERG on 11th February and this has been included as an Appendix in the ERG report.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

There is a clear and accurate overview of the disease provided in the MS (MS pages 14-19).

2.2 Critique of manufacturer's overview of current service provision

There is no discussion of the current service provision for ustekinumab, although at the time of report submission by the manufacturer this was not a licensed therapy. On page 19 a statement on what the suggested place of ustekinumab is within current alternatives is given. The MS does not indicate (MS p19) who will administer the drug but the draft Summary of Product Characteristics (SmPC) in Appendix 1 of the MS suggests that self administration is a possibility. Comparator drugs are discussed in respect to their background and current guidance, although on page 17 of the MS the SmPC doses for etanercept describe a dose which is not currently recommended by NICE.

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The population described in the decision problem appears to be appropriate for the NHS. The MS does not explicitly state that the population are those in which there is a failure to respond, or contraindication/intolerance to other systemic therapies however this is likely to be covered in the statement 'within its licensed indication' given on page 6 of the MS.

2.3.2 Intervention

At the time of the submission from the manufacturer there was no marketing authorisation. However ustekinumab was subsequently licensed on 16th January 2009 for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and Psoralen and UVA (PUVA).

The dose in the decision problem (page 6 of the MS) is stated as 45mg but the marketing authorisation indicates that a dose of 90 mg may be used in patients with a body weight greater than 100 kg. This 90mg dose is reflected within the MS in the results for those over 100kg (see section 3.3.4 below) but is only briefly mentioned under the decision problem special considerations (MS p8).

2.3.3 Comparators

The comparator interventions described in the decision problem appear to be appropriate for the NHS, although it should be noted that the doses of etanercept include a dose which is not recommended by NICE.

2.3.4 Outcomes

The outcomes stated in the MS appear to be appropriate and as clinically meaningful as is available. The Psoriasis Area and Severity Index (PASI) is used in all trials as an outcome measure and this is reflected in the MS. The PASI is not an ideal measure of the severity of psoriasis and the limitations of the PASI are well documented,[1] however it is often the best measure available.

2.3.5 Special considerations

The MS (pages 8 and 23) discusses the possible issue around adjustment of the dosing for people over 100kg and how the manufacturer aims to deal with equity issues regarding this. Currently a patient access scheme (PAS) has been agreed so that the pricing is the same as for those under 100kg. In Appendix 4 (page 18) the manufacturer suggests that this PAS is for the current year only. However, in a response to a question from NICE (Appendix 1) the manufacturer stated that this PAS would apply until at least any review of NICE guidance.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

The search strategy is appropriate, mostly adequately documented and is reproducible. It had a few shortcomings and minor inconsistencies as outlined below. Searches run by the ERG did not identify additional relevant results.

3.1.1.1 Clinical effectiveness searches

The search strategy is clearly documented for Medline and Embase, dates and search strategies were specified. The searches were run on the 19th September 2008 and terms were mostly free text mapped to find descriptors. A full randomised controlled trial (RCT) filter was not applied. Ustekinumab and CNTO-1275 were applied, the related term Stelara was not used, however the ERG search on Stelara identified no further studies. There are some minor discrepancies, around the recording of host systems, free text for some terms does not allow for English and American spelling, and no record of the search strategy for Cochrane was provided, however the ERG re-run of the searches produced similar results.

The MS (MS Appendix 2) lists additional searches to identify ongoing trials in key dermatology conferences (American Academy of Dermatology (AAD); Society of Investigative Dermatology (SID); European Academy of Dermatology & Venereology (EADV); International Congress on Psoriasis (ICP)) and MS section 6.1 lists databases for ongoing trials that were searched. The ERG ran additional searches on UK Clinical Research Network (UKCRN), Food and Drug Administration (FDA), European Medicines Agency (EMEA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) databases, and re-checked clinicaltrials.gov. No new relevant trials were found.

3.1.1.2 Cost effectiveness searches

All searches in Medline, Medline in Progress (MEIP), Embase, NHS Economic Evaluation Database (NHSEED) and the Cochrane Library are clearly documented and are reproducible. Ustekinumab and related terms Stelara and CNTO-1275 were not included in the cost search strategy. The searches were run on the 18th November 2008. The search history (MS

Appendix 2) records limitation by publication years for Medline as 2004-2008, Embase and Cochrane is limited in the search strategy to 2004-2007. No language restrictions were applied. The ERG ran cost filter searches on ustekinumab related terms in Embase and Medline but did not retrieve additional results.

No other sources were used to try and identify ongoing studies such as an in-house company database.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The inclusion and exclusion criteria used to select studies are clearly stated (MS p26, reproduced below in Table 1). Study eligibility was determined by three reviewers. It is not clear whether potential studies were assessed independently by each reviewer to achieve a consensus about which papers should be included, or whether the reviewers divided the task between them, each potential study being assessed by only one reviewer. The MS states that the inclusion and exclusion criteria apply to both the systematic review and the mixed treatment comparison (MTC) (MS p56); however the systematic review is limited to the trials of ustekinumab versus either placebo or one of the other biologics. Trials that did not include ustekinumab were specifically excluded from the manufacturer's systematic review. In contrast the MTC has the criterion that to be included trials had to include at least one of the biologics.

Table 1: Inclusion and exclusion criteria for MS systematic review

Inclusion criteria	Exclusion 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.	• 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.

Table 2: Inclusion and exclusion criteria for MS MTC

Inclusion and exclusion criteria
• The same as for the systematic review, with the additional inclusion criterion that the trials needed to include at least one of the available biologics (adalimumab, efalizumab, etanercept and infliximab as well as ustekinumab).

Whilst the inclusion and exclusion criteria broadly reflect the nature of the decision problem they do not include a description of severity of psoriasis. A dose (amount or dose schedule) description is also not included among the inclusion criteria, or among the listed exclusion criteria. However it should be noted that the MS states (MS 6.2.3 p26) that the T04 trial results have been excluded due to different dosing regimens used within this trial which are not included in the SmPC. The T04 trial was a phase 2 RCT with the primary aim of evaluating the safety and efficacy of single and multiple doses of ustekinumab. Trial quality and setting were also not included within the manufacturer's stated inclusion and exclusion criteria.

There is no flow diagram for the systematic review which includes only three RCTs. A flow diagram is provided for the MTC (MS p56 Fig 6.6.1) which shows that 20 RCTs are included in the meta-analysis. The flow diagram indicates how many studies were excluded from the MTC on the basis of screening abstracts and provides the reasons for rejecting these studies. The flow diagram also indicates how many of the full references, that were retrieved for more detailed examination, were excluded. The reasons for excluding these studies from the MTC are provided in MS Appendix 9.

The MS does not indicate whether the methods used for selecting studies were associated with any potential for bias. The ERG believes a potential for bias arises from not including all the studies that contributed to the MTC in the systematic review. This is because the studies included in the systematic review underwent a detailed quality assessment, whereas there was no detailed quality assessment of the MTC studies.

3.1.2.1 Identified studies

Three RCTs (all phase three studies) are included in the systematic review.

- Phoenix 1, ustekinumab versus placebo[2]
- Phoenix 2, ustekinumab versus placebo[3]
- ACCEPT, ustekinumab versus etanercept[4]

An additional 17 RCTs (i.e. making a total of 20 RCTs) are included in the MTC. All but one of the studies used placebo/supportive care as a comparator, i.e. the manufacturer has made the assumption that placebo and supportive care are the same thing. The additional 17 RCTs were:

- 3 trials of adalimumab vs. placebo
- 5 trials of efalizumab vs. placebo
- 5 trials of etanercept vs. placebo
- 4 trials of infliximab vs. placebo
- 2 trials of ustekinumab vs. placebo
- 1 trial of ustekinumab vs. etanercept

Electronic copies of published papers relating to the included studies, and Clinical Study Reports (CSRs) for the included ustekinumab trials arrived two and a half weeks after submission of the MS. The ERG has not assessed the CSRs, which range in size from 439 to 1250 pages.

For each included study, one investigator extracted data for the MS onto a form designed for this purpose. A physician independently checked each data extraction. Any discrepancies in extracted data were resolved between the investigator and the physician, with the involvement of a third party where necessary to settle disagreements. The quality of each RCT was scored using the Jadad instrument (MS p25) and the NICE validity assessment questions.

The following summary details are provided for the three RCTs included in the systematic review (selected details reproduced in Table 3):

- *Trial design* – all three trials began with randomised comparisons. However, in the two placebo controlled ustekinumab trials (Phoenix 1[2] and Phoenix 2[3]) further randomisations occurred at later time points (MS p30-32). Diagrams are provided in the MS to show the different study phases, and randomisation and blinding methods are described (MS p30-32). The manufacturers were asked to clarify whether the division of the placebo group at week 12 in the Phoenix 1[2] and Phoenix 2[3] trials was randomised (MS p30 and p31, division in each trial at 12 weeks labelled 3a and 3b) as this was not clearly stated. The manufacturer's response to the ERG was that participants in the placebo group were randomly assigned at week 12 to either ustekinumab 45mg or ustekinumab 90mg on a 1:1 ratio using a biased-coin minimisation assignment via centralised interactive voice response system.
- *Intervention* – drug doses and trial lengths are given with details of crossovers and withdrawal phases (MS p30-32).

- *Population* – Inclusion criteria are given for each included trial and countries in which the trials took place is noted. Baseline characteristics of enrolled participants are presented for age, sex, weight, duration and severity of psoriasis and previous therapies received. There is no information about the ethnicity of participants.
- *Patient numbers (eligible, randomised, allocated, crossed over, drop outs)* – Flow charts on MS p37-39 provide the details.
- *Outcomes* – provided on MS p40-41
- *Statistical analysis (power/sample size calculations, description of ITT analysis, subgroups etc)* – Tabulated within MS 41-43.

Table 3 Summary of characteristics of the included ustekinumab trials

Study	Trial methods	Participants	Outcomes
Phoenix-1[2]	*Design*: RCT *Duration*: 5 years *Interventions*: 1) Ustekinumab 45mg 2) Ustekinumab 90mg 3) Placebo	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 1) n=255 2) n=256 3) n=255	*Primary outcome* Participants achieving PASI 75 at week 12 *Secondary outcomes* PGA DLQI Time to loss of PASI 75 *Other key outcomes* Participants achieving PASI 90 &/or PASI 50 at week 12 SF-36
Phoenix-2[3]	*Design*: RCT *Duration*: 5 years *Interventions*: 1) Ustekinumab 45mg 2) Ustekinumab 90mg 3) Placebo	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 1) n=409 2) n=411 3) n=410	*Primary outcome* Participants achieving PASI 75 at week 12 *Secondary outcomes* PGA DLQI *Other key outcomes* Participants achieving PASI 90 &/or PASI 50 at week 12
ACCEPT[4]	*Design*: RCT *Duration*: 64 weeks *Interventions*: 1) Ustekinumab 45mg 2) Ustekinumab 90mg 3) Etanercept 50mg	Age ≥18 years with a diagnosis of plaque psoriasis for at least 6 months. BSA ≥10% baseline PASI ≥12. Candidate for phototherapy or systemic therapy. Failure to respond to, or had a contraindication to, or intolerant to ciclosporin A, methotrexate, or PUVA. 1) n=209 2) n=347	*Primary outcome* Participants achieving PASI 75 at week 12 *Secondary outcomes* PGA Participants achieving PASI 90 at week 12 Weight based analysis of PASI 75 at week 12

		3) n=347	*Other key outcomes* Participants achieving PASI 50 at week 12

BSA - Body Surface Area; DLQI – Dermatology Life Quality Index; PGA – Physicians Global Assessment; SF-36 – Short Form-36

The MS also contains some summary information for the additional 17 trials that are included within the MTC:

- *Trial design* – All studies included within the MTC were RCTs
- *Intervention* – intervention and control treatments are listed,
- *Population* – a brief summary including an indication of the severity of psoriasis and treatment history (e.g. whether naïve to biological therapy) of trial participants is provided
- *Patient numbers (eligible, randomised, allocated, crossed over, drop outs)* – Numbers of participants in each trial arm provided, but no further details such as number of drop outs.
- *Outcomes* – A summary of key outcomes provided

No details are provided regarding the statistical analysis methods used for the trials included in the MTC, except for those details on the three ustekinumab trials which are presented as part of the systematic review.

The MS does not state who funded the three trials included within the systematic review. The ERG has found that they were all sponsored by the manufacturer. The funders of the remaining 17 RCTs that contribute data to the MTC are not known.

No non randomised studies are included in the MS systematic review. The ERG has not assessed trial clinical effectiveness data for the three trials included in the systematic review beyond the 12 week time point. At 12 weeks participants in the placebo arm were randomised to cross over to one of two treatment groups. Those in the treatment groups were also re-randomised at later time points; in effect beyond 12-weeks the trials are non-randomised studies. All the trials included in the MTC are also described as RCTs but full details of the trial designs are not provided. It is therefore unclear whether these trials also include crossovers or non-randomised sectors. The ERG has presumed that the data contributing to the MTC comes

from time points where initial randomisation in these trials was still maintained although this is not explicitly stated.

None of the included trials report DLQI >10 as an inclusion criteria. In Table 4 it can be seen that mean DLQI was greater than 10 in the two Phoenix trials,[2;3] although there is some degree of variance around these means. DLQI was not reported in the ACCEPT trial.[4] The MS states that for each of the three RCTs included in the systematic review "baseline demographics and patient characteristics were well balanced" amongst study groups (see Table 4). However no statistical test results are reported to support this statement (MS p33-36). Baseline data for participants in Phoenix 1[2] and Phoenix 2[3] are provided as numbers and % for dichotomous data, and means ± standard deviations (SDs) for continuous data. For the ACCEPT RCT[4] continuous data are presented as means and medians but no measure of variance was provided. For ACCEPT fewer baseline characteristics are reported (no data on DLQI, previous treatments, or patients with latent tuberculosis which are each reported for Phoenix 1 and Phoenix 2). In general groups within the trials do appear reasonably balanced, the characteristics that seem less well balanced are:

Phoenix 1:[2]

- there appear to be fewer patients with psoriatic arthritis in the ustekinumab 45mg group than the 90mg or placebo groups (29% vs 36.7% and 35.3% respectively).
- Fewer participants in the placebo group appear to have received photo-therapy (58.5% vs 67.8% in 45mg group and 66% in 90 mg group) or conventional systemic therapy (50.2% vs 55.3% in 45mg group and 55.1% in 90 mg group).

Phoenix 2:[3]

- 58.8% of placebo participants had received conventional systemic therapy compared to 54.5% in both the ustekinumab groups.

ACCEPT:[4]

- The etanercept arm has more men (70.9% vs 63.6% and 67.4% in ustekinumab 45mg and 90mg arms respectively)

Participant characteristics are not reported by trial arms for the studies contributing to the MTC.

The MS does not comment on whether baseline characteristics of participants were similar across the RCTs included in the systematic review. Observation of the baseline data presented for participants within each trial suggests that patient characteristics between trials are broadly similar for most reported characteristics. Since baseline data on DLQI, previous treatments, or patients with latent tuberculosis are not reported for ACCEPT[4] it is unclear whether these factors are similar between ACCEPT[4] and Phoenix 1[2] and Phoenix 2.[3] Apparent differences the ERG has noted are:

Phoenix 1:[2]

- Participants in Phoenix 1 are a little heavier than in the Phoenix 2 and ACCEPT (average of means for study groups calculated by ERG reviewer are 93.9 kg vs 91.0 kg and 90.8 kg respectively), a greater proportion have psoriatic arthritis (33.7 % vs 24.9 % and 27.9 % respectively, again average of means for study groups calculated by ERG reviewer) and have received previous biological therapy (average of means for study groups calculated by ERG reviewer 51.2 % vs 37.9 % in Phoenix2, data not presented for ACCEPT).

Phoenix 2:[3]

- Fewer participants in Phoenix 2 have a PGA of marked or severe (average of means for study groups calculated by ERG reviewer 39.7 % (Phoenix 2) versus 43.7 % (Phoenix1) and 43.2 % (ACCEPT).

ACCEPT:[4]

- ACCEPT participants have a very slightly shorter duration of psoriasis (average of means for study groups calculated by ERG reviewer 18.8 years, vs 19.9 years and 20.1 years in Phoenix 1[2] and Phoenix 2[3] respectively).

Table 4: Baseline Demographics and Disease Characteristics of participants in the trials included in the systematic review

Characteristic	Phoenix 1[2]			Phoenix 2[3]			ACCEPT[4]		
Study arm	Ustekinumab 45mg (n=255)	Ustekinumab 90mg (n=256)	Placebo (n=255)	Ustekinumab 45mg (n=409)	Ustekinumab 90mg (n=411)	Placebo (n=410)	Etanercept 50mg (n=347)	Ustekinumab 45mg (n=209)	Ustekinumab 90mg (n=347)
Age years [a]	44.8 (12.5)	46.2 (11.3)	44.8 (11.3)	45.1 (12.1)	46.6 (12.1)	47.0 (12.5)	45.7 (45.0)	45.1 (45.0)	44.8 (45.0)
Male sex number (%)	175 (68.6)	173 (67.6)	183 (71.8)	283 (69.2)	274 (66.7)	283 (69.0)	246 (70.9)	133 (63.6)	234 (67.4)
Weight Kg [a]	93.7±23.8	93.8±23.9	94.2±23.5	90.3±21.0	91.5±21.3	91.1±21.6	90.8 (89.0)	90.4 (87.0)	91.0 (88.2)
Duration of psoriasis years [a]	19.7±11.7	19.6±11.1	20.4±11.7	19.3±11.7	20.3±12.3	20.8±12.2	18.81 (17.41)	18.87 (16.71)	18.74 (17.63)
Involved body surface area % [a]	27.2±17.5	25.2±15.0	27.7±17.4	25.9±15.5	27.1±17.4	26.1±17.4	23.8 (19.0)	26.7 (20.0)	26.1 (20.0)
PGA marked or severe [b] (%)	114 (44.7)	109 (42.6)	112 (43.9)	169 (41.3)	159 (38.7)	160 (39.0)	148 (42.7)	98 (46.9)	144 (41.6)
PASI score [a]	20.5±8.6	19.7±7.6	20.4±8.6	19.4±6.8	20.1±7.5	19.4±7.5	18.64 (16.80)	20.49 (17.00)	19.87 (17.15)
DLQI score	11.1±7.1	11.6±6.9	11.8±7.4	12.2±7.1	12.6±7.3	12.3±6.9			
Patient with psoriatic arthritis (%)	74 (29.0)	94 (36.7)	90 (35.3)	107 (26.2)	94 (22.9)	105 (25.6)	95 (27.4)[h]	62 (29.7)[h]	95 (27.4)[h]
Patients treated previously – no. (%)									
Topical agent [c]	245 (96.1)	239 (93.4)	242 (94.9)	393 (96.1)	384 (93.4)	396 (96.6)			
Phototherapy [d]	173 (67.8)	169 (66.0)	150 (58.5)	286 (69.9)	267 (65.0)	276 (67.3)			

Conventional systemic therapy [e]	141 (55.3)	141 (55.1)	142 (55.7)	223 (54.5)	224 (54.5)	241 (58.8)			
Biological therapy [f]	134 (52.5)	130 (50.8)	128 (50.2)	157 (38.4)	150 (36.5)	159 (38.8)			
Patients with latent tuberculosis [g] (%)	8 (3.1)	7 (2.7)	10 (3.9)	16 (3.9)	16 (3.9)	11 (2.7)			

Plus-minus data are Mean±SD. [a] Data from ACCEPT trial are means (medians)
[b] Rated as cleared (0), minimal (1), mild (2), moderate (3), marked (4), or severe (5) in Phoenix 1. Rating not stated for Phoenix 2 and ACCEPT.
[c] 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
[d] Includes UVB
[e] Includes PUVA, methotrexate, acitretin and ciclosporin
[f] Includes etanercept, alefacept, efalizumab, infliximab or adalimumab
[g] Latent tuberculosis was identified by a purified protein derivative test without evidence of active tuberculosis
[h] Rates in powerpoint presentation appear to be different from these.

The MS does comment on whether baseline characteristics of participants were similar across the RCTs contributing to the MTC (MS p58). A number of differences between trial populations as implied by the trial inclusion and exclusion criteria are pointed out. Some differences in the baseline PASI scores of participants within the trials are also noted. Unsurprisingly there is a greater variability between the participants in these trials.

The MS includes some trials in the MTC that do not meet the stated criteria. The exclusion criteria listed on MS p26 include "Any study which has one or more arms of <50 participants". This exclusion criterion should therefore also apply to the MTC as this is stated to have followed the same methodology (MS p56). On this basis the following three trials should have been excluded from the MTC:

- Gordon 2006 trial of adalimumab because one of the trial arms has only 45 participants (with 50 and 52 in the other two arms)
- Van der Kerkhof 2008 trial of Etanercept because placebo arm has only 46 participants (96 in etanercept arm)
- Chaudhari 2001 trial of infliximab because all three groups have only 11 participants

The literature search tree (MS p56) indicates that the head to head study of ustekinumab versus etanercept (ACCEPT trial[4]) was not identified via the systematic review. The reason is not given. The poster summarising the ACCEPT trial was presented at the EADV conference 17th to 20th September 2008. The MS states that annual proceedings abstracts, including those of the EADV conference, were searched between 2005 and 2008 (MS p24). If the search cut-off date for these searches was 19th September 2008, as it was for the literature search of electronic databases, the poster for the ACCEPT trial should have been identified. However, if the search of EADV conference abstracts took place earlier than September 2008 this would explain why the poster was not identified by searching. It appears likely that all relevant RCTs have been identified.

The three ustekinumab trials (Phoenix 1[2] and Phoenix 2,[3] and ACCEPT[4]) are all ongoing (MS p29). The anticipated completion dates are not provided. No other ongoing trials are noted in the MS.

3.1.3 Description and critique of the approach to validity assessment

The manufacturers used NICE criteria to critically appraise the three RCTs included within their systematic review. As can be seen from Table 5 for most items the ERG agrees with the manufacturer's assessment. The items where the ERG's assessment differs from that of the manufacturer are:

Question 3: Was a justification of the sample size provided, and Question 10: Were the statistical analyses used appropriate.

- It is unclear whether the sample sizes provide sufficient power for the weight based subgroup analysis (particularly the 10kg increment analysis). There is a lack of information on the methods of subgroup analysis so it is difficult to determine whether the methods used were appropriate. The ERG asked the manufacturers to provide details of the subgroup-analysis and a description of the method used which justified the cut-off weight of 100kg for the use of a higher dose of ustekinumab. The manufacturers provided some additional information to support the 100kg cut off but their response did not clarify the method of subgroup analysis any further (see Appendix 1).

The manufacturer's also scored the quality of each of the three RCTs included in the systematic review using the Jadad instrument. The Jadad scores are reported within MS Table 6.6.1 (MS p60 to MS p63). Phoenix 1[2] and Phoenix 2[3] both scored 5 (the maximum score) but a Jadad score for the ACCEPT trial[4] is not reported. The other 17 RCTs contributing to the MTC were also quality assessed using the Jadad instrument and assigned Jadad scores of either 4 or 5. The ERG has not checked the Jadad summary score assigned to either the RCTs within the systematic review or the additional studies included within the MTC.

Table 5: Manufacturer and ERG assessment of trial quality

NICE QA Criteria for RCTs			
1. Adequacy of allocation concealment			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-2[3]	Trial 3: ACCEPT[4]
MS:	See below	See below	See below
ERG:	Adequate	Adequate	Adequate
Comment: Those preparing the MS have not understood the difference between allocation concealment and blinding. Although treatment assignment can sometimes be predicted with minimisation techniques (breaking allocation concealment) the biased-coin approach and centralised system employed here make it very unlikely that treatment assignment could have been determined by study personnel. Therefore allocation concealment should have been maintained.			
2. Adequacy of randomisation technique			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	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 which the subject had an inadequate response, intolerance, or contraindication.	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 baseline weight (≤90kg or >90kg).	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.
ERG:	Adequate	Adequate	Adequate
Comment:			
3. Was a justification of the sample size provided?			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	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*
ERG:	Adequate for primary outcome but unclear whether trial powered correctly for secondary outcomes or subgroup analyses.	Adequate for primary outcome but unclear whether trial powered correctly for secondary outcomes or subgroup analyses.	Adequate for determining treatment differences between etanercept and both the 45mg and 90mg doses of ustekinumab.
*NB: Section 6.3.3 describes sample size calculations.			
4. Was follow-up adequate?			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	The follow-up is adequate and did concur with	The follow-up is adequate and did concur with	The follow-up is adequate and did

	EMEA recommendations	EMEA recommendations	concur with EMEA recommendations
ERG:	Adequate	Adequate	Adequate
5. Were outcome assessors aware of allocation?			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	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	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 (see MS page 43 for further details).
ERG:	Adequate	Adequate	Adequate
Comment: Although ACCEPT was an unblinded study the investigators appear to have put in place a strict protocol to ensure that efficacy evaluators and safety evaluators were blind to participant treatment. In all studies unblinding was allowed if necessary for safety reasons but the MS does not indicate whether it was necessary to unblind for these reasons during the course of the studies.			
6. Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	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
ERG:	Trial has a mixed design that begins with a 12 week parallel groups phase. Randomisation is then lost in the second phase (weeks 12 to 40) as the placebo group is split into two and crosses over to treatment. The final phase (weeks 40 to 76) involves withdrawal from treatment, and retreatment once 50% of the PASI improvement is lost.	Trial has a mixed design that begins with a 12 week parallel groups phase. Randomisation is then lost in the second phase (from week 12) as the placebo group is split into two and crosses over to treatment. The final phase (weeks 28 to 52) involves randomisation of partial responders in the original ustekinumab treatment groups to dose intensification (shorter dosing intervals) or continuing with initial treatment schedule.	Parallel groups to week 12
Comment: The MS does not comment on the possibility or length of any carry-over effects.			
7. 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?			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	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	The study was conducted in 67 sites in the UK, Austria, Belgium, Canada, Denmark, Finland, Germany, the Netherlands and the

		countries is unlikely to differ from UK practice.	USA
ERG:	48 sites: USA, Canada and Belgium.	70 sites: Austria, Canada, France, Germany, Switzerland, UK, USA.	67 sites: Austria, Belgium, Canada, Denmark, Finland, Germany, the Netherlands, the UK and the USA.
Comment: Number of sites in each location unknown.			
8. How do those included in the RCT 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.			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	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.
ERG:	Broadly similar	Broadly similar	Broadly similar
Comment: It was a condition of the ACCEPT trial that patients had to have failed to respond to, or had a contraindication to, or were intolerant to ciclosporin A, methotrexate, or PUVA. This was not a condition of the two Phoenix trials.			
9. Were the study groups comparable?			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	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
ERG:	Appear to be fewer patients with psoriatic arthritis in the Ustekinumab 45mg group than the 90mg or placebo groups (29% vs 36.7% and 35.3% respectively). Fewer participants in the placebo group appear to have received photo-therapy (58.5% vs 67.8% in 45mg group and 66% in 90 mg group) or conventional systemic therapy (50.2% vs 55.3% in 45mg group and 55.1% in 90 mg group).	58.8% of placebo participants had received conventional systemic therapy compared to 54.5% in both the ustekinumab groups.	Etanercept arm has more men (70.9% vs 63.6% and 67.4% in ustekinumab 45mg and 90mg arms respectively)
Comment: No statistical tests are reported to demonstrate that there were no statistically significant differences between the groups for each patient characteristic.			
10. Were the statistical analyses used appropriate?			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	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.
ERG:	Unclear – MS p41 does not indicate methods used for the weight based analysis described	Unclear – MS p42 provides some information regarding analysis of dichotomous endpoints	Unclear – MS p41 indicates that the weight based analysis was a

	on MS p53	with weight as a stratification factor.	predefined secondary outcome. However methods used for this analysis are not described in the MS
Comment: The main areas of uncertainty are the subgroup analyses because the ERG is concerned that there may not have been sufficient statistical power to undertake these analyses.			
11. Was an intention-to-treat analysis undertaken?			
	Trial 1: PHOENIX-1[2]	Trial 2	Trial 3: ACCEPT[4]
MS:	An intent-to-treat analysis was undertaken.	An intent-to-treat analysis was undertaken.	An intent-to-treat analysis was undertaken.
ERG:	Analysis described as ITT	Analysis described as ITT	Analysis described as ITT
Comment: Text on MS p48 and MS p50 seems to suggest that not all randomised patients were included in the analysis; however numbers in table and charts suggest ITT. The ERG requested clarification from the manufacturers who indicated that an ITT analysis had been conducted and the text on MS p48 and MS p50 had been included in error (see Appendix 1)			
12. Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	None	None	None
ERG:	No	No	No
13. For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?			
	Trial 1: PHOENIX-1[2]	Trial 2: PHOENIX-1[3]	Trial 3: ACCEPT[4]
MS:	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 weeks or escalate to dosing every 8 weeks. Escalated dosing every 8 weeks is not within the summary of product characteristics	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.
ERG:	Doses appropriate	Doses for the portion of the study at which primary outcome measured appropriate	Ustekinumab doses appropriate. Etanercept dose, 50mg twice weekly, is a greater dose than that recommended in NICE guidance (25mg twice weekly).

3.1.4 Description and critique of manufacturer's outcome selection

The outcomes reported in the MS appear appropriate and in general match those listed in the NICE decision problem (severity of psoriasis, remission rate, relapse rate, adverse effects of treatment, health related quality of life (QoL)).

All three ustekinumab trials report the primary outcome of severity of psoriasis using an improvement on the PASI of at least 75% (PASI 75). In the summary information on 17 comparator trials included in the MTC, PASI 75, PASI 90 (an improvement on the PASI of at least 90%), and PASI 50 (an improvement on the PASI of at least 50%) outcomes are reported but is not clear what the primary outcome measure was for these 17 studies.

The two placebo controlled ustekinumab trials Phoenix 1 and Phoenix 2 included in the MS systematic review report PASI 90 and PASI 50, PGA, and DLQI as secondary outcomes. Phoenix 1 also reports on time to loss of PASI 75 response (this followed the re-randomisation at trial week 40), and SF36 was a further secondary outcome in this trial. The ACCEPT trial[4] reports the secondary outcomes of PASI 90, PASI 50, and PGA. There appears to be a reporting error in the footnote to the table of outcomes (MS Section 6.3.2, MS p41). This states that the PGA rates the patient's psoriasis overall relative to baseline as 0 (clear), 1 (minimal), 2 (moderate), 3 (marked), or 5 (severe). The ERG believes this should read 0 (clear), 1 (minimal), 2 (mild), 3 (moderate), 4 (marked) or 5 (severe) which are the standard values, and which are stated in the CSRs.

An appendix (MS Appendix 7) lists additional outcomes for the ustekinumab trials included within the MS systematic review which are not reported within the MS. These outcomes include impact of weight on psoriasis improvement (briefly reported on within the MS but without much detail to indicate how weight based results were derived). The two placebo controlled trials Phoenix 1 and Phoenix 2 included efficacy of ustekinumab with self-administration as an outcome which is also not reported on within the MS.

Adverse events are reported for the three ustekinumab trials Phoenix 1,[2] Phoenix 2[3] and ACCEPT.[4] A fourth trial T04,[5] which was excluded from the MS systematic review and MTC, is also included for the reporting of adverse events. The MTC, in common with other MTCs undertaken in this topic area, does not include adverse events.

QoL is reported by the Phoenix 1 and Phoenix 2 trials as DLQI, Phoenix 1 also reports SF-36 (a general QoL measure). Both the DLQI and the SF-36 are validated measures. Text on MS p51 indicates that the outcomes of anxiety and depression from the Hospital Anxiety and Depression Scale (HADS), and work limitations from the Work Limitations Questionnaire (WLQ), were also gathered during the trial but no numerical data are reported. No health related QoL outcomes appear to have been part of the ACCEPT trial[4] (none reported in the MS and none listed in MS appendix 7).

For the MTC the MS states (MS p58) that the data incorporated in the analysis are shown in Table 6.6.2 (MS p64-74). Table 6.6.2 provides outcome data for PASI 50, PASI 75 and PASI 90. However, PGA, DLQI and safety outcomes are also present in this table (where the RCTs included in the MTC had reported on these) and the ERG do not believe that these outcomes were incorporated into the MTC.

3.1.5 Description and critique of the manufacturer's approach to trial statistics

The MS reports trial results for the relevant outcome measures of the three ustekinumab trials included in the MS systematic review. An intention to treat (ITT) analysis was used in analysing data from these three trials. This was confirmed by the manufacturer who indicated that the text in MS sections 6.4.1 (MS p48) and 6.4.2 (MS p50), which stated a lesser number of participants were included in the efficacy analyses than had been randomised, had been included in error (see Appendix 1).

An indication or discussion of what would be considered clinically important differences for the reported outcomes has not been found within the MS.

Phoenix 1

Primary outcome: This is the dichotomous outcome of achieving or not achieving PASI 75 at trial week 12, and it is reported as n/N and %. The p-values for the statistical comparison of each dose of ustekinumab with placebo are provided. Difference in response between groups was not reported (which it is for PGA as noted below).

Secondary outcomes:
PASI 50 and PASI 90 are reported in the same way as PASI 75, with PASI 90 being used as the indicator of remission.

PGA is reported as a combined outcome of either 'cleared' or 'minimal', reported as n/N and %. The differences in response of ustekinumab 45mg versus placebo, and ustekinumab 90mg versus placebo, are reported with a 95% CI, and p-values for each comparison.

DLQI is reported as mean change scores with SD, and p-values are reported for the comparison of each dose of ustekinumab with placebo.

Time to loss of PASI response is also reported for the participants who had received therapy with ustekinumab and who were then re-randomised at trial week 40 to placebo or continued treatment. These data are presented as small graphs (A and B on MS p48) showing median percentage improvement with a measure of variance that it not described. Numerical values are not provided but a p value is given for the comparison of participants continuing to receive ustekinumab (maintenance therapy) versus those participants withdrawn from therapy.

Small bar charts are presented (C and D on MS p48) but no indication of what these represent is provided. The ERG believes these charts show median change in DLQI between study weeks 40 and 76, again with a measure of variance that is not described.

The SF-36 outcome is briefly reported although no numerical values are presented. The text just states that there were significant improvements and provides a p-value for the comparison of each ustekinumab group versus placebo.

<u>Phoenix 2</u>
Primary outcome: This is the dichotomous outcome of achieving or not achieving PASI 75 at trial week 12 and is reported as n/N and %. The p-values for the statistical comparison of each dose of ustekinumab with placebo are provided. These data are also presented in the form of a small bar chart (MS p50). Difference in response between groups is reported with 95% CI and p-values (which is not the case for Phoenix 1).

Secondary outcomes:
PASI 50 and PASI 90 reported in a similar way to PASI 75 except that the difference in response between groups is not reported. PASI 90 is used as the indicator of remission.

PGA is reported as a combined outcome of either 'cleared' or 'minimal', reported as n/N and %. The differences in response of ustekinumab 45mg versus placebo, and ustekinumab 90mg versus placebo, are reported with a 95% CI, and p-values for each comparison.

DLQI is reported as mean change scores with SD, and p-values are reported for the comparison of each dose of ustekinumab with placebo.

ACCEPT[4]

Primary outcome: This is again the dichotomous outcome of achieving or not achieving PASI 75 at trial week 12 and is reported as n/N and %. The p-values for the statistical comparison of each dose of ustekinumab with etanercept are provided. The difference in response between groups was not reported.

Secondary outcomes:
PASI 50 and PASI 90 are reported in the same way as PASI 75, with PASI 90 being used as the indicator of remission.

PGA is reported as a combined outcome of either 'cleared' or 'minimal', reported as n/N and %. Difference in response between groups is not reported but p-values for the comparison of each dose of ustekinumab with etanercept are provided.

Weight based dosing analysis for Phoenix 1, Phoenix 3 and ACCEPT trials

The MS presents results from weight based dosing analysis (MS p53 and p54) but the methods used to obtain these results are not clearly documented within the MS. Additional details were requested from the manufacturer but the ERG remains uncertain whether the manufacturer's approach to sub-group analysis is correct as insufficient information has been provided (see Appendix 1).

Trials contributing to the MTC

The MS presents summary outcome results from the additional 17 RCTs that contribute data to the MTC (MS Table 6.6.2a on p63-71) but no indication is given in the MS as to whether these are results from ITT analyses. For PASI 50, PASI 75, PASI 90 and PGA cleared/minimal outcomes are provided as percentages only i.e. n/N is not reproduced in the MS table. DLQI data, if available, are presented in a variety of ways. The column header to MS table 6.6.2a indicates that mean values or change values are being presented, but for some of the studies included in the MTC it is unclear what format of outcome result is being reproduced in the table.

3.1.6 Description and critique of the manufacturer's approach to the evidence synthesis

Individual trials' data for the three trials included in the systematic review are tabulated on p.47-53 of the MS, but there is no overall narrative summary or tabulation of outcomes across the three included trials. The data in the tables correspond with those in the published papers, although there are some minor differences. For the tabulated data of the weight based dosing analysis (MS p.54) the data for the active treatment arms matches the corresponding CSRs. However, data for the placebo groups and alternative groups were not presented in the MS despite being reported in the CSRs.

On page 56 of the MS, the authors state that a dedicated meta-analysis of ustekinumab study data from the three trials included within the MS systematic review has not been carried out. However, an MTC of 20 studies (the three ustekinumab studies plus 17 RCTs that assessed comparators) was carried out, and this appears to have included a pair-wise meta-analysis of data for each of the drugs. The included trials were appropriate for pooling. The manufacturer assigned Jadad scores, but it is not clear whether this quality assessment was carried out by one or two reviewers. A fixed effect model was used for the MTC, and the authors of the MS justify their choice of a fixed effect model for the MTC. It is assumed that a fixed effect method was also used for the meta-analysis, although this is not stated explicitly as there was no description of the methodology used for the meta-analysis. The forest plots in Figures 6.6.6, 6.6.7 and 6.6.8 show the odds ratios for PASI 50, PASI 75 and PASI 90, respectively. Treatment effects in tables 6.6.3 to 6.6.6 have mean, 2.5% and 97.5% values. No meta-analysis or MTC results are presented for other outcomes such as PGA and DLQI.

The meta-analysis does not include a statistical assessment of heterogeneity. The Winbugs code used in the MS was reported by the MS authors to be different to that used in the review by Woolacott and colleagues.[1] The ERG is unable to comment on whether this is appropriate. In addition, data from the weight based dosing analysis of ustekinumab was taken from a sub-group of the trial data, whereas for the comparator trials all patient data were used. It is unclear to the ERG if participants in the comparator trials over a certain weight would also have responded differently to each of the respective treatments.

Table 6: ERG appraisal of MTC approach

Appraisal criteria	Criteria met (yes / no / unclear / not applicable)
A. CONCEPTUAL BASIS	
1. Is a justification given for conducting an MTC?	Yes
B. SYSTEMATIC PROCESSES	
2. Is a comprehensive and transparent search strategy reported?	Yes
3. Are inclusion / exclusion criteria adequately reported?	Yes
4. Is the number of included /excluded studies from the MTC reported, with reasons for exclusions?	Yes
5. Is a visual representation of the data networks provided?	Yes, supplied on request.
6. Are the data from included studies extracted and tabulated?	Yes
7. Is the quality of the included studies assessed?	Yes
C. STATISTICAL ANALYSIS	
8. Are the statistical procedures adequately described and executed?	unclear
9. Is there a sufficient discussion of heterogeneity?	no
10. Is the type of model used (i.e. fixed or random effects) reported and justified?	yes
11. Was sensitivity analysis conducted?	no
12. Is any of the programming code used in the statistical programme provided (for potential verification?)	yes
D. PRESENTATION AND INTERPRETATION OF THE EVIDENCE	
13. Is there a tabulation/ illustration of results for each intervention and for each outcome?	yes
14. Is there a narrative commentary on the results?	Yes, but limited
15. Does the discussion of the results reflect the data presented?	Yes
16. Have the authors commented on how their results compare with other published studies (e.g. MTCs), and offer any explanation for discrepancies?	No.
17. Have the authors discussed whether or not there are any differences in effects between the direct and indirect evidence?	No

The MTC included three trials which had treatment arms containing fewer than 50 patients. These trials therefore did not strictly meet the manufacturer's inclusion criteria. It is difficult for the ERG to speculate about what the impact would be on the results of the MTC if these three trials were removed. However, the impact is likely to be small because these trials include relatively small numbers of participants, and there are other, larger trials that also contribute data to the same drug comparisons within the MTC network. The included trials were similar

enough to be pooled in the MTC, although there is no mention of any formal analysis of statistical heterogeneity. There is very little description in the text of the methodology used for the MTC, although the WinBUGs code is provided in an appendix. A fixed effect model was used, and this is justified by the MS authors. There is some discrepancy between this code and that reported in a previous review,[1] with some contradictions in the MS text around this point. The MS contains results from the MTC using the all-patient (as randomised) groups from the ustekinumab trials, and also reports an MTC using outcomes from the weight-based dosing groups for ustekinumab.

There is an uncertain degree of bias associated with the MTC since it is not clear whether all trials should have been included, whether ITT results were used for the 17 non-ustekinumab trials, and whether the subgroups used in the MTC for weight-based dosing were analysed appropriately.

3.2 Summary statement of manufacturer's approach

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research? Ie all studies identified	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Is sufficient detail of the individual studies presented?	Yes – for systematic review of ustekinumab evidence
5. Are the primary studies summarised appropriately?	Yes

The systematic review methodology was carried out appropriately, although it is not clear how many reviewers screened the studies for inclusion. The submitted evidence generally reflects the decision problem defined in the MS. For the systematic review of ustekinumab, there is a low risk of bias, for the MTC there is an uncertain risk of bias.

3.3 Summary of submitted evidence

In this section of the report, the ERG concentrates on the main outcomes of the included RCTs of ustekinumab after 12 weeks of treatment, which is the randomised comparison. Data have been checked by the ERG and summarised for each of the key outcomes below. There were a few differences between the data presented in the MS and the data in the trials; however these were generally minor discrepancies. The data presented in the tables below are the ERG

checked data. The MS also presented data at additional time points from the included trials however, as these results are not of part of randomised comparisons these are not repeated here. Occasionally data are presented from the trial CSRs in confidence where it was not available in the MS or the trial publication. In addition to the three trials of ustekinumab, results of trials of relevant comparator interventions were also presented. However the ERG has not checked the data presented with the relevant trial publications (for comment generally on the MTC please see Section 3.1.6 above).

3.3.1 PASI

PASI 75

The proportion achieving a PASI 75 response was the stated primary outcome in all three included studies. Table 7 shows that in both of the Phoenix trials[2;3] greater proportions of participants treated with ustekinumab showed a PASI 75 response compared with those treated with placebo, after 12 weeks. This was statistically significantly different for both doses of ustekinumab compared to placebo, in both trials. Rates appear to be similar between the two ustekinumab doses in both trials, although no formal analysis of these data was presented. No meta-analysis of these data was presented in the MS except as part of the MTC.

Table 7: PASI 75 response for placebo controlled trials

Study	Ustekinumab 45mg	Ustekinumab 90mg	Placebo	Differences between groups
Phoenix-1[2] (12 weeks)	171/255 (67.1%)	170/256 (66.4%)	8/255 (3.1%)	p<0.0001 for both groups versus placebo
Phoenix-2[3] (12 weeks)	273/409 (66.7%)	311/411 (75.7%)	15/410 (3.7%)	p<0.0001 for both groups versus placebo

In the ACCEPT[4] trial, after 12 weeks, the proportion of participants achieving a PASI 75 in those treated with ustekinumab 45mg was statistically significantly greater than the proportion in the etanercept 50mg twice weekly group (see Table 8). The PASI 75 results for the comparison of those treated with ustekinumab 90mg compared to etanercept 50mg were similarly statistically significant. No comparison was made between the two ustekinumab treatment groups, although PASI 75 rates appear to be similar.

Table 8: PASI 75 response for ACCEPT trial

Study	Ustekinumab 45mg	Ustekinumab 90mg	Etanercept 50mg	Differences between groups
ACCEPT[4] (12 weeks)	141/209 (67.5%)	256/347 (73.8%)	197/347 (56.8%)	p=0.012 45mg vs etanercept p<0.001 90mg vs etanercept

No discussion is made in the MS about what proportion of participants achieving a PASI 75 is deemed to be clinically significant. In those treated with ustekinumab in these three studies proportions achieving PASI 75 are in the region of 66-76%. The ERG clinical expert suggests that this is similar to that seen with methotrexate, ciclosporin and adalimumab and slightly less than that seen with infliximab.

PASI 50

Achievement of a PASI 50 response was a secondary outcome in all three included trials. Table 9 shows that in the two placebo-controlled studies (Phoenix 1[2] and 2[3]) there was a statistically significant difference in PASI 50 response at 12 weeks between those treated with ustekinumab 45mg and placebo, and between those treated with ustekinumab 90mg and placebo in both studies. No meta-analysis of these data was presented in the MS.

Table 9: PASI 50 response for placebo controlled trials

Study	Ustekinumab 45mg	Ustekinumab 90mg	Placebo	Differences between groups
Phoenix-1[2] (12 weeks)	213/255 (83.5%)	220/256 (85.9%)	26/255 (10.2%)	p<0.0001 for both groups versus placebo
Phoenix-2[3] (12 weeks)	342/409 (83.6%)	367/411 (89.3%)	41/410 (10.0%)	p<0.0001 for both groups versus placebo

In the ACCEPT[4] trial comparing ustekinumab with etanercept the PASI 50 results appear to be similar across the three treatment groups, however, no statistical analysis of these data was presented (Table 10).

Table 10: PASI 50 response for ACCEPT trial

Study	Ustekinumab 45mg	Ustekinumab 90mg	Etanercept 50mg	Differences between groups
ACCEPT[4] (12 weeks)	181/209 (86.6%)	320/347 (92.2%)	286/347 (82.4%)	Not reported

PASI 90

Achievement of a 90% reduction in PASI at week 12 was also a secondary outcome in the three included trials. In both of the Phoenix trials[2;3] a statistically significant difference was observed between the ustekinumab 45mg and placebo groups and between the ustekinumab 90mg and placebo groups (see Table 11). No meta-analysis of these data was undertaken.

Table 11: PASI 90 response for placebo controlled trials

Study	Ustekinumab 45mg	Ustekinumab 90mg	Placebo	Differences between groups
Phoenix-1[2] (12 weeks)	106/255 (41.6%)	94/256 (36.7%)	5/255 (2%)	p<0.0001 for both groups versus placebo
Phoenix-2[3] (12 weeks)	173/409 (42.3%)	209/411 (50.9%)	3/410 (0.7%)	p<0.0001 for both groups versus placebo

Table 12 shows that rates of participants achieving a PASI 90 at week 12 was statistically significantly different between those treated with ustekinumab 45mg and those treated with etanercept 50mg in the ACCEPT[4] trial. Similarly a statistically significant difference in PASI 90 was observed between the ustekinumab 90mg group and the etanercept 50mg group.

Table 12: PASI 90 response for ACCEPT trial

Study	Ustekinumab 45mg	Ustekinumab 90mg	Etanercept 50mg	Differences between groups
ACCEPT[4] (12 weeks)	73/209 (34.9%)	155/347 (44.7%)	80/347 (23.1%)	p<0.001 for both ustekinumab groups versus etanercept

3.3.2 Physicians Global Assessment

In both the Phoenix 1[2] trial and the Phoenix 2[3] trial assessment of the PGA was made at 12 weeks. This measure used a 6-point scale rating the psoriasis from severe to clear. In each of these trials outcomes were reported for the proportion achieving a rating of 'clear' or 'minimal'. As can be seen in Table 13 below in both trials there was a statistically significant difference in the proportions rated as 'cleared or minimal' in the ustekinumab treated participants compared to the placebo treated participants. Table 14 shows that in the ACCEPT[4] trial those treated with

ustekinumab were statistically significantly more likely to achieve a rating of cleared or minimal than those treated with etanercept 50mg.

Table 13: PGA response for placebo controlled trials

Study	Ustekinumab 45mg	Ustekinumab 90mg	Placebo	Difference in response
Phoenix-1[2] (12 weeks)	154/255 (60.4%)	158/256 (61.7%)	10/255 (3.9%)	p<0.0001 for both groups versus placebo
Phoenix-2[3] (12 weeks)	278/409 (68.0%)	302/411 (73.5%)	20/410 (4.9%)	p<0.0001 for both groups versus placebo

Table 14: PGA response for ACCEPT trial

Study	Ustekinumab 45mg	Ustekinumab 90mg	Etanercept 50mg	Differences between groups
ACCEPT[4] (12 weeks)	136/209 (65.1%)	245/347 (70.6%)	170/347 (49%)	p<0.001 for both ustekinumab groups versus etanercept

3.3.3 Dermatology Life Quality Index

Change in score on the DLQI was reported in both of the included placebo-controlled comparisons.[2;3] The DLQI is a 10-question validated measure for patients with psoriasis with a score which ranges from 0 to 30, with lower scores corresponding to better QoL. Mean and median change from baseline scores on this measure can be seen in Table 15, where a negative value indicates an improvement in score from baseline. Statistical significance testing was undertaken on the median change scores (although the MS suggests this was on the mean change score) and showed a statistically significant difference in the rate of change between those treated with either dose of ustekinumab compared to those treated with placebo in both of the included trials.

Table 15: DLQI for placebo controlled trials

Study	Ustekinumab 45mg	Utsekinumab 90mg	Placebo	Differences in response
Phoenix-1[2] (12 weeks) **mean change (SD)**	n=254 -8.0 (6.87)	n=249 -8.7 (6.47)	n=252 -0.6 (5.97)	Not reported for mean change
Phoenix-1[2] (12 weeks) **median change (inter-quartile range)**	n=254 -6 (-12 to -3)	n=249 -7 (-12 to -4)	n=252 0 (-3 to 3)	p<0.0001 for both groups versus placebo
Phoenix-2[3] (12 weeks) **mean change (SD)**	n=401 -9.3 (7.12)	n=402 -10.0 (6.67)	n=400 -0.5 (5.66)	Not reported for mean change
Phoenix-2[3] (12 weeks)	n=401	n=402	n=400	p<0.0001 for

median change (inter-quartile range)	-8 (-14 to -4)	-9 (-14 to -5)	-0.5 (-4 to 3)	both groups versus placebo

3.3.4 Sub-group analyses results

The MS presents PASI 75 data from a weight based dosing analysis for each of the three included trials.[2-4] As noted in sections 3.1.3 and 3.1.5 above, the MS description of the analysis of these data from the trials is limited, and no results of any statistical analyses as to the threshold of weight used for these results are presented. These data were not available in the published trials but were available in the confidential CSRs submitted to the ERG. The ERG has checked the data presented in the MS with that of the CSR and reproduced it (Table 16 below) but reiterate that it is unclear whether these are appropriate sub-group analyses. In addition the MS only reports data selectively for those who were greater than 100kg in weight and allocated to the 90mg treated groups, and for those who were 100kg or less in weight and allocated to the 45mg treated groups. The ERG has therefore also extracted the data for those in the alternative groups, for information. No data were presented in these categories for those in the placebo arms of the Phoenix trials[2;3] or the etanercept arm of the ACCEPT[4] trial. Table 16 shows the results presented from the weight based dosing in the three included trials.

Table 16: PASI 75 response for weight based analysis (Academic in confidence data)

PASI 75	**Ustekinumab 45mg**		**Utsekinumab 90mg**	
Study [a]	≤100kg	>100kg	≤ 100kg	>100kg
Phoenix-1[2] (12 weeks)	124/168 (73.8%)	47/87 (54%)	107/164 (65.2%)	63/92 (68.5%)
Phoenix-2[3] (12 weeks)	218/297 (73.4%)	55/112 (49.1%)	225/289 (77.9%)	86/121 (71.1%)
ACCEPT[4] (12 weeks)	109/151 (72.2%)	32/58 (55.2%)	189/244 (77.5%)	67/103 (65.0%)

[a] The denominators in this table agree with the information provided by the manufacturer in response to clarification questions (Appendix 1) regarding the baseline proportion of participants who were above and below 100kg .

3.3.5 Mixed Treatment Comparison results

As discussed above the results of the trials of ustekinumab were presented within the MTC in two ways. An all participant analysis included participants from ustekinumab trials as randomised to their respective groups (45mg or 90mg) and a weight based analysis included only subgroups of participants from the ustekinumab trials with dose by weight (≤ 100kg and given 45mg, or > 100kg and given 90mg). As stated previously it is unclear if these subgroups have been identified using appropriate statistical methods as no details were provided. For the comparator trials all participant data were used although it is unclear if these data were from the

ITT populations. Only PASI 50, 75 and 90 results were presented and can be seen in Tables 6.6.3 to 6.6.6 in the MS, pages 75-76.

The weight based analysis suggests, in terms of the primary outcome of PASI 75, that infliximab has the highest response (mean PASI 75 was 80%), ustekinumab 45mg [redacted] and ustekinumab 90mg [redacted] are the second and third most effective interventions respectively (MS p75, Table 6.6.3). Results for the other comparators are also presented in the MS. In the analysis of all participants (ustekinumab participants analysed in the groups to which they were randomised) infliximab is seen to be the most efficacious (mean PASI 75 was 80%), ustekinumab 90mg (mean PASI 75 was 74%) and 45mg (mean PASI 75 was 69%) are the second and third most efficacious in this population (MS p76, Table 6.6.5). Again the results for the other comparators are also presented in the MS. The MS on page 78 states that the estimate of response rate for the comparator intervention adalimumab is lower than reported in the TA146 manufacturer submission and that this was owing to the WinBugs code change that was implemented in the ustekinumab MS. This change was from a random effects model to a fixed effect model. This comment from the MS suggests that the change has had an effect on the estimates of response rate for at least this one comparator intervention. The ERG is unable to check if this changes the ranking of any other of the respective treatments or if this has had an effect on the estimates of response from any of the other comparator drugs.

Although no pair-wise meta-analysis was reported to have been undertaken, the MS presents in Figures 6.6.6-6.6.8 (MS pages 79-81), forest plots of the MTC analysis, which also include pair-wise meta-analyses results for each intervention. No detail is provided but the ERG have interpreted these data as being from the weight based dosing data given the numbers of participants provided. It can be seen that for PASI 75 the MTC outcome shows a greater effect than the pair-wise meta-analysis for the 45mg ustekinumab comparison with placebo (OR MTC 82.01 [95% CI 61.01, 116.86] versus OR Pairwise M-A 77.43 [95% CI 48.68, 123.16]). For the 90mg comparison the pair-wise meta-analysis shows the greater effect (OR MTC 60.93 [95% CI 44.79, 89.75] versus OR Pairwise M-A 65.66 [95% CI 39.36, 109.53]). For the comparison of the 45mg with the 90mg dose groups in the included ustekinumab studies the PASI 75 pair-wise meta-analysis and MTC 95% Confidence Intervals cross the line of no effect. This suggests that there is no difference on PASI 75 between the different doses in the weight-based dosing sub-groups.

3.3.6 Summary of adverse events

The MS provides an overview of the safety of ustekinumab. An overview of combined data for rates of serious infections, cardiovascular and cerebrovascular events and neoplasms is provided in the MS which includes data from the three included trials and the T04 study[5] which was excluded from the MS systematic review of clinical effectiveness due to the different dosing regimens used in this trial. A summary of the 12-week placebo controlled period and the period until the end of follow-up is presented. The ERG has been unable to check these rates owing to the inclusion of data from the T04 trial. In addition it appears that the numbers of participants in each group are lower for ustekinumab than would be expected.

Data from comparative trials at 12 weeks are also presented for key safety findings from the individual trials and are reproduced below (Table 17 and Table 18). Additionally comment is provided on other adverse events, which reflects data from all three trials. These rates appear to be appropriate with the data presented in the individual trial publications, although headaches also occurred with similar frequency to upper respiratory tract infections in the included trials but were not mentioned in the narrative comment in the MS. Longer term, non comparative data is also presented for some key safety outcomes from the follow-up studies, however these data have not been checked by the ERG.

Overall there don't appear to be any great differences in adverse events reported across treatment/placebo groups in any of the included trials, although this was not statistically tested. Withdrawals due to adverse events at the 12-week follow-up have also been tabulated below (Table 19) and show fewer withdrawals in the ustekinumab group than the placebo[2;3] or etanercept[4] groups of the three respective studies, although this is again based on observation of the data only.

Table 17: Key adverse events from placebo controlled trials

Phoenix-1[2] (12 weeks)	**Ustekinumab 45mg, n=255**	**Ustekinumab 90mg, n=255***	**Placebo, n=255**
≥ 1 adverse event	147 (57.6%)	131 (51.4%)	123 (48.2%)
≥ 1 serious adverse event	2 (0.8%)	4 (1.6%)	2 (0.8%)
≥ 1 infection	80 (31.4%)	66 (25.9%)	68 (26.7%)
≥ 1 serious infection	0	2 (0.8%)	1 (0.4%)
≥ 1 malignancy	0	0	0
≥ 1 cardiac/cerebrovascular event	1 (0.4%)	0	0
Phoenix-2[3] (12 weeks)	**Ustekinumab 45mg, n=409**	**Ustekinumab 90mg, n=411**	**Placebo, n=410**
≥ 1 adverse event	217 (53.1%)	197 (47.9%)	204 (49.8%)
≥ 1 serious adverse event	8 (2.0%)	5 (1.2%)	8 (2.0%)

≥ 1 infection	88 (21.5%)	92 (22.4%)	82 (20.0%)
≥ 1 serious infection	0	1 (0.2%)	2 (0.5%)
≥ 1 malignancy	0	1 (0.2%)	1 (0.2%)
≥ 1 cardiac/cerebrovascular event	0	1 (0.2%)	0

*256 were randomised but one participant received no treatment

Table 18: Key adverse events from ACCEPT trial

ACCEPT[4] (12 weeks)	**Ustekinumab 45mg, n=209**	**Ustekinumab 90mg, n=347**	**Etanercept 50mg, n=347**
≥ 1 adverse event	138 (66.0%)	237 (68.3%)	241 (69.5%)
≥ 1 serious adverse event	4 (1.9%)	4 (1.2%)	4 (1.2%)
≥ 1 infection	59 (28.2%)	93 (26.8%)	93 (26.8%)
≥ 1 serious infection	0	3 (0.9%)	1 (0.3%)
≥ 1 malignancy	3 (1.4%)	1 (0.3%)	0
≥ 1 cardiac/cerebrovascular event	0	1 (0.3%)	0

Table 19: Participant withdrawals due to adverse events

Phoenix-1[2] (12 weeks)	**Ustekinumab 45mg, n=255**	**Ustekinumab 90mg, n=255**	**Placebo, n=255**
	0	2 (0.8%)	6 (2.4%)
Phoenix-2[3] (12 weeks)	**Ustekinumab 45mg, n=409**	**Ustekinumab 90mg, n=411**	**Placebo, n=410**
	2 (0.5%)	5 (1.2%)	8 (2.0%)
ACCEPT[4] (12 weeks)	**Ustekinumab 45mg, n=209**	**Ustekinumab 90mg, n=347**	**Etanercept 50mg, n=347**
	1 (0.5%)	1 (0.3%)	6 (1.7%)

3.4 Summary

Overall the MS contains an unbiased estimate of the effectiveness of ustekinumab at 12 weeks based on the results of the three randomised comparisons. The estimates of the effectiveness in relation to differential weight based dosing is less clear as is the estimate of the effect of ustekinumab in relation to other drugs of this class.

The ERG note the following factors which have the potential to bias the interpretation of the evidence:

- It is unclear if the methods for the subgroup analyses of the weight-based dosing of ustekinumab were appropriate and if the sample sizes were adequate for these analyses.
- Few methodological details were provided on the MTC approach taken. It is also unclear whether there is any impact from the use in the MS of a fixed effect model rather than the random effects model which was used by the assessment group who

developed the original MTC. There was only minimal discussion of any possible clinical heterogeneity between the included trials in the MTC.

- A standard pair-wise meta-analysis was not carried out, therefore the only indication of the overall efficacy of the intervention comes from the results of the MTC. Results of pair-wise meta-analysis of the weight based dosing were shown as part of the discussion of the results of the MTC but little commentary was provided of the relationship between these results and the results in the MTC. Similar plots for the all participant analyses are not provided.

The manufacturer interpretation of the evidence does not appear to the ERG to be fully justified on the basis of the evidence provided.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

i) A review of the economic literature. The review aimed to identify published economic evaluations of therapies used for psoriasis. Six studies were identified as being eligible for inclusion. These included the appraisal of etanercept and efalizumab for psoriasis commissioned by NICE (TA103).[1] This is extensively referred to in this ERG report as the York Model. All six studies identified are described in the MS, with a brief critical appraisal (discussed further in section 4.2).

ii) a report of an economic evaluation undertaken for the NICE STA process. The MS includes an economic model of treatments for psoriasis comparing ustekinumab with other biological therapies (adalimumab, efalizumab, etanercept, infliximab) and supportive care, detailed in section 7.2.6 of the MS. The decision problem was stated in the MS (p6) as being the treatment of moderate to severe chronic plaque psoriasis in patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate and PUVA. The model includes a series of one-way sensitivity analyses, and a probabilistic sensitivity analysis.

4.1.1 Manufacturer's review of published economic evaluations

A systematic literature review of published economic evaluations identified six studies that met the inclusion criteria presented in MS Table 7.1.1, (p93). The ERG replicated the MS search

strategy and did not identify any additional studies. One of the studies is a review of clinical and economic evidence and a budget impact analysis of adalimumab, alefacept, efalizumab, etanercept and infliximab for severe psoriasis undertaken by the CADTH (2007) which did not include an independent cost-effectiveness analysis. Only two out of the remaining five studies were critically appraised by the manufacturer: Woolacott and colleagues (2006)[1] and Pearce and colleagues (2006).[6] The former includes the York model, which provided a template for the economic analysis presented in MS. The rest of the identified studies were briefly described but not subjected to the detailed critical appraisal by the manufacturer. The stated reasons for the exclusion from the appraisal seem to be based on "basic methodological flaws" and a "simple modelling approach" (p93 of MS). The MS does not provide a summary of identified methodological limitations in the published cost-effectiveness analyses.

4.1.2 CEA Methods

The model assumes that adults with moderate to severe psoriasis who have failed to respond to, or have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA, receive one of the alternative biological therapies for a short period of time, called a "trial period", during which their response to treatment is assessed. Individuals will continue treatment if they have a sufficiently good response, in terms of improved PASI scores, at the end of this trial period. These responders progress to treatment for a maximum of ten years. The expected length of time that individuals would spend receiving treatment after the trial period was estimated through a Markov type process using a discount rate of 3.5%.

Responders were assumed to have quality of life improvements, which in the base case analysis were assessed using the EQ-5D utility scale. These utility estimates are associated with the primary clinical outcome - change in PASI scores. These quality of life improvements are combined with the direct costs associated with each therapy and also costs associated with being a non-responder. The analysis is based closely upon the York Model.[1]

The base case analysis estimated an incremental cost per incremental Quality Adjusted Life Year (QALY) relative to supportive care and to each of the alternative treatments. The base case analysis employed a weighted average efficacy estimate assuming that 80% of patients receive ustekinumab 45mg (patients with the baseline weight ≤ 100kg) and 20% of patients

receive ustekinumab 90mg (patients with the baseline weight > 100kg). However, as discussed in section 3.1.3, 3.1.5 and 3.3.4 the MS did not include a statistical analysis that demonstrates a statistical significance of the dose by weight interaction while independently controlling for other confounding factors. Therefore the sub-group analysis included in the MS (section 6.4.4 p53 of MS) is not consistent with NICE methodological guidance.[7]

4.1.2.1 Natural history

The modelling of disease progression closely follows that used in the York model. Individuals are assumed to be in one of two health states: responders or non-responders. These categories are based upon response to treatment in an initial trial period. Response to treatment is defined in terms of change in PASI scores from baseline and the response category corresponding to different changes in PASI score are presented here in Table 20. The analysis assumes that the disease is non-progressive once severe. Individuals who respond to treatments other than intermittent etanercept 25mg remain at the same PASI response level for as long as they remain responders. Different assumptions apply to maintaining PASI response in patients treated with intermittent etanercept 25mg. These are discussed in section 4.3.2.2. Non-responders are assumed to have PASI response rates equivalent to supportive care. No differential mortality risk between the alternative therapies was assumed, and so mortality was not included in the model.

Table 20: Definition of responders and non-responders used in the economic model

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

4.1.2.2 Treatment effectiveness

Treatment effectiveness is defined in terms of a change in PASI score from baseline, achieved at the end of the trial period. No other indicator of effectiveness is used in the model. As discussed in section 3.3.5, evidence was synthesised from a variety of trials by including direct and indirect treatment comparisons in an MTC to obtain response rates for all therapies considered in the model. However, as further discussed in section 4.3.2.2, the evidence used in the base case analysis was obtained from the selected subgroup of patients enrolled in the ustekinumab RCTs rather than from all patients according to their randomisation outcome.

4.1.2.3 Health related quality-of-life

Patients' health related quality of life in the base case analysis was assumed to be related to changes in PASI score. The utility estimates were derived from the PASI responses in a two-stage process using DLQI outcomes as an interim measure. The approach is discussed in more detail in section 4.3.2.3 of this report. Utility gains associated with changes in PASI scores (see Table 7.2.4, p115 of MS) were applied to the proportion who achieve each PASI score from the data obtained in the PHOENIX 1[2] and in the PHOENIX 2[3] trials, (see ERG report, section 3, for further details of these studies). These values were then multiplied by the length of time individuals spent on the therapies in the trial and treatment periods to generate estimated QALYs for each of the therapies and for supportive care.

4.1.2.4 Resources and costs

Resources were estimated for the initial trial period (16 weeks for ustekinumab) and the subsequent treatment period. Resources included in the model were: acquisition cost of therapies, blood tests and monitoring, outpatient visits, and inpatient care for individuals on supportive care. The model distinguishes between the cost of care provided to the patients who responded to the treatment after the trial period (ie. achieved PASI response ≥75%) and non-responders. Non-responders receive supportive care, which is associated with increased rate of hospitalisation comparative to the active treatment with biological therapies. The cost of treatment with biological therapies was partially offset by savings made by reducing the number of individuals on supportive care. The ERG discusses the resources used in more detail in section 4.3.2.4.

The costs of outpatient and inpatient care were taken from NHS reference costs[8] and expressed in 2006/2007 prices (see Table 7.2.10 of the MS). The costs of laboratory tests were taken from the unit costs used in the York model[1] and inflated to 2006 prices. Drug costs were assessed in 2007/2008 prices.

4.1.2.5 Discounting

The annual 3.5% discount rate was incorporated into the model by estimating discounted 'treatment' duration. This is consistent with the approach used in the original York model.

4.1.2.6 Sensitivity analyses

A series of univariate sensitivity analyses were carried out and these are presented in the MS, Table 7.3.6 (p132 of MS). This table should not be confused with another Table 7.3.6 on p130 of the MS, which presents the results of a scenario analysis using all patient data according to their randomisation outcome (regardless of the baseline weight). Results of a probabilistic sensitivity analysis (PSA) are presented in Table 7.3.3 (p128 of MS).

4.1.2.7 Model validation

The MS model data, code and the MTC were subsequently reviewed by consultants [redacted]. They confirmed the MS model consistency with the structure of the other models included in the NICE appraisals of the biological treatments of psoriasis.

4.1.2.8 Results

The results of the model are reported as incremental costs (erroneously labelled “mean” costs in the MS Tables), incremental QALYs, and cost per QALY comparing ustekinumab vs other treatments and all drugs vs supportive care. Table 21 presents the results that correspond to the MS base case results for ustekinumab compared to supportive care, efalizumab, etanercept 25mg continuous, etanercept 25mg intermittent, etanercept 50mg, adalimumab and infliximab (Table 7.3.1, p126 of MS). The results are calculated using the MTC clinical effectiveness outcomes with the data from the selected subgroups of patients. As discussed in section 3.3.5, this version of MTC analysis estimated probabilities of PASI response separately for patients with baseline weight<100kg receiving ustekinumab 45mg and patients with baseline weight>100kg receiving ustekinumab 90mg. The weighted average of efficacy outcomes was then calculated assuming that 80% of patients receive ustekinumab 45mg (patients with baseline weight<100kg) and 20% receive ustekinumab 90mg (patients with baseline weight>100kg) and used as a model input. As discussed in section 3.3.4 there are concerns about the validity of the manufacturer’s claim of the differential clinical effectiveness associated with the baseline weight of the patients. Therefore the results presented in the MS as base case results should be viewed with caution.

Table 21: Summary of base case deterministic analysis (weighted average - weight by dose) assuming the price for ustekinumab 45mg is equal to the price of ustekinumab 90mg (Table 7.3.1 in MS)

Treatment	Incremental QALYs	Incremental costs	ICER ustekinumab vs other treatments	ICER all drugs 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 (weighted average of 45mg & 90mg)	**0.1560**	**£4,615**	**-**	**£29,587**
Infliximab	0.1616	£6,327	£304,566*	£39,153

* this ICER compares infliximab to ustekinumab.

For the deterministic results based on the weighted average efficacy, the ICER for ustekinumab 45mg versus supportive care is estimated to be £29,587 per QALY. In comparison to etanercept 25mg intermittent the ICER is £26,637. Ustekinumab is reported to dominate adalimumab.

Table 22 below shows alternative results for all the patient analysis for ustekinumab compared to supportive care, efalizumab, etanercept 25mg continuous, etanercept 25mg intermittent, etanercept 50mg, adalimumab and infliximab (Table 7.3.6, p130 of MS).

Table 22: Summary of deterministic analysis (all patients according to their randomisation outcome) assuming the price for ustekinumab 45mg is equal to the price of ustekinumab 90mg (Table 7.3.6 in MS)

Treatment	Incremental QALYs	Incremental costs	ICER ustekinumab 45mg vs other treatments	ICER ustekinumab 90mg vs other treatments	ICER all drugs 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.

As discussed in section 3.3.4 the clinical effectiveness estimates used in the MS base case analysis are derived from a subgroup of patients selected without an appropriate statistical analysis that would support the weight-base categorisation, and may produce the biased estimates. For the deterministic results based on efficacy data for all patients, the ICER for ustekinumab 45mg versus supportive care is £30,664 per QALY which is higher than the ICER in the MS base case analysis. The ICER for ustekinumab 90mg versus supportive care is estimated to be £29,520 per QALY or about the same as the ICER in the MS base case analysis. In comparison to etanercept 25mg intermittent the ICER is £36,272 and £28,126 for ustekinumab 45mg and 90mg respectively. Both estimates are higher than the corresponding ICER of £26,637 in the base case analysis. The ICER for ustekinumab 45mg versus adalimumab is estimated to be £16,400 per QALY ie. ustekinumab 45mg does not dominate adalimumab when all patient efficacy data are included in the model, however the dominance of ustekinumab 90mg in comparison to adalimumab remains. It should be noted that all results of the economic evaluation presented in the submission are conditional on the price of ustekinumab 90mg indicated in a PAS. As discussed in section 4.3.2.5, the time frame for the PAS is uncertain, therefore the results presented in Table 21 and Table 22 are only valid for the duration of the pricing arrangements in the PAS. See section 4.3.4.2 for estimates of cost-effectiveness of ustekinumab conducted by the ERG.

4.2 Critical appraisal of the manufacturer's submitted economic evaluation

The ERG did not undertake an independent appraisal of the papers identified by the MS literature search. Although the MS does not clearly specify the exclusion/inclusion criteria, it does appear that, with exception of the York model, the identified economic evaluations have limited relevance to the decision problem for the following reasons:

- modelled economic evaluations assumed a short time horizon of 12-16 weeks, which is considered inadequate for the chronic disease;
- modelled economic evaluations use intermediate outcomes (PASI 75 response rate) rather than final outcomes (eg. QALYs);
- results are predominately reported in terms of the average rather than the incremental cost-effectiveness ratios, which is inconsistent with the NICE reference case;
- the outcomes of most economic evaluations are based on the USA patterns of resource use and the corresponding unit costs and may not be generalisable to the UK current clinical practice.

4.2.1 Critical appraisal of economic evaluation methods

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 23 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[9]). The NICE reference case requirements have also been considered, see Table 24.

Table 23: Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	The decision problem is described in the MS on page 6-9. The MS estimates the cost-effectiveness of treatment with ustekinumab for adults with moderate to severe chronic plaque psoriasis relative to the comparators as stated in the decision problem.
Is there a clear description of alternatives?	Yes	Section 7.2.3 lists the comparators used in economic evaluation. These are: • Adalimumab 80mg initially, then 40mg at week 1 then every 2 weeks thereafter; • Efalizumab initial dose of 0.7mg/kg then weekly injections of 1.0 mg/kg; • Etanecept 25mg twice weekly administered either continuously or intermittently; • Etanecept 50mg twice weekly administered continuously for the first 12 weeks, then 25mg administered twice weekly thereafter; • Infliximab 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks thereafter. Supportive care including inpatients stay and clinic visits.
Has the correct patient group / population of interest been clearly stated?	Yes?	The target population is defined as 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. Patients with PASI score >10 and DLQI score >10 are considered to have moderate to moderate to severe psoriasis (p6 of MS). The SmPC clearly specified different dosing regimens for the subgroups of target population based on the baseline weight claiming a differential clinical effect in the subgroup of patients with the baseline weight of >100kg. The claim of the differential superior efficacy in the subgroup of patients with a body weight >100kg was not supported by the subgroup analysis according to the NICE Guide to HTA[7] *(see also section 4.3.2.1)*.
Is the correct comparator used?	Yes	All alternative treatments shown above are compared to supportive care. In addition, the ICERs comparing ustekinumab to each of the comparators are presented.

Is the study type reasonable?	Yes	Cost-utility analysis is reasonable, as the major effects of biologics would be improvement in QoL.
Is the perspective of the analysis clearly stated?	Yes	The MS section 7.2.4, p104 states the perspective of the economic evaluation is that of the NHS and Personal Social Services (PSS) in England and Wales.
Is the perspective employed appropriate?	Yes	Perspective is in accordance with the NICE framework.
Is effectiveness of the intervention established?	Yes?	The effectiveness of ustekinumab is established with respect to placebo (Phoenix 1[2] and Phoenix 2[3] trials). An MTC evidence synthesis was undertaken to determine the comparative efficacy (PASI response) of the various treatments. To estimate the probability of the PASI 75 response, the MS utilised clinical evidence from the entire range of the comparators identified in the decision problem. However, as discussed in section 3 of the ERG report, it is not clear whether the use of clinical evidence from the subset of rather than from all patients has produced the unbiased MTC estimates of clinical effectiveness.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	The time horizon was 10 years in common with the York model and the subsequent STA of infliximab[10] and adalimumab.[11] The choice of ten years is justified by the observation that nearly all costs and effects are accrued by this point due to the annual 20% drop out rate.
Are the costs and consequences consistent with the perspective employed?	Yes	Only direct NHS costs are included
Is differential timing considered?	Yes	Costs and health benefits discounted at 3.5% per year
Is incremental analysis performed?	Yes	Presented in the MS Table 7.3.1-7.3.2 (MS p126-127) for base case and Table 7.3.3 for PSA (MS p128).
Is sensitivity analysis undertaken and presented clearly?	Yes	Results of the series of univariate sensitivity analyses are presented in Table 7.3.6 of the MS p132. PSA for the base-case is presented in Table 7.3.3. (MS p128) is given for the in section 6.3.2.6 of the MS.

NICE reference case

Table 24 NICE reference case requirements

NICE reference case requirements:	Included in Submission
Decision problem: As per the scope developed by NICE	Yes[a]
Comparator: Alternative therapies routinely used in the UK NHS	Yes
Perspective on costs: NHS and PSS	Yes[b]
Perspective on outcomes: All health effects on individuals	Yes[c]
Type of economic evaluation: Cost effectiveness analysis	Yes
Synthesis of evidence on outcomes: Based on a systematic review	Yes
Measure of health benefits: QALYs	Yes
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes[d]

Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes[e]
Source of preference data: Representative sample of the public	No
Discount rate: 3.5% pa for costs and health effects	Yes[f]
Notes: N/A=not applicable	

a. The submission derived EQ-5D utilities from the change in DLQI from the baseline. Only the patients with the baseline DLQI ≥10 were included. Scope refers to patients with moderate to severe psoriasis
b. Costs are for NHS only
c. Only those health effects associated with reductions in PASI score
d. EQ-5D
e. Yes, with reference to caveats raised in sections 3.2
f. The model applies a discounting rate of 3.5% to estimate a length of the treatment period rather than directly to costs and health effects

4.3 Critical appraisal of modelling methods in the manufacturer's economic evaluation

An outline critical review of modelling methods has been undertaken by the ERG. The review has used the framework for good practice in modelling presented by Philips and colleagues[12] as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty.

4.3.1 Modelling approach / Model Structure

The MS presents a schematic for the model in Figure 7.2.1 (MS page 105). This consists of two health states: responders and non responders. The model comprises two periods: a trial and a treatment period. The model estimates the cost and utility benefit for each of these periods for each of the treatments and compares them with supportive care. The trial period lasts for between 10 and 16 weeks (16 weeks for ustekinumab) and all patients in each group receive the intervention being evaluated. Patients in the trial period are assigned a probability of achieving a PASI response (defined as PASI < 50; PASI ≥ 50 and <75; PASI ≥75 or PASI ≥ 90) as determined by the MTC and detailed in the MS Table 6.6.3 - 6.6.5 (MS p75-76). The QALY gains achieved in the trial period are calculated by multiplying the probability of being in any particular PASI response state by the utility value associated with that PASI response, detailed in the MS Table 7.2.4 (MS p115). The costs of each therapy for this period are detailed in the MS section 7.2.9.1 (MS p 118). Those who respond to treatment in the trial period (defined as PASI ≥75 or PASI ≥ 90) continue with treatment during the treatment period and are assumed to stay at this level of improvement for a period of time and then become a non-responder. The average duration of treatment is estimated using an annual drop out rate of 20%. The average

discounted treatment duration was calculated using a Markov model with three monthly cycles as 3.65 years (Table 7.2.2 p109 of MS). Those who respond to treatment incur both the drug treatment cost and the QALY benefit for this 3.65 year period. Those who do not respond to treatment receive non-responder supportive care, again for this same time period. The model estimates the total costs and benefits for all the treatments and these are compared to supportive care for the same time period equivalent to the trial and treatment period.

4.3.1.1 Structural Assumptions

The model structure is not reported in detail in the MS. However it is based upon the York model which the MS notes was also used subsequently for the NICE appraisals of adalimumab and infliximab STAs.[10;11] The ERG considers that the structure of the model is reasonable and reflects the disease under evaluation. The MS does not provide a list of all assumptions or a justification of each assumption as required in Section 7.2.6.1 of the MS template. Nevertheless, some of the assumptions must be the same as in the original York model:[1] i) the model assumes that the disease is not progressive once severe, ii) the benefits from treatments are determined by examination of their impact on disease severity, specifically their impact on PASI response, iii) for the same PASI response, the improvement in utility is the same regardless of the treatment received, iv) the model excludes adverse effects of treatment from the calculation of costs and QALYs. The ERG considers these assumptions to be reasonable.

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

Duration of trial and treatment period

The initial 'trial' period was estimated based on the time frame of the included RCTs for each comparator. These are presented in Table 7.2.2 (p109 of MS). The trial periods are consistent

with the York model[1] and subsequent STAs of infliximab[10] and adalimumab.[11] The primary outcome (PASI 75 response) in the ustekinumab RCTs was assessed at week 12, but the next dose was given at week 16. The manufacturer sought clinicians' opinion to determine the appropriate duration of the initial 'trial' period of ustekinumab to be included in the model. Clinicians agreed that week 16 (immediately prior to the third injection) was the more appropriate time to use in the model (Appendix 11 of MS). The MS stated that in the model the efficacy of ustekinumab at 16 weeks is assumed to be the same as at 12 weeks. The costs of the first two injections occur prior to week 12th and no additional cost is assumed to occur between the 12th and the 16th weeks.

The assumption that the efficacy of ustekinumab at 16 weeks is the same as at 12 weeks is conservative only if there is evidence of a non-declining trend in the rates of PASI-75 response in the period between the 12th and the 16th weeks from the baseline. Clarification on this point was sought from the manufacturer (question A7 (Appendix 1)). The manufacturer provided a table with the rates of PASI 75 responses over the period of 28 weeks with a four week interval between the observation points. Although the response rates to ustekinumab 45mg do not appear to decline in the period between the 12th and the 16th weeks this is less evident in relation to ustekinumab 90mg. There are also a few uncertainties associated with these new data: a) whether the base for calculation of PASI rates includes only the patients from the active treatment arms (ie. whether patients originally randomised to the placebo arm and assigned to ustekinumab at week 12 are excluded); b) whether the PASI 75 response rates relate to "responders" as defined in Table 20 in section 4.1.2.1 (ie. whether the reported estimates include those patients achieving PASI ≥90 response rate at week 16).

4.3.2 Data Inputs

The following data inputs were used in the MS as the model parameters:

- Clinical efficacy data (ie. PASI 50, PASI 75 and PASI 90 response rates);
- Utility gain associated with the various PASI response categories;
- Initial trial period costs and annual treatment costs

4.3.2.1 Target patient population and subgroups

The licensed indication identifies the target population as 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. Patients

with PASI score ≥10 and DLQI score >10 are considered to have moderate to moderate to severe psoriasis (p6 of MS). As discussed in section 3.1.3 the clinical evidence used to estimate the probability of PASI response was obtained from the population with characteristics broadly similar to the target UK population. However, there is possible heterogeneity in the baseline characteristics of patients from different trials included in the MTC.

The ustekinumab SmPC specifies two different dose regimens for the subgroups of target population based on their baseline weight. It recommends that 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 those patients <100kg in weight). For patients with a body weight >100kg a 90mg dose is recommended. The rationale appears to be that 90mg resulted in a greater efficacy (p4 of MS) in patients weighing more than 100 kg, although 45mg was also shown to be efficacious in this subgroup. As discussed in sections 3.1.3, 3.1.5 the analysis for this subgroup is not defined adequately. Visualising results aggregated by groups of patients with 10kg increments, as suggested in the MS section 7.2.2.1 (see also response to question A6 in Appendix 1), is not an appropriate statistical analysis of the patient-level data.[7] No statistical modelling of patient-level data appears to have been undertaken to assess the statistical significance of the dose by weight interaction while controlling for weight, dose and other confounding factors, such as the baseline level of psoriasis severity.

Therefore the ERG concluded that the rationale of using the clinical effectiveness data from the selected subgroup of ustekinumab patients as a model input is not justified and is likely to produce a biased estimate of cost effectiveness.

4.3.2.2 Clinical Effectiveness

There were two pieces of clinical evidence that were used to determine the model parameters. These are the PASI response rates discussed in this section and the estimates of quality of life discussed in section 4.3.2.3.

PASI response rates

The probabilities of achieving a specified PASI response for each of the treatment alternatives and supportive care were estimated from the MTC analysis. Treatment effectiveness was defined in terms of a change in PASI score from baseline, achieved at the end of the trial period

(see Table 20 in section 4.1.2.1.) The responders (patients with a change in PASI ≥ 75% and PASI ≥ 90%) are assumed to retain this level of response for a maximum of ten years unless they drop out. This applies to all treatments with the exception of etanercept 25mg intermittent. Unlike the approach used in the York model, where it was conservatively assumed that the reduced cost of intermittent etanercept was not associated with any reduction in clinical effectiveness, the model presented in the MS assumed a reduction in efficacy of intermittent dosing of etanercept 25mg compared to continuous dosing.

The MS did not identify an RCT of intermittent etanercept that would match the inclusion criteria and this comparator treatment was not included in the MTC. The clinical effectiveness of intermittent etanercept was estimated by using the estimates of clinical effectiveness of continuous etanercept (rates of achieving PASI≥75 and PASI≥90). These were reduced in proportion to the relative risk of intermittent versus continuous dosing of etanercept 50mg observed in the randomised open-label study by Moore and colleagues, 2007.[13] The reduction in PASI response rates of 80.6% was applied to both groups of responders for the period from 24 weeks onwards.

The study by Moore and colleagues, 2007[13] was first introduced in the cost-effectiveness part of the MS and was not assessed according to the criteria of the systematic review of clinical evidence that applied to other RCTs that provided the evidence base for the MS. Although the outcomes seem to have demonstrated a clinical superiority of continuous dosing of etanercept 50mg in comparison to intermittent dosing, there is a considerable uncertainty associated with the use of this clinical evidence in an economic evaluation of ustekinumab. Firstly, the outcomes of the trial reported in Moore and colleagues, 2007[13] relate to etanercept 50mg rather than etanercept 25mg. Secondly, the primary effectiveness outcome was assessed as a PGA score rather than PASI score. Thirdly, the same proportional reduction in clinical effectiveness was applied to the responders in both PASI≥75 and PASI ≥90 categories. The MS provides no justification for this assumption. Therefore clinical effectiveness estimates of intermittent dosing of etanercept 25mg used in the economic evaluation may be biased, with ustekinumab becoming relatively more cost-effective as the effectiveness of intermittent etanercept relative to continuous etanercept decreases. The estimated ICER comparing ustekinumab with intermittent etanercept 25mg should therefore be viewed with caution. The ERG undertook a scenario analysis producing the ICER where the clinical effectiveness of intermittent etanercept 25mg

was assumed to be equal to continuous etanercept 25mg, as assumed in the York model.[1] The results are reported in section 4.3.4.4.

Clinical evidence was synthesised from a variety of trials by including direct and indirect treatment comparisons in an MTC to obtain PASI response rates for all therapies considered in the model. This includes the only head-to-head RCT comparing ustekinumab with etanercept 50mg. The MS (page 100) stated that the data from the head to head comparison of ustekinumab with etanercept 50mg was not used in the 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. The clinical efficacy input used in the base case analysis was obtained from the MTC. The MTC estimate of the PASI response rates for etanercept 50mg are 52% and 24% for PASI≥75 and PASI≥90 respectively. This is lower than the PASI≥75 response rate observed in the ACCEPT head-to-head RCT comparing ustekinumab with etanercept 50mg. The observed response rates were 57% and 23.1%. However the ICER estimate changed little when the MTC PASI ≥75 response rate of 52% was substituted for PASI ≥75 response rate of 57% in the base case analysis.

Infliximab is currently only recommended for patients with very severe psoriasis. At the time of writing efalizumab is only recommended as a third line treatment for patients who did not respond to etanercept. Therefore the appropriateness of inclusion of infliximab and efalizumab in the MTC may not be relevant.

Adverse events were not directly included in the model. As stated by the MS, this assumption is in line with the York model[1] and the previous appraisals of biological treatments for moderate to severe psoriasis (STA of infliximab[10] and adalimumab[11]).

Psoriasis-specific measure of quality of life (DLQI) and the generic index SF-36

Patient outcomes assessed in the ustekinumab RCTs did not include a utility-based estimate of quality of life (QoL). Therefore the utility estimates for each health state used in the model had to be produced from the surrogate measures of QoL. Two surrogate QoL outcomes were available from the PHOENIX trials.[2;3] Both PHOENIX trials assessed the psoriasis specific QoL using the DLQI. In addition, the PHOENIX 1 trial also assessed patients' QoL with the SF-36 - a standardised generic QoL assessment tool. The ACCEPT trial[4] did not include any measures of QoL. The MS presented two alternative methods of deriving utility estimates from the

ustekinumab patient data, one method utilised DLQI outcomes and another utilised the SF-36 values. These are described in the following section 4.3.2.3.

4.3.2.3 Patient outcomes

Patient outcomes used in the model were utility changes associated with changes in PASI scores. The MS stated that methods for calculating utility estimates replicated the method used in the original York model.[1]

Derivation of EQ-5D utility values using DLQI values from the PHOENIX trials.

To derive EQ-5D utility values the individual patient data were aggregated according to the PASI response observed at week 12 in the Phoenix trials. The data were limited to patients with DLQI ≥10 observed at baseline. This restriction was applied to ensure that the data from the target population of patients with moderate to severe psoriasis were included in the analysis. The mean change in DLQI from baseline observed at week 12 was calculated for each PASI response category. Results are reported in Table 7.2.3 (p114 of MS).

In the original York model[1] the second stage involved data from the Health Outcomes Data Repository (HODaR) database. This provided data for establishing the relationship between utility values assessed in EQ-5D and DLQI scores. A linear regression analysis, using ordinary least squares (OLS) regression, was employed to relate EQ-5D scores to DLQI and this was used to quantify the utility change associated with changes in PASI scores. The estimates of the regression coefficients were not reported in Woolacott and colleagues (2006),[1] however the MS estimated the regression coefficients from the published scatter-plot reported in Woolacott and colleagues (2006).[1] The MS produced results of the OLS linear regression that quantified the relationship between DLQI and EQ-5D values are EQ-5D = -0.0162*DLQI + 0.8554 (Figure 7.2.3 p115 of MS). The value of R^2=0.1315 indicates a rather poor goodness-of-fit as only 13% of the total variation is explained. However it is unlikely that the goodness-of-fit of the regression equation produced, though not reported, by Woolacott and colleagues (2006)[1] is substantially higher. Both MS and Woolacott and colleagues (2006)[1] assumed a linear relationship between DLQI and EQ-5D values but do not provide any justification for this assumption. Estimates of the regression parameters presented in the MS were validated against the results of an independently conducted linear regression analysis that related EQ-5D scores to DLQI values observed in 3,500 psoriasis patients.

[redacted]

[redacted] Note, to calculate the utility gains (as opposed to absolute utility values) only the slope of the regression equation is required.

The MS identified the mean utility gains for each PASI response as "conditional on baseline DLQI severity" (p115 of MS). The ERG considers that the multiple regression equation controlling for the baseline DLQI values would be a more appropriate approach to establishing the relationship between the EQ-5D and DLQI values and would likely to be associated with a better goodness-of-fit. However, the MS did not explore this approach. The reference to the "conditional on baseline severity" DLQI values are more likely to reflect the fact that only a selected subgroup of patients with the baseline DLQI ≥10 was included in the analysis.

The utility gains for each PASI response category used in the base case analysis are shown here in Table 25 along with utility gains derived from the German "utility mapping study" and utility gains used in the York model.[1] All the estimates from Table 25 are derived using a linear regression approach.

Table 25: Utility gains for each PASI response category used in the base case analysis and the alternative utility gains used in the sensitivity analysis

PASI response	Utility gains estimated by the MS (table 7.2.4 of MS)	Utility gains estimated by German study (table 7.2.13 of MS)	Utility gain estimated by Woolacott et al (2006)[1] (Table 48)
<50	0.04	0.04	0.05
≥50-<75	0.17	0.16	0.17
≥75-<90	0.22	0.22	0.19
≥90	0.25	0.25	0.21

The utility values are similar across all three sets of estimates, however, the values used in the base case analysis presented in the MS are higher for each of the PASI response category. The highest difference of 0.04 points is the PASI ≥ 90 category and relates to the difference between the utility estimates used in the original York model[1] and utility estimates used in the MS base case analysis. However, the results of the modelled economic evaluation are not sensitive to the small changes in the estimated utility gains.

Derivation of SF-6D utility values using SF-36 values from the PHOENIX 1 trial.

The generic quality of life SF-36 values were collected from patients enrolled in the PHOENIX 1 trial. Patient level SF-36 responses were reported to be converted into SF-6D utility scores. The conversion algorithms or a reference to the published source is not provided in the MS. There were insufficient details in the MS to fully understand the methods used though it appeared to be based on individual patient data analyses. The MS reasonably suggests that the SF-6D utility estimates have the advantage of being directly estimated from SF-36 that in turn can be related directly to the patient PASI responses. The MS indicated that no "secondary mapping exercise" (presumably a mathematical model algorithm such as linear regression) was used to relate PASI responses to changes in SF-36.

Despite acknowledging the advantages of utility estimates based on the patient level data that relate SF-36 to PASI responses, the MS stated that for the base case analysis the "mapping methodology" was preferred while SF-36-based utility values and EQ-5D utility values from the adalimumab MS were used in the sensitivity analysis (the reasons are discussed in section 4.3.4.1). The SF-6D values and these EQ-5D values used in the sensitivity analysis are presented in Table 26. The EQ-5D values derived from DLQI used in the base case analysis (replicated from Table 25 above) are included for completeness.

Table 26: Comparison of utility gains used in the base case analysis with the alternative utility gain estimates.

PASI response	DLQI-based utility gains used in base case analysis (table 7.2.4 of MS)	EQ-5D utility gains used in the STA of adalimumab[11]	SF-36-based utility gains (table 7.2.13 of MS)
<50	0.04	0.063	0.0016
≥50-<75	0.17	0.178	0.0424
≥75-<90	0.22	0.178	0.0970
≥90	0.25	0.308	0.1276

There are a few discrepancies in utility gain estimates presented in Table 26

a) In the PASI <50 and PASI≥90 response category, the EQ-5D values reported in the adalimumab MS are the highest;

b) the EQ-5D values reported in the adalimumab MS are the same for the PASI ≥50-<75 and PASI≥75-<90 response categories whereas for the corresponding DLQI-based EQ-5D utility gain estimates and SF-36-based estimates, there was a difference of 5 points.

c) the utility gain estimates based on SF-36 patient level data are considerably lower than the other sets of estimates for each of the PASI categories. The MS does not provide any comment on this difference.

The results of the modelled economic evaluation when comparing ustekinumab with etanercept intermittent are not very sensitive to the choice of utility gain estimates. However when comparing ustekinumab with supportive care for the weight-based population mix used in the base case analysis chosing SF-6D utility values over DLQI-based utility value resulted in the ICER increasing to £49,371 versus supportive care compared to the base case estimate of £29,587. It appears that the choice of DLQI-based utility values favours ustekinumab over comparator treatments.

The MS present several QoL studies that describe the quality of life gains for patients with different PASI responses. The utility gain estimates based on the SF-36 patient level data had the lowest values and those based on EQ-5D utility gains from a previous STA for adalimumab had the highest values. The MS does not make a clear justification for why the dataset they used is the most appropriate.

4.3.2.4 Resource use

Resources included in the model were: acquisition cost of therapies; laboratory tests; outpatient visits; and inpatient care for individuals on supportive care (Tables 7.2.6 to 7.2.8 of the MS, page 119-120). Drug dosage and frequency were assigned according to the British Association of Dermatologists (BAD) guidelines and the SmPC for ustekinumab. Unit costs of drugs were taken from the British National Formulary (BNF) 56.[14] The MS indicated that the assumptions about the amount of health care resources used in monitoring patients' response to therapies is consistent with the BAD guidelines for the treatment of psoriasis and/or the assumptions of the York model.[1] Expert opinion was used to determine the frequency of outpatients visits and laboratory tests associated with ustekinumab treatment. The MS does not provide sufficient information about the way the experts were identified and the method of elicitation of experts' opinion. The MS referred to Appendix 11, however this Appendix does not clarify these uncertainties.

The model distinguishes between the amount of health care resources provided to the patients who responded to the treatment after the trial period (ie. achieved PASI response ≥75%) and non-responders, with non-responders receiving supportive care, which is associated with an increased rate of hospitalisation compared to active treatment with biological therapies. Cost of treatment with biological therapies was partially offset by savings made by reducing the number of individuals on supportive care. The model does not seem to differentiate between the number of outpatient visits required by responders in comparison to non-responders. This is consistent with assumptions about resource use in the original York model.[1]

The main resource associated with supportive care was inpatient stays. All individuals on supportive care who have a PASI response below 75% are assumed to be non-responders. These individuals are assumed to have one inpatient stay per year which has duration of 21 days. The frequency of one admission per year is derived from the manufacturer's expert opinion and found by the ERG's clinical expert to be reasonable. The duration of 21 days is said to be supported by the manufacturer's expert opinion and found by the ERG's clinical expert to be reasonable. The duration of 21 days is also supported with reference to the analysis of the hospitalisation (SLIM) database (Appendix 5) and is consistent with the assumption used in York model.[1]

4.3.2.5 Costs

Drug acquisition costs are taken from the BNF[14] and appear to be reasonable. However, the MS assumes a different cost estimate for intermittent use of etanercept to the York model. The York model assumed the cost for intermittent use was 74% the cost of continuous etanercept whereas the MS assumes a cost of 88% of the cost of continuous etanercept. This assumption was validated with experts' opinion and, as stated by the MS, is consistent with the assumption used in the adalimumab HTA (TA146[9]).

The list price of an ustekinumab 45mg vial is £2,147 with the list price of 90mg (2x45mg) being £4,294. The MS stated that under the terms of the PAS patients who are over 100kg in weight and who are prescribed the 90mg (2x45mg) dose will receive both doses for a total cost of £2,147 (see Appendix 4 of the MS).

[redacted]

As there appears to be some uncertainty associated with duration of the PAS arrangements, the

results of the economic evaluation presented in the MS should be interpreted with caution. The ERG undertook a sensitivity analysis using the listed price of ustekinumab 90mg in the manufacturer's model. See section 4.3.4.2 for details.

The MS includes unit costs for administering the drugs (Table 7.2.11 and 7.2.12 p121-122 of MS). There is insufficient explanation of the cost of £120 associated with drug administration during the 10 to 16 weeks of the trial. For all the treatments other than infliximab, which is administered by infusions during an outpatient session, the cost appears to be relating to nurse training sessions being needed for learning to self-inject. The assumption about the number and duration of nursing sessions was not explained but presumed to be consistent with the York model calculations of cost of drug administration of £102 for etanercept and efalizumab based upon three 1-hour nurse sessions.

The number of outpatient visits required for each treatment alternative is presented in Table 7.2.6 (p119-120 of MS). For infliximab some of the routine outpatient visits take place during the infusion visits. Only those visits that are additional to infusion visits are counted as extra outpatient visits to avoid double counting. This is a reasonable assumption. The MS assumes the cost of visits to receive infliximab infusion is no different than the cost for a standard dermatology outpatient visit but provides no justification for this assumption.

Monitoring costs include various laboratory tests and appear reasonable.

The MS uses a value of £288.74 per bed day for an "elective inpatient major dermatological conditions" from the NHS Reference cost (2006-2007). No further clarification is provided. The footnote to this parameter in the EXCEL spreadsheet states that the value of £288.74 per bed day was calculated as weighted average of cases with and without complications by number of the finished consultant episodes (FCEs). Using a cost per day of £288.74 for 21 days would give a value of £6063.54 per year for inpatient stays which is used in the model.

The ERG could not establish whether the resulting cost of inpatient admission is an underestimate or an overestimate of the real cost as no details on the method for calculation of the unit cost of an inpatient admission were provided. The ERG undertook a sensitivity analysis varying the total cost of a single inpatient admission. See section 4.3.4.2 for details.

4.3.3 Consistency

4.3.3.1 Internal consistency

Random checking has been undertaken for some of the key equations in the model. The ERG has not undertaken a comprehensive check of all cells in the model. The model is fully executable and the inputs changed on the 'Parameters' and 'Drug costs' worksheets produce changes in the deterministic results by clicking on the 'Run deterministic' button on the 'Main' worksheet. These can be used to replicate the results presented in the MS and univariate sensitivity analyses for the base case model, as reported in Table 7.3.6 of the MS (p 130). Checking of the model was also carried out to see if results were in the expected directions and had expected magnitude.

The model is generally well presented and documented and user friendly. The model includes a worksheet that summarises the model inputs (clinical effect parameters, cost and utilities) on the 'Inputs' worksheet. The ERG views the model as a reasonable approach to modelling the cost effectiveness of ustekinumab and from random checking the 'wiring' of the model appears to be accurate.

The ERG has noticed the following errors:

i) The trial period used in the calculations for etanercept and infliximab is 0.25, rather than the correct values of 0.23 and 0.19 respectively.

ii) The equations used in the MS differ slightly from those used in the York report for the cost of non responders during the treatment period subtracted by the costs of supportive care. This cost has not included the duration of the trial, d^{trial}. The cost for the MS is given as: $-(p_t^{pasi75} \times d_{t,disc}^{treatment}) \times c_{Supp}^{treatment}$, whereas in the York report it is given as $-(d^{trial} + p_t^{pasi75} \times d_{t,disc}^{treatment}) \times c_{Supp}^{treatment}$.

4.3.3.2 External consistency

The model has been developed based upon the original York model. [redacted]

They state that the reviewers confirmed that the MS model followed the same structure as the other models submitted as part of previous NICE appraisals on biologics in psoriasis (STAs of infliximab[10] and adalimumab[11]), including the York model.[1]

No other detail of external validity is given and the MS results have not been compared with the published economic literature to determine if the results were consistent. The ERG compared the MS results with those from the STA of adalimumab[11] and found them to be generally consistent.

4.3.4 Assessment of Uncertainty

4.3.4.1 One-way sensitivity analyses

A series of one way sensitivity analyses were carried out on the base case model. The MS provided no rationale for the choice of variables included (or excluded) in the sensitivity analysis. The following variables were subjected to sensitivity analysis: length of stay, drop out rate, duration of initial trial period, utility values, percent of patients with the baseline weight of >100kg, discount rate and the relative efficacy of intermittent etanercept as a % of efficacy of continuous etanercept 25mg and relative cost of etanercept 25mg as a % of cost of continuous etanercept. Some key parameters (such as cost of ustekinumab and cost of an inpatient stay) which might be expected to be influential on the cost effectiveness results have been omitted from the sensitivity analyses.

- According to the MS, the model results are most sensitive to the number of hospital days associated with supportive care, the estimate of the cost of dosing for intermittent etanercept 25mg and the use of SF-6D utility scores instead of EQ-5D utility scores.
- Compared to supportive care, the ICER varies between £34,387 and £20,672 for hospital stays between 17.5 and 20.5 days respectively. When using SF-6D utility values, the ICER is £49,371 versus supportive care compared to the base case of £29,587.
- For intermittent etanercept 25mg as a % of cost of continuous etanercept the ICERs range from ustekinumab dominating etancercept 25 mg intermittent at the 98% level to £68,339 when using the price ratio of 74%.
- When efficacy of intermittent etanercept as the percentage of efficacy of continuous etanercept 25mg varied from 71% to 91%, the ICER of ustekinumab compared with etancercept 25mg intermittent varies from £22,634 to £32,949.

The ERG considers that the ranges chosen for the sensitivity analyses are reasonable and appropriate, with the exception of the ranges chosen for the percentage of patients weighing more than 100 kg. For this parameter, both ranges, 6% and 17% chosen are less than the value used in the base case. The ERG conducted a sensitivity analysis using the broader range for the percentage of patients weighing more than 100 kg. See section 4.3.4.2 for the results.

The result of the use of the SF-6D utility estimates instead of the DLQI-based EQ-5D utility estimates (discussed in section 4.3.2.3) is a dramatic increase in the ICER comparing ustekinumab with supportive care. The MS stated (p117) that choosing the DLQI-based EQ-5D utility estimates in their base case analysis is justified because the method is consistent with the method used in the York model.[1] Other reasons seem to relate to the NICE preference for EQ-5D; and the perceived limitation associated with "well reported limitation" of SF-6D utility scale. The MS does not provide any reference that supports this claim.

4.3.4.2 ERG sensitivity analysis

All results of the modelled economic evaluation presented in the MS are calculated assuming that there would be no extra cost for 90mg ustekinumab compared to 45mg as stated in the terms of the PAS (MS Appendix 4), see also comments above (4.3.2.5). The ERG have run a sensitivity analysis on the MS base case analysis using the price for 90mg ustekinumab as double the list price of 45mg ustekinumab. The results are presented in Table 27 and show that the cost effectiveness of ustekinumab increases to £40,952 per QALY compared to supportive care and over £300,000 compared to adalimumab.

Table 27: Ustekinumab deterministic results with ustekinumab 90mg costed at twice price of ustekinumab 45mg

Treatment	Incremental Costs	Incremental QALYs	ICER Ustekinumab vs other drugs (£)	ICER all drugs vs supportive care (£)
Supportive care	£0	0.0000	40,952	-
Etanercept 50mg	£5,333	0.1483	137,323	35,964
Etanercept 25mg	£3,989	0.1325	102,034	30,111
Etanercept 25mg continuous	£4,829	0.1409	103,157	34,281
Efalizumab	£5,264	0.1308	44,597	40,250
Infliximab	£6,327	0.1616	Dominated	39,153
Adalimumab	£4,660	0.1502	300,063	31,022
Ustekinumab	£6,387	0.1560	-	40,952

The ERG has undertaken a sensitivity analysis using the efficacy data from all patients according to their randomisation outcome and the price for 90mg ustekinumab as double of the list price of 45mg ustekinumab.

Table 28: Sensitivity results using the efficacy data from all patients according to their randomisation outcome, and price of ustekinumab 90mg as double the price of ustekinumab 45mg

Treatment	Incremental QALYs	Incremental costs	ICER ustekinumab 45mg vs other drugs	ICER ustekinumab 90mg vs other drugs	ICER vs supportive care
Supportive care	£0	£0	29,334	88,417	-
Etanercept 50mg	0.1483	£5,333	Dominant	1,411,694	35,964
Etanercept 25mg intermittent	0.1325	£3,989	25,035	444,131	30,111
Etanercept 25mg continuous	0.1409	£4,829	Dominant	661,382	34,281
Efalizumab	0.1308	£5,264	Dominant	357,606	40,250
Adalimumab	0.1502	£4,660	Dominant	2,266,322	31,022
Ustekinumab 45mg	0.1564	£4,588	-	Dominated	29,334
Ustekinumab 90mg	0.1542	£13,631	Dominant	-	88,417
Infliximab*	0.1616	£6,327	£334,205*	Dominated	39,153

*this ICER compares infliximab to ustekinumab.

Table 28 shows that ustekinumab 45 mg dominates all other biologics, including ustekinumab 90mg, except etanercept 25mg intermittent. The cost –effectiveness of ustekinumab compared to etanercept is £25,035. Importantly, infliximab dominates ustekinumab 90mg.

The ERG also conducted a bivariate sensitivity analysis varying the proportion of patients with weights more than 100 kg. In the manufacturer's clarification (Appendix 1), it was reported that in the Phoenix 1 trial there were 35% of participants with a weight in excess of 100 kg, and the ERG have assumed this as the highest estimate included in the sensitivity analysis. In this analysis it was also assumed that the price for 90mg ustekinumab is double of the list price of 45mg ustekinumab. The ICER for ustekinumab varied between £38,000 and £50,000 versus supportive care when the proportion of individuals with weights more than 100 kg varied between 15% and 35% respectively (Table 29).

Table 29: Ustekinumab sensitivity analysis results for varying proportion of individuals more than 100kg and price of ustekinumab 90mg as double the price of ustekinumab 45mg

Proportion > 100kg	ICER vs supportive care, £	ICER vs Adalimumab, £	vs Etanercept Intermittent 25mg, £
15%	37,996	216,640	82,218
20%	40,952	300,063	102,034
25%	43,871	385,450	121,751
35%	49,779	568,278	162,132

The results of the sensitivity analysis indicate that the ICER is sensitive to the assumptions about the proportion of patients weighing more than 100 kg.

The ERG also conducted a sensitivity analysis varying the total cost of an inpatient admission incurred by patients in supportive care. This cost offsets the cost associated with treatment with biological drugs. (Table 30).

Table 30: Ustekinumab sensitivity analysis results for varying the total cost of inpatient admission

Total cost of inpatient admission	ICER vs supportive care, £	ICER vs Adalimumab, £	vs Etanercept Intermittent 25mg, £
£5,000	34, 639	243	31,643
£5,500	32, 264	dominant	29,290
£6063.54 (base case analysis)	**29,587**	**dominant**	**26,637**
£6,500	27,514	dominant	24,582

The results of the sensitivity analysis indicate that the ICER for ustekinumab is fairly sensitive to the assumptions about the total cost of inpatient admission. The ICER for ustekinumab increased to £34,500 versus supportive care when the total cost of a single admission decreased by £1,000. Under this assumption ustekinumab no longer dominates adalimumab.

4.3.4.3 Scenario Analysis

The MS presents two scenario analyses comparing ustekinumab to alternative biological therapies and using the MTC estimates of efficacy outcomes other than those used in the base case analysis. The first scenario analysis presented in MS is called "weight based dosing" and is based on the selected efficacy data from the subgroups of patients. The results of ustekinumab 45mg include observations in patients who were randomised to ustekinumab 45mg arm but are limited to the patients with the baseline weight less than 100kg. The results of ustekinumab 90mg include observations only in patients with the baseline weight more than 100kg. The second analysis included the efficacy data for all patients according to the randomisation outcomes. These results are fully reproduced in the section 4.1.2.8 (The MS results) along with results of the MS base case analysis. Table 31 contains extracts from MS Tables 7.3.5 and 7.3.6.

Table 31: MS scenario analyses for weight based dosing and all patients analysis (MS Tables 7.3.5 and 7.3.6)

Treatment	Incremental QALYs	Incremental costs	ICER vs supportive care	ICER vs Adalimumab	ICER vs Etanercept intermittent
Scenario 1: Weight based dosing					
Ustekinumab 45mg	0.1564	£4,588	£29,334	Dominant	£34,244
Ustekinumab 90mg	0.1542	£4,732	£30,693	£18,204	£25,035
Scenario 2: All patients analysis					
Ustekinumab 45mg	0.1544	£4,735	£30,664	£16,400	£36,272
Ustekinumab 90mg	0.1563	£4,613	£29,520	Dominant	£28,126

As discussed in Sections 3.1.5 and 3.3.4 the clinical effectiveness estimates used in the MS base case analysis are derived from a subgroup of patients selected without an appropriate statistical analysis that would support the weight-base categorisation, therefore the results of both the MS base case analysis (based on the weighted average efficacy outcomes) and the results presented in Table 31 (weight based dosing) should be viewed with caution. The most striking result of the scenario analyses is the reversal of the order of dominance when

comparing ustekinumab with adalimumab. In the weight based dosing ustekinumab 45mg dominates adalimumab while in the "all patient analysis" ustekinumab 90mg dominates adalimumab. This suggests that the outcomes of the model are sensitive to the choice of the patient-level efficacy data. In addition, all the outcomes of the economic evaluation presented in the MS are conditional on the price of ustekinumab 90mg indicated in the PAS (see section 4.3.2.5 for further discussion). Therefore the results presented in Table 31 are valid only for the duration of the pricing arrangements of the PAS.

4.3.4.4 ERG scenario analysis

The MS undertook a sensitivity analysis (results are reported in Table 7.3.6 p132) calculating ICER estimates under the alternative assumptions of relative efficacy of intermittent etanercept 25mg in comparison to continuous etanercept. It was assumed that the efficacy of intermittent etanercept varies within the range from 71% to 91% of efficacy of continuous etanercept. As discussed in section 4.3.4.1, this produced the ICER estimates for ustekinumab compared to intermittent etancercept 25 mg between £22,634 and £32,949. The model appears to be sensitive to the assumptions about the relative efficacy of intermittent etanercept 25mg in comparison to continuous etanercept.

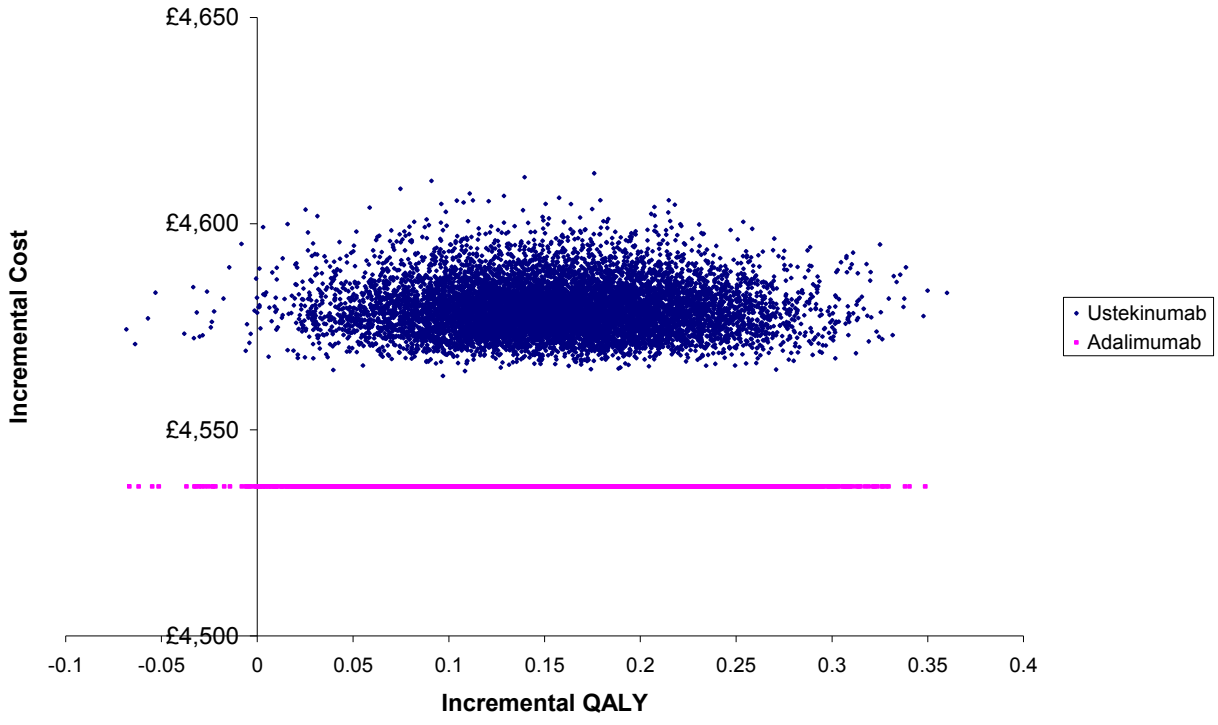
As discussed in section 4.3.2.2 there is considerable uncertainty associated with methods for estimating the relative efficacy of intermittent etanercept 25mg in comparison to continuous etanercept. The ERG undertook a scenario analysis where the model assumption of the superior efficacy of intermittent etanercept 25mg in comparison to continuous etanercept 25mg was overruled and was assumed to be the same as for continuous etanercept 25 mg. This is a conservative assumption which is also consistent with approach used in York model.[1] Under this assumption ICER of ustekinumab compared to intermittent etanercept 25mg in the base case analysis becomes £41,449, which is considerably higher that the base case estimate of £26,637.

4.3.4.5 Probabilistic Sensitivity Analysis

The MS contains a probabilistic sensitivity analysis which is run by clicking on the probabilistic analysis button on the 'Main' worksheet. The PSA takes approximately 5 minutes to run 10,000 iterations on T.8 GHZ computer. Table 7.2.1 (MS p107) contains the list of parameters and the type of distributions used in the probabilistic sensitivity analysis in the original York model[1]. The

MS indicated that these distributions also applied to their model (p125). The MS does not provide sufficient details on the variables and distributions used in the PSA. The ERG has checked the distributions used in the model. The MS appeared to only include variable for the utilities, the treatment response, and the proportion of people above 100 kg. The original York model[1] tested uncertainty of the "cost of treatment" parameter using a gamma distribution this parameter was not included in the MS. Furthermore the MS does not include variables in the PSA which were shown to be highly influential in the sensitivity analysis, ie for the number of hospital days and for the effect of different cost and effectiveness of intermittent etanercept. For these reasons, the ERG considers the PSA to be inappropriate and does not show the true uncertainty of the model. The ERG has run the PSA in the MS model and produced a scatterplot of the results for ustekinumab and adalimumab (Figure 1). As can be seen from the figure, there is no variation around the costs for adalimumab (and the other alternative biologics) and limited variation in the costs for ustekinumab.

Figure 1: Cost-effectiveness scatterplot for ustekinumab and adalimumab in the base case



The MS presents the results for the probabilistic sensitivity analyses derived from the mean costs and effects across 10,000 Monte Carlo simulations.

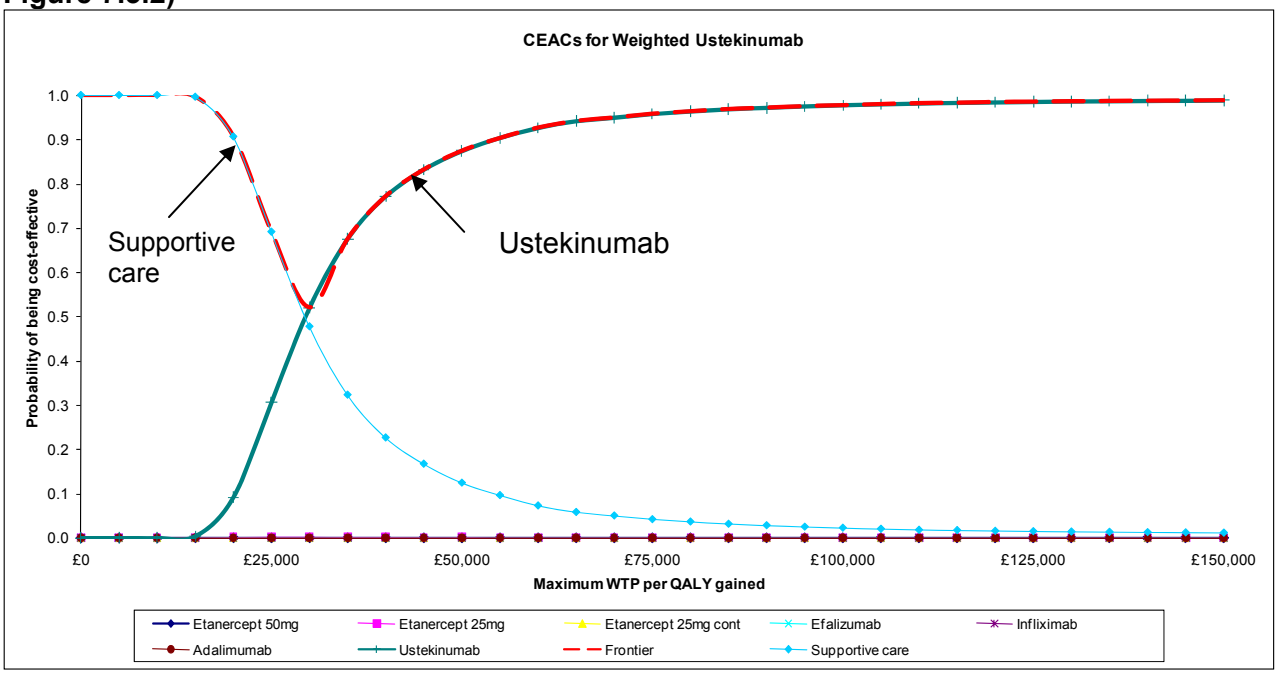
Table 32: Base case probabilistic results (MS Table 7.3.3)

Treatment	Incremental QALYs	Incremental 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.

Figure 2 (MS Figure 7.3.2) shows the cost-effectiveness acceptability curve resulting from the probabilistic sensitivity analysis. According to the MS PSA results, ustekinumab has the highest probability of being cost-effective at conventional NICE thresholds whereas all other biologics have a zero probability of being cost-effective. The probability of ustekinumab being cost effective at £20,000 and £30,000 thresholds is 7.4% and 48.5% respectively.

Figure 2: Cost-effectiveness acceptability curves for biologics in the base case (MS Figure 7.3.2)



4.3.4.6 ERG Probabilistic Sensitivity Analysis

The ERG conducted a probabilistic sensitivity that included variables that were omitted from the PSA undertaken by the manufacturer, that were shown to be highly influential in the sensitivity analysis, ie the number of hospital days and for the effect of different cost and effectiveness of intermittent etanercept. The ERG also varied the drop out rates. These variables were varied using the ranges from the sensitivity analyses with distribution around them.

For the basecase, the scatterplot for adalimumab and ustekinumab is shown in Figure 3: which shows a more realistic uncertainty in the model results. As can be seen in the Figure 3 the results for ustekinumab and adalimumab largely overlap. However the CEAC for these results does not differ significantly to that shown in the MS (Figure 2).

Figure 3: Cost-effectiveness scatterplot for ustekinumab and adlimumab in the base case scenario with uncertainty included for additional parameters

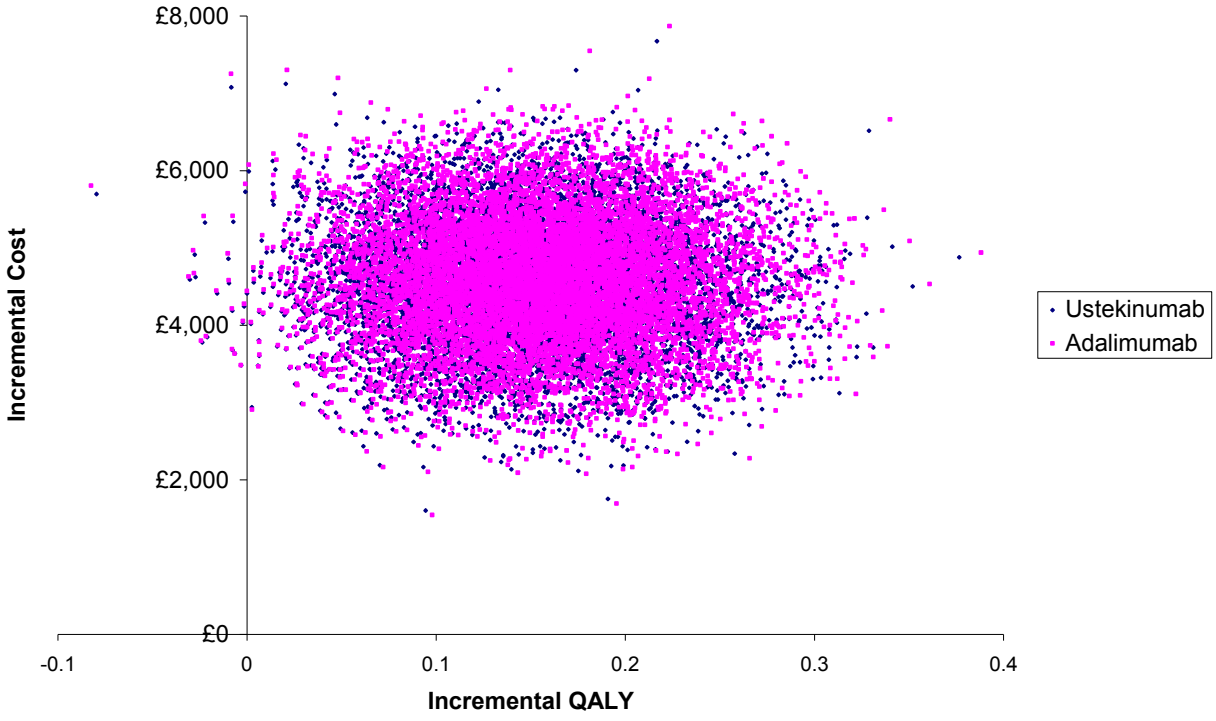


Figure 4 presents the cost-effectiveness acceptability curves based on the probabilistic sensitivity analysis using the weighted average efficacy outcomes (ie. 80% of patients receive ustekinumab 45mg (patients with baseline weight<100kg) and 20% receive ustekinumab 90mg (patients with baseline weight>100kg) and assuming that the price for ustekinumab 90mg is twice the list price of ustekinumab 45mg. The results show that the probability of ustekinumab being cost effective at £20,000 and £30,000 per QALY is zero.

Figure 4: CEAC for PSA results with ustekinumab 90mg costed at twice price of ustekinumab 45mg with additional with uncertainty included for additional parameters

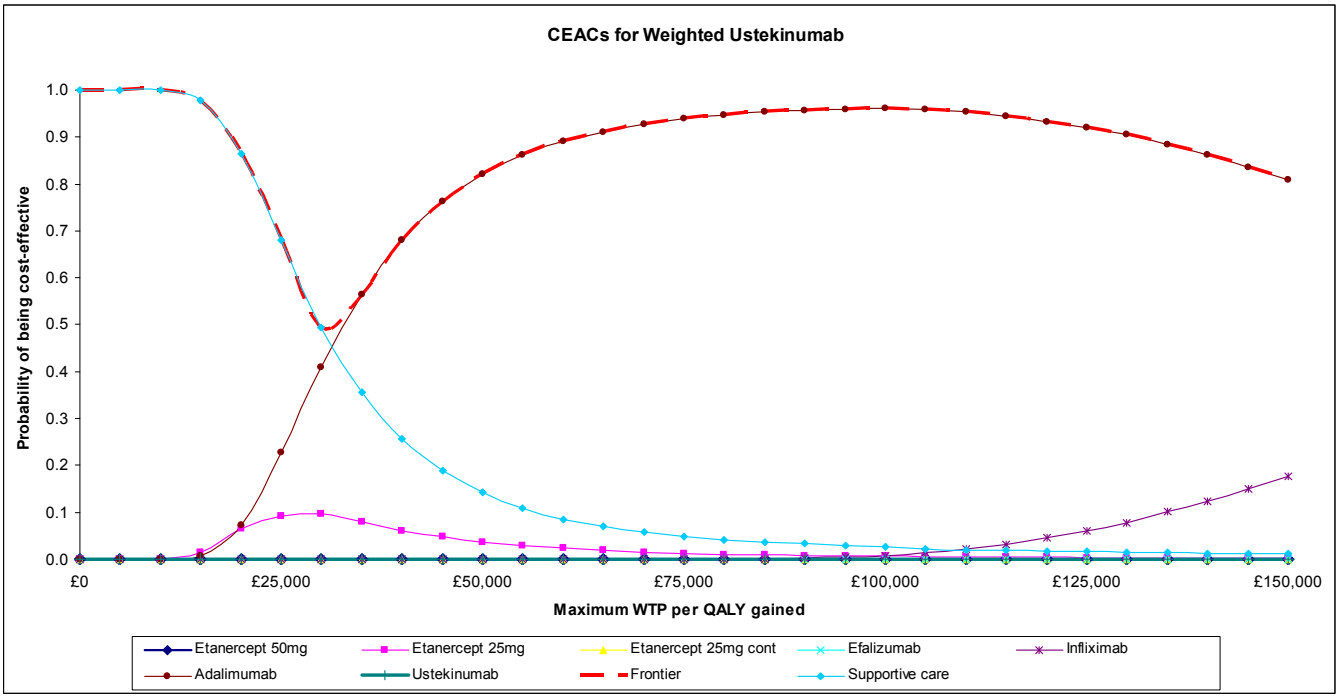
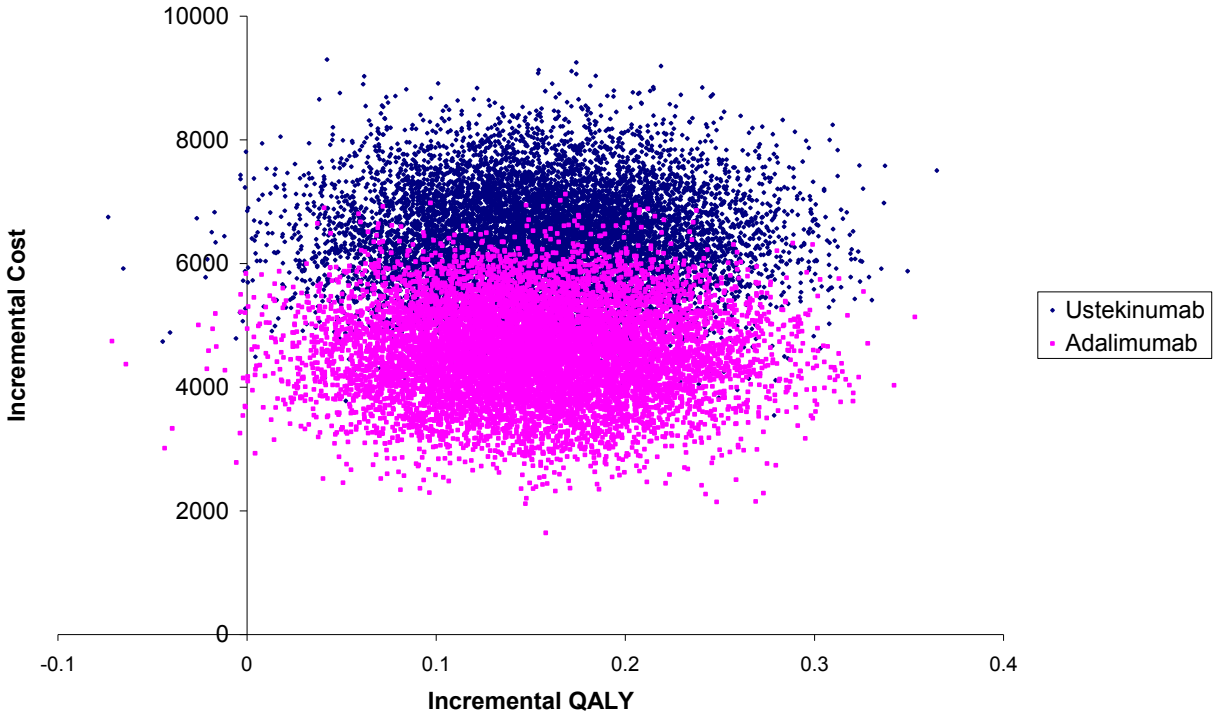


Figure 5: Cost-effectiveness scatterplot for ustekinumab and adlimumab with ustekinumab 90mg costed at twice price of ustekinumab 45mg



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

Notwithstanding the concerns outlined above, the modelling approach to cost-effectiveness analysis used in the MS seems reasonable.

4.3.6 Summary of uncertainties and issues

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

1. Clinical effectiveness estimates used in the MS base case analysis are derived from a subgroup of patients selected without an apparent appropriate statistical subgroup analysis that would support the weight-base categorisation. Using the clinical effectiveness data from the selected subgroups of ustekinumab patients is likely to produce the biased ICER estimates.

2. Although it appears reasonable to assume that continuous etanercept 25mg is associated with higher clinical effectiveness than intermittent etanercept 25mg, there is a considerable

uncertainty surrounding the estimate of the relative risk used in the model. Therefore the clinical effectiveness estimates of intermittent dosing of etanercept 25mg used in the economic evaluation are likely to be biased, with ustekinumab becoming relatively more cost-effective as the relative risk of intermittent etanercept in comparison to continuous etanercept decreases.

3. According to MS the SF-6D utility estimates has the advantage of being directly estimated from SF-36 patient-level data that in turn can be related directly to the patients' PASI responses. Nevertheless, the alternative, EQ-5D values derived indirectly using the DLQI surrogate outcomes were used in the base case analysis. The utility gain estimates based on the SF-36 patient level data have resulted in the considerably lower values in comparison to the DLQI-based EQ-5D estimates. It is uncertain which set of utility gains presented in the model are the most accurate in terms of validity and generalisability. The choice of utility estimates has a major impact on the estimated cost-effectiveness of ustekinumab in comparison to supportive care.

4. Non-responders are assumed to have an annual inpatient admission of 21 days associated with in supportive care. This is an important assumption as the costs of biological treatment are offset by reductions in supportive care costs. The MS does not provide sufficient details about the method of calculating the estimated cost per bed day. However the results are fairly sensitive to the total cost of an inpatient admission.

5. All the outcomes of the economic evaluation presented in the MS are conditional on the price of ustekinumab 90mg as indicated in the PAS. Doubling the price of ustekinumab 45mg resulted in ustekinumab no longer dominating the comparators in the range of £20,000 to £30,000 per QALY.

5 Discussion

5.1 Summary of clinical effectiveness issues

The MS includes evidence on the efficacy of ustekinumab from three RCTs, two comparing ustekinumab with placebo, and one comparing ustekinumab with etanercept. Overall the MS contains an unbiased estimate of the efficacy of ustekinumab at 12 weeks based on the results of the three trials. The estimates of the effectiveness of ustekinumab in relation to comparator

interventions are less clear. The analysis of data for the manufacturer's recommended weight based dosing is also unclear.

5.2 Summary of cost effectiveness issues

The MS includes a report on the cost effectiveness literature, and an economic evaluation using a decision-analytic model. The cost effectiveness analysis estimates the mean length of time that an individual would respond to treatment, and the utility gains associated with this response. The model is based closely on the model reported in Woolacott and colleagues.[1] The results are presented for ustekinumab versus comparators as outlined in the decision problem.

The model is generally internally consistent and appropriate to psoriasis, in terms of structural assumptions, and the cost effectiveness analysis generally conforms to the NICE Reference Case and the scope / decision problem. However, the results are sensitive to the assumptions about the differential clinical effectiveness in the subgroup of patients with the baseline weight of more than 100kg; the relative clinical effectiveness of intermittent etanercept 25mg in comparison to continuous etanercept 25mg; and the cost of ustekinumab 90mg. The results are also sensitive to the values of the model parameters: a) the cost of inpatient admissions for those on supportive care and b) the utility gain achieved by responders. The values assigned to these parameters are important in determining the cost-effectiveness of ustekinumab for the treatment of psoriasis.

6 References

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7 Appendices

Appendix 1: Response from Janssen-Cilag to clarification questions

Following on from your letter dated 28th January 2009, please find below Janssen-Cilag Ltd's responses to the clarification questions on the clinical and cost-effectiveness data contained within our original submission.

Section A: Clarification on effectiveness data

A1. In the Phoenix 1 and 2 trials, the placebo treatment arms divide at 12 weeks. Please clarify if this was a randomised split or if the population was split by some other means.

The placebo arms of the PHOENIX 1 and 2 trials were randomised to either the ustekinumab 45mg or 90mg groups at week 12. Patients were randomly assigned to either group on a 1:1 ratio using a biased-coin minimisation assignment via centralised interactive voice response system. In PHOENIX 1, the investigators were blinded until week 76 whereas in PHOENIX 2, investigators were blinded until week 52.

A2. Table 6.3.1., page 30, does not include the proportion of people in each ustekinumab trial arm who were above and below 100kg. Please provide this information.

The following table shows the percentages of patients in each trial who were above and below 100kg at baseline:

	≤100kg % (n)	**>100kg % (n)**
PHOENIX 1		
Ustekinumab 45mg	65.9% (168/255)	34.1% (87/255)
Ustekinumab 90mg	64.1% (164/256)	35.9% (92/256)
Placebo	65.1% (166/255)	34.9% (89/255)
PHOENIX 2		
Ustekinumab 45mg	72.6% (297/409)	27.4% (112/409)
Ustekinumab 90mg	70.6% (290/411)	29.4% (121/411)
Placebo	70.7% (290/410)	29.3% (120/410)
ACCEPT		
Ustekinumab 45mg	72.2% (151/209)	27.8% (58/209)
Ustekinumab 90mg	70.3% (244/347)	29.7% (103/347)
Etanercept 50mg twice Weekly	72.3% (251/347)	27.7% (96/347)

The percentage of patients who are >100kg is [redacted] in the three clinical trials than the UK specific estimate we have used within the main submission (20%) to estimate the weighted average ICERs for ustekinumab.

[redacted]

[redacted]

A3. In section 6.4.1, page 47, the text states that 742 participants were included in the efficacy analysis. However, the corresponding figure suggests all 766 were included. The same issue appears on page 50 for the Phoenix 2 trial. Please clarify which figures were used for the efficacy analyses.

Our apologies for any confusion. We can clarify that the number of patients included in the efficacy analyses for the PHOENIX 1 and PHOENIX 2 trials were 766 and 1,230, respectively. This relates to the intention-to-treat (ITT) population. The text above the table was included incorrectly and was a typographic error.

A4. In Table 6.6.2, page 74, the ustekinumab weight based results across the three trials show the same number of participants for the 45mg and 90mg. Please clarify if this is an error, and if so, please correct the table accordingly.

Thank you for bringing this to our attention. We can clarify that the patient numbers reported for PHOENIX 2 and the ACCEPT trials in Table 6.6.2b have been reported incorrectly. We have provided a corrected table below:

Table 6.6.2b Patient characteristics and main results - baseline severity

	PASI (0-72)	PGA (0-5)	DLQI
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) adalimumab (n=108) : 20.2, 7.5 (10.4-52.9)	Very severe psoriasis (%) Placebo (n=53): 3.8 methotrexate (n=110): 5.5 adalimumab (n=108):8.4 Moderate to severe psoriasis (%) Placebo (n=53): 58.5 Methotrexate (n=110): 41.8 adalimumab	NR

		(n=108) :43 Moderate psoriasis (%) Placebo (n=53): 37.7 methotrexate (n=110): 52.7 adalimumab (n=108): 47.7	
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):		

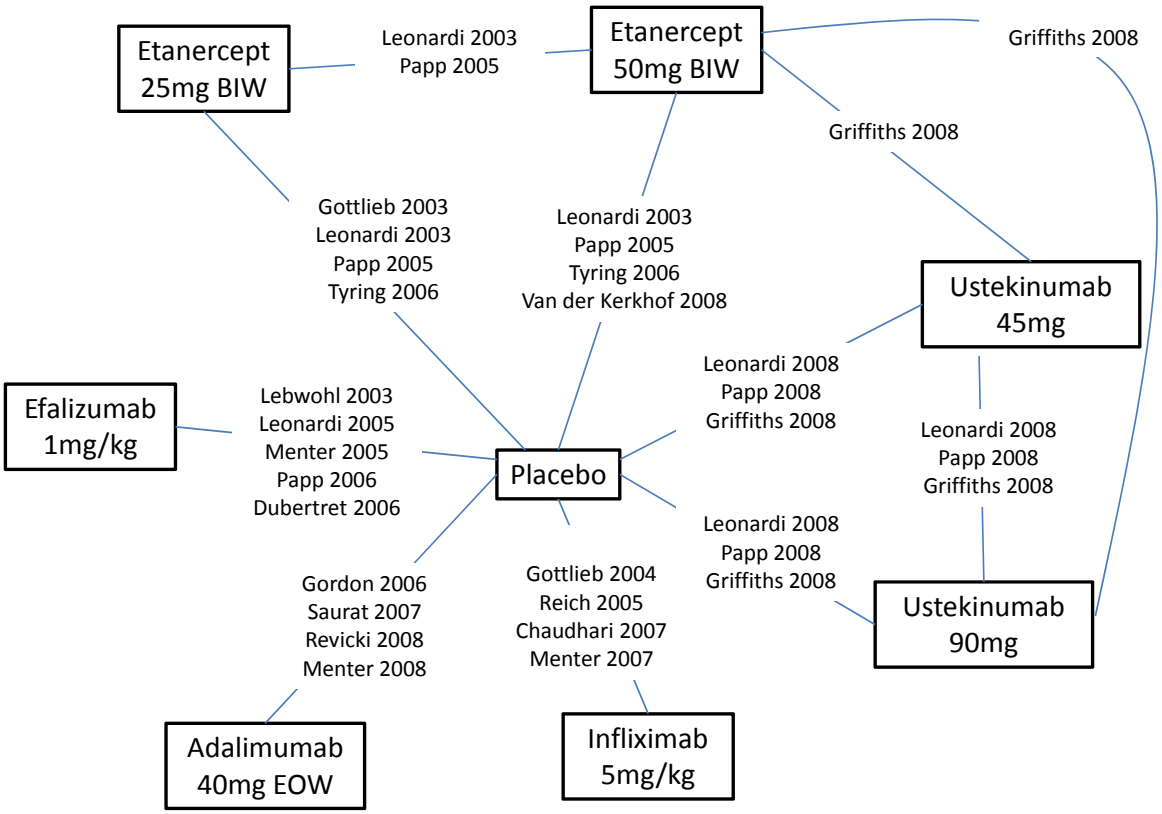
	19(9.6-57.6) Efalizumab 1mg/kg/wk (n=162):18.6 (11.9-50.1) Efalizumab 2mg/kg/wk (n=166):18.9 (10-55.6)	NR	NR
Menter 2005	Mean (range) Placebo (n=187): 19.4 (11.4-50.3) Efalizumab (n=369):19.4 (10.1-58.7)		
Papp 2006	Mean (SD) Placebo (n=236): 18.69,7 (10.5-49.6) Efalizumab (n=450): 19.14,7.5 (10.2 – 54.6)	Mild, n (%) 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 Infliximab 3mg/kg (n=313): 20.1(7.9), 17.6 Infliximab 5mg/kg (n=314): 20.4 (7.5), 18.6	NR	Mean (SD), median Placebo (n=208): 13.4 (7.3), 13 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 (PHOENIX 1)	Mean (SD) Placebo (n=255):	Marked or severe, n (%)	Mean (SD) Placebo (n=255)

ITT	20.4 (8.6) Ustekinumab 45mg (n=255): 20.5 (8.6) Ustekinumab 90mg (n=256): 19.7 (7.6)	Placebo (n=255):112 (43.9) Ustekinumab 45mg (n=255):114 (44.7) Ustekinumab 90mg (n=256):109 (42.6)	= 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 (PHOENIX 2) 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=297) 19.6 (7.2) Ustekinumab 90mg (n=121) 21.2 (7.9)		Mean (SD) Ustekinumab 45mg (n=297) 12.4 (7.1) Ustekinumab 90mg (n=121) 13.4 (7.9)
Griffiths 2008 (ACCEPT) 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	NR

		(n= 209): 11 (5.3) Ustekinumab 90mg (n= 347): 9 (2.6)	
ACCEPT Weight based	Mean (SD) Ustekinumab 45mg (n=151) 20.5 (9.1) Ustekinumab 90mg (n=103) 21.4 (9.6)		Not applicable

A5. Please provide a network diagram for the mixed treatment comparison (MTC)
Below is a network diagram for the mixed treatment comparison:



This excludes all comparisons which have not been included in the meta-analysis and would not have added to the network, for example the adalimumab comparison versus methotrexate in the CHAMPION trial (Saurat 2007).

A6. We note that a subgroup will be recommended in the SPC. Please provide details of the analysis for this sub-group, the results of which are used in the MTC and the economic model. In particular, please provide a description of the method used which justified the cut-off weight of 100kg for the use of a higher dose of ustekinumab.

The PASI 75 response rate at week 12 for both doses of ustekinumab were analysed for each 10kg increment of patient weight in a pooled analysis of PHOENIX 1 and PHOENIX 2. In this pooled analysis, the response rates for the 45mg and 90mg doses were comparable for each 10kg increment of patient weight below the 100kg cut-off. However, for patients weighing >100kg, there was a greater difference in efficacy between the 45mg and 90mg groups (see figure 7.2.1 in the original submission document).

The dose/response relationship for ustekinumab observed at the 100kg cut-off in the PHOENIX 1 and PHOENIX 2 trials has been further confirmed by pharmacokinetic research published in February 2009 (Zhu et al, 2009[1]). In pharmacokinetic modelling of the apparent clearance (CL/F) and apparent volume of distribution (V/F) of ustekinumab, Monte Carlo simulation indicated that the mean steady-state trough serum concentration of ustekinumab with every-12-week dosing for patients weighing more than 100kg was approximately 30% lower than for patients weighing 100kg or less.

Finally, based on the dose/response relationship observed in the PHOENIX 1 and PHOENIX 2 trials, the Phase III ACCEPT trial was designed with weight-based efficacy as a major secondary endpoint. In this analysis, the combined ustekinumab group (weight-based) was composed of subjects randomised to ustekinumab 45mg and with baseline weight ≤100kg and those randomised to ustekinumab 90mg and with baseline weight >100kg.

A7. On page 109, the submission indicated that it has been demonstrated that the response rate for ustekinumab continues to rise after 12 weeks and therefore the assumption that the response at 16 weeks is the same as 12 weeks is justified. This statement is not referenced back to another section of text in the submission. Please clarify which section of the submission you are referring to.

The longer term efficacy of ustekinumab has been demonstrated in the PHOENIX trials and can be seen in section 6.4.5. However, 12 weeks was the final randomised comparison to placebo and therefore we have assumed equal efficacy with this time point. To further illustrate the longer term efficacy of ustekinumab, the percentage of patients achieving a PASI 75 at various time points up to week 28 are shown in the table below:

	PHOENIX 1 (weight based analysis*)		**PHOENIX 2 (weight based analysis*)**	
% PASI 75	**Ustekinumab 45mg**	**Ustekinumab 90mg**	**Ustekinumab 45mg**	**Ustekinumab 90mg**
at Week 4	10.7%	9.8%	20.9%	11.6%
at Week 8	61.3%	45.6%	62.0%	58.8%
at Week 12	73.8%	68.5%	73.4%	71.1%
at Week 16	73.8%	67.8%	76.0%	68.1%
at Week 20	80.1%	80.0%	80.6%	78.4%

[1] Zhu et al. Population pharmacokinetic modelling of ustekinumab, a human monoclonal antibody targeting IL-12/23p40 in patients with moderate to severe plaque psoriasis. *J Clin Pharmacol* 2009; 49; 162

at Week 24	82.5%	80.0%	80.1%	79.8%
at Week 28	79.3%	74.4%	75.6%	73.9%

* Ustekinumab 45mg for patients ≤100kg and ustekinumab 90mg for patients >100kg

Section B: Clarification on cost-effectiveness data

B1. Please clarify the number of references/studies deemed appropriate for critical appraisal in the cost-effectiveness literature search. The numbers in 7.1.1 (overview of literature review results, page 93) do not appear to add up.

Thank you again for drawing this to our attention. We can clarify that overall, six references were identified for potential inclusion into the review (Woolacott et al. 2006[15], Pearce et al. 2006, CADTH 2007, Nelson et al, 2008, Menter & Baker 2005[16] and Hankin et al. 2005). Of these, two were deemed to be appropriate for data extraction and full appraisal (Woolacott et al. 2006 and Pearce et al. 2006). One further reference provided an overview of all other studies (CADTH 2007), and 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 (Menter & Baker 2005[16], Hankin et al. 2005 and Nelson et al. 2005).

B2. Please provide the source for the range of the efficacy variable for intermittent etanercept used in the sensitivity analysis in Table 7.2.13, page 125.

No measure of uncertainty or other criteria was available to inform this decision and as such a total range of 20% was considered appropriate to assess the sensitivity to plausible uncertainty in this parameter. It should be noted that subsequent to publication a further study (Ortonne et al, 2008[2]) has addressed the question of the efficacy of intermittent etanercept and has shown consistent results with Moore et al, 2008 where intermittent etanercept is significantly less effective than continuous etanercept treatment. This study involved patients with moderate to severe plaque psoriasis who were randomised to receive continuous etanercept 25mg twice weekly or 'paused' etanercept for 54 weeks. Among 711 patients evaluable for efficacy, the mean PGA score averaged over 54 weeks (primary endpoint) was significantly lower in the continuous etanercept group than in the 'paused' etanercept group (1.98 vs. 2.51, respectively; $p<0.001$). Mean PGA was significantly reduced from baseline (3.6, both groups) to week 54 in the continuous (1.9) and paused groups (2.4; $p<0.01$). Mean PASI was significantly decreased from baseline (21.9 and 22.8, respectively) to week 54 with continuous (7.1) and paused therapy (9.5; $p<0.01$). PASI improved by 68% and 59% from baseline to week 54 in patients receiving continuous and paused etanercept, respectively.

B3. Please provide an additional economic analysis that does not incorporate the patient access scheme.

Below is the weighted average base case analysis for ustekinumab without the patient access scheme.

[2] Ortonne J-P et al. Efficacy and safety of continuous versus paused etanercept treatment in patients with moderate-to-severe psoriasis over 54 weeks: the CRYSTEL study. *Expert Rev. Dermatol.* 3(6), 657-665 (2008)

Treatment	Mean costs	Mean QALYs	ICER Ustekinumab vs other treatments	ICER vs supportive care
Supportive care	£0	0.0000	£40,952	-
Efalizumab	£5,264	0.1308	£44,597	£40,250
Etanercept 25mg intermittent	£3,989	0.1325	£102,034	£30,111
Etanercept 25mg continuous	£4,829	0.1409	£103,157	£34,281
Etanercept 50mg	£5,333	0.1483	£137,323	£35,964
Adalimumab	£4,660	0.1502	£300,063	£31,022
Ustekinumab	£6,387	0.1560	-	£40,952
Infliximab	£6,327	0.1616	Dominated	£39,153

Please note: the weighted average has been estimated where 80% of patients are ≤100kg and receive ustekinumab 45mg and the remaining 20% of patients are >100kg and receive ustekinumab 90mg.

In addition, please find below the weight by dose for ustekinumab deterministic analysis excluding the patient access scheme.

Treatment	Mean costs	Mean QALYs	ICER Ustekinumab 45mg vs other treatments	ICER Ustekinumab 90mg vs other treatments	ICER vs supportive care
Supportive care	£0	0.0000	£29,334	£88,417	-
Efalizumab	£5,264	0.1308	Dominant	£357,606	£40,250
Etanercept 25mg intermittent	£3,989	0.1325	£25,035	£444,131	£30,111
Etanercept 25mg continuous	£4,829	0.1409	Dominant	£661,382	£34,281
Etanercept 50mg	£5,333	0.1483	Dominant	£1,411,694	£35,964
Adalimumab	£4,660	0.1502	Dominant	£2,266,322	£31,022
Ustekinumab 90mg	£13,631	0.1542	Dominant	-	£88,417
Ustekinumab 45mg	£4,588	0.1564	-	Dominated	£29,334
Infliximab	£6,327	0.1616	£334,423	Dominated	£39,153

B4. Please provide an economic analysis that uses a 28-week stopping rule for the trial period, as per the guidance given in the SPC.

Per the recommendation in the ustekinumab SPC that consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment, we have run a cost-effectiveness analysis using a 28-week stopping rule for ustekinumab.

[redacted], but with the 28-week stopping rule, assumes that there are 3 doses of ustekinumab used during the 28-week trial period (week 0, 4, and 16) as opposed to 2 doses used in the base case trial period of 16 weeks. Both costs and utilities have been adjusted for the 28-week stopping rule in the results tables shown below.

We are presenting two analyses with varying assumptions to estimate the cost-effectiveness of ustekinumab with a 28-week trial period:

Analysis One

We have applied week 28 PASI responses for all patients who were randomised to receive ustekinumab (either dose) at baseline from the PHOENIX trials instead of the mixed treatment comparison (for ustekinumab alone). This has been carried out for the following reasons:

- Patients who were randomised to ustekinumab 45mg or 90mg at week 0 were included in the analysis.
- There is no placebo comparison beyond 12 weeks within the clinical trials. As such, response rates from the mixed treatment comparison cannot be calculated beyond 12 weeks, because the mixed treatment comparison is dependent on placebo as the common comparator for all agents.
- The database lock for the ACCEPT trial up to 28 weeks has not yet been completed.

Below are the cost-effectiveness results from this analysis:

Treatment	Mean costs	Mean QALYs	ICER Ustekinumab vs other treatments	ICER vs supportive care
Supportive care	£0	0.0000	£31,533	-
Efalizumab	£5,264	0.1308	Dominant	£40,250
Etanercept 25mg intermittent	£3,989	0.1325	£38,944	£30,111
Etanercept 25mg continuous	£4,829	0.1409	£8,781	£34,281
Etanercept 50mg	£5,333	0.1483	Dominant	£35,964
Adalimumab	£4,660	0.1502	£41,548	£31,022

Ustekinumab	£4,978	0.1579	-	£31,533
Infliximab	£6,327	0.1616	£364,595	£39,153

In this analysis, ustekinumab dominates both etanercept 50mg twice weekly and efalizumab. When compared against the most commonly used biologic in the UK, continuous etanercept 25mg twice-weekly, the ICER is £8,781. When compared against adalimumab and intermittent etanercept 25mg twice weekly, the ICERs have increased to £41,548 and £38,944, respectively.

Versus supportive care, the ICER for ustekinumab is £31,533 compared to £29,587 in the original base case analysis presented in section 7.3.1.1 in our submission. This suggests that when comparing against supportive care, the duration of the trial period has a relatively modest impact on the ICER.

The limitation of the analysis provided above relates to the lack of placebo control at the 28 week time point for ustekinumab, however placebo response up to 12 weeks was low and given the severe treatment refractory population enrolled into the studies it is unlikely that this placebo response would have increased greatly with no additional treatment.

Analysis Two

We are also presenting a cost-effectiveness analysis which assumes that all biologics have a 28 week trial period. This assumes that the response rate at the end of the original trial period is maintained at 28 weeks for all treatments. The results are as follows:

Treatment	**Mean costs**	**Mean QALYs**	**ICER Ustekinumab vs other treatments**	**ICER vs supportive care**
Supportive care	£0	0.0000	£32,662	-
Efalizumab	£6,070	0.1056	Dominant	£57,497
Etanercept 25mg intermittent	£4,883	0.1127	£4,259	£43,331
Etanercept 25mg continuous	£5,598	0.1198	Dominant	£46,712
Etanercept 50mg	£5,878	0.1309	Dominant	£44,903
Adalimumab	£5,270	0.1476	Dominant	£35,706
Ustekinumab	£5,063	0.1550	-	£32,662
Infliximab	£7,070	0.1440	Dominant	£49,106

In this analysis, ustekinumab dominates adalimumab, efalizumab, continuous etanercept 25mg and 50mg twice weekly and infliximab. When compared to intermittent etanercept

25mg twice weekly, the ICER is low at £4,259. Similar to the previous analysis, the comparison (ICER) against supportive care has not altered significantly despite applying the less favourable 12 week efficacy in place of the 28 week efficacy described above.

B5.

[redacted]

[redacted]

B6. Please clarify the assumption that all patients will be able to self-inject. If there is a proportion of patients that are unable to self-inject, please provide an estimate of this proportion.

Each patient will be trained to self-inject. This training will be provided by Janssen-Cilag Ltd. In addition, Janssen-Cilag Ltd is funding (via a third party) nurses to visit patients in their homes to assist with administering the injections if necessary. The costs of providing this service are met fully by Janssen-Cilag Ltd, and we would be happy to provide more details on this if that would be helpful.

B7. Appendix 11 does not appear to contain any methodological details. Given the role that the outcomes of this meeting played in deriving assumptions used in the model, please provide further information on the nature of the advisory board and the way the information was obtained.

The advisory board was externally moderated by SJK Consulting Ltd and included dermatologists and dermatology pharmacists. The information was presented to the group via a PowerPoint presentation (slides are detailed in Appendix 11 of the original submission). This began with an overview of the design of the cost-effectiveness model and then followed with details of each variable including the source information and also Janssen-Cilag Ltd's proposal for each variable estimate. Each was extensively discussed, and a consensus was obtained on each variable.

Section C: Textural clarifications and additional points

C1. Please provide a copy of the draft or final CHMP EPAR

The final CHMP EPAR is attached to this document.

C2. Please provide a list of abbreviations (for example it is unclear what eCRF, CNTO stand for).

See attached document for a full list of abbreviations.

C3. In section 6.9.1, the text is obliterated by the table 6.9. Please replicate the paragraph that cannot be seen on page 89.

We apologise for this formatting issue. The paragraph which appears on page 89 is as follows with referencing as per the original submission:

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)[17] (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[18] (see Appendix 6). Therefore, this is an appropriate comparator for ustekinumab in relation to the decision problem.

11th February 2009