NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Ustekinumab for the treatment of moderate to severe psoriasis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Janssen-Cilag Ltd	Overall, Janssen-Cilag Ltd agrees with the Appraisal Committee's preliminary recommendation of ustekinumab being recommended as a treatment option for adults with plaque psoriasis based on the specific criteria stated in section 1.1 of the ACD. In addition, we agree with the recommendation of the 16 week assessment of response, where treatment with ustekinumab is stopped if people with psoriasis have not responded adequately.	Comments noted, no changes to the FAD required.
Janssen-Cilag Ltd	We have some comments on the wording of some of the sections of the ACD which are addressed below. Section 2.3 In section 2.3, it states that 'The cost of ustekinumab for the two loading doses (at 0 and 4 weeks) is £4,294. The cost in the first year is £12,882, with an annual cost thereafter of £9,335'. The cost of a 6th dose falls at the end of year 1/start of year 2 and is actually more likely to occur in the second year of treatment. Therefore, in our view, the cost would be better stated as being £10,735 based on five injections in the first year for those patients who continue on treatment beyond the trial period.	Comments noted. The FAD has been amended accordingly.
Janssen-Cilag Ltd	Section 3.5 In section 3.5, it states that 'DLQI data were not reported in the ACCEPT trial'. We would like to clarify that these data were not collected in the ACCEPT trial rather than were not reported. We propose that the wording is amended to: 'DLQI data were not collected in the ACCEPT trial' to reflect this.	Comments noted. The FAD has been amended accordingly.
Janssen-Cilag Ltd	Section 3.11 In this section, it states that the assessment point for infliximab was 14 weeks. We can confirm that the assessment point was actually 10 weeks for infliximab.	Comments noted. The FAD has been amended accordingly.
Janssen-Cilag Ltd	Section 3.17 In section 3.17, it states 'SF-36 values collected in the PHOENIX trials'. We would like to clarify that SF-36 values were collected only in the PHOENIX 1 trial.	Comments noted. The FAD has been amended accordingly.

Consultee	Comment	Response
Janssen-Cilag Ltd	Section 3.20 In relation to the text featured in section 3.20, we would like to clarify that the mixed treatment comparison (MTC) used in the appraisal of efalizumab and etanercept (TA103) is identical to our MTC as described in the main body of the text in the Woolacott review. This analysis was previously accepted by NICE in the Multiple Technology Appraisal of efalizumab and etanercept. The differences lie within the WinBUGS code that appears in the appendix to the original appraisal group report that incorrectly included a random effect baseline. The main body of the report states a fixed effects baseline was used and consultation with the original authors has confirmed that this was indeed the analysis used for the appropriate methodological reasons stated in our submission.	Comments noted, no changes to the FAD required.
Janssen-Cilag Ltd	Section 3.23 Whilst the results referred to in section 3.23 are rather redundant given the acceptance of the scheme, we appreciate that it may provide context to help the NHS understand why one was proposed in the first place. However, the statement 'the probability of ustekinumab being cost-effective was zero' could be misinterpreted by those who are unfamiliar with PSA methods (who will form the majority of the audience). If you have a zero chance of being cost-effective, people may conclude that there would be no circumstances under which the 90mg dose could be cost effective. It sounds like an immovable fact and yet we know that this is not the case when one considers the scheme. We would therefore prefer an amended sentence that conveys the intent of the paragraph whilst averting the potential for misinterpretation. We would suggest the following wording would achieve this: "When the ERG repeated the analysis assuming that the cost of ustekinumab 90mg was twice that of 45mg, the PSA results showed that ustekinumab would not be considered cost-effective at conventional thresholds".	Comments noted. The FAD has been amended to state "the results showed that the probability of ustekinumab being considered cost-effective at £20,000 and £30,000 was zero." See FAD section 3.23.
Janssen-Cilag Ltd	Section 4.6 In section 4.6, it is noted that there is uncertainty about whether the	Comments noted. The FAD has been amended accordingly. See FAD section 4.7

Consultee	Comment	Response
	MTC had used a random or fixed effects baseline. We can confirm that as per section 6.6 or our original submission we used a fixed effects baseline, which was the same approach as that used in the Multiple Technology Appraisal of efalizumab and etanercept (TA103).	
Janssen-Cilag Ltd	Section 4.12 Section 4.12 – same comment as in section 3.17 above.	Comments noted. The FAD has been amended accordingly. See FAD section 4.16.
British Association of Dermatologists	**Do you consider that all of the relevant evidence has been taken into account?** Yes	Comments noted, no changes to the FAD required.
British Association of Dermatologists	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** Yes, however we are concerned that the emphasis is on cost effectiveness and there is little comment on relative safety evidence. Because of the much wider clinical experience with the anti-TNF alpha agents in both Rheumatology and Dermatology, there are a lot more long term safety data. Perhaps the relative quantity of longer term safety data ought to attract heavier weighting for a drug which has a biological effect which lasts so long.	The appraisal has been completed in accordance with the published guide to the methods of technology appraisal (June 2008). The Committee considered the adverse effect profile of ustekinumab when making its recommendations. See FAD section 4.4.
British Association of Dermatologists	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** Yes	Comments noted, no changes to the FAD required.
British Association of Dermatologists	**Are there any equality related issues that need special consideration that are not covered in the ACD?** No	Comments noted, no changes to the FAD required.
British Association of Dermatologists	Because of the lack of longterm safety data it would be useful to state that it should be mandatory that all patients commenced on the drug are entered onto the BADBIR register. This is the BAD Biologics register which is already established and being used to monitor patients on the other biologic agents for psoriasis.	Comments noted. The FAD has been amended to include a statement about the BAD Biologics register. See FAD section 6, recommendations for further research.

Consultee	Comment	Response
British Association of Dermatologists	We fully support the planned MTA	Comments noted, no changes to the FAD required.
British Association of Dermatologists	We have no comments on the executable model	Comments noted, no changes to the FAD required.
Royal College of Nursing	**Has the relevant evidence been taken into account?** The evidence considered seems comprehensive.	Comments noted, no changes to the FAD required.
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** This seems appropriate.	Comments noted, no changes to the FAD required.
Royal College of Nursing	**Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comments noted, no changes to the FAD required.
Royal College of Nursing	**Are there any equality related issues that need special consideration that are not covered in the ACD?** None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	Comments noted, no changes to the FAD required.
Royal College of Physicians	The Royal College of Physicians wishes to endorse the comments submitted by the BAD on the ACD	Comments noted, no changes to the FAD required.

Consultee	Comment	Response
Psoriasis and Psoriatic Arthritis Alliance	We welcome the prelimary recommendation of ustekinumab as a treatment option for moderate to severe psoriasis. As an organisation which is primarily patient driven, our concerns for the use of these treatments are still around the long-term adverse events. We believe that the treatment needs to be carefully prescribed by an appropriate centre and trained specialist.	The Committee considered the adverse effect profile of ustekinumab when making its recommendations. See FAD section 4.4. The marketing authorisation for ustekinumab states that it should be used under the supervision of an experienced physician.
Psoriasis and Psoriatic Arthritis Alliance	In section 6 of the ACD *Research Recommendations,* we believe that stronger emphasis should be placed on head-to-head trials with other biologic agents, in order to see which perform more effectively, provide best use of available funds whilst avoiding serious adverse events.	Comments noted. The FAD has been amended to include reference to head-to-head trials. See FAD section 6, recommendations for further research.

Consultee	Comment	Response
Psoriasis and Psoriatic Arthritis Alliance	We also think that the sentiments in NICE guidance *TA103 etancercept and efalizumab for treatment for adult with psoriasis* Section 6 item 6.2 as set out below should also be included in all guidance related to use of biologics in psoriasis: *6 Recommendations for further research* *6.2 Efforts should be made to ensure the rapid establishment of the proposed BADBIR. This will enable the collection of information on long-term outcomes including adverse events, and also potentially facilitate the identification of subgroups of people who respond better to the drugs. Procedures should be implemented to allow cross-referencing of BADBIR with information from people with PsA enrolled in the British Society for Rheumatology biologicals register.* The BADBIR is now established and recruiting and therefore an implicit statement in NICE guidance will make those prescribing more likely to enter patients into the register or refer to centres which are more equipped to carry out this important process in patient safety. With more of these agents in research, it would be an advantage to patients if the manufacturers took on board that considering the number of established therapies currently available with NICE guidance, future research with biologic agent comparators should be seen as a priority of research and evidence submissions.	Comments noted. The FAD has been amended to include reference to the BAD Biologics register. See FAD section 6, recommendations for further research.
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation	Comments noted, no changes to the FAD required.
Welsh Assembly Government	We are content with the technical detail of the evidence supporting the appraisal and have no further comments to make at this stage	Comments noted, no changes to the FAD required.

Comments received from clinical specialists and patient experts

No comments received

Comments received from commentators

Commentator	Comment	Response
Wyeth Pharmaceuticals	The British Association of Dermatologists draft Guidelines for Biological Interventions for Psoriasis 2009 state that in light of limited patient exposure, ustekinumab should be reserved for use in patients with severe psoriasis who fulfil the stated disease severity criteria AND where anti-TNF therapy has failed or is contra-indicated.	Comment noted. The Committee discussed the sequential use of agents and decided that it could not make a specific recommendation about the use of ustekinumab after the failure of TNF inhibitors because no evidence for its use in this position had been placed before the Committee. See FAD section 4.9.
Wyeth Pharmaceuticals	In the manufacturers cost-effectiveness model the assessment points were at 12 weeks for etanercept. Evidence from clinical studies demonstrates that the effectiveness of etanercept increases to up to 24 weeks. Therefore the assessment point should be at 24 weeks.	Comment noted. The economic model for ustekinumab included assessments points stipulated in current NICE guidance. For etanercept this is 12 weeks. No changes made to the FAD.
Wyeth Pharmaceuticals	The utility data used in the model were based on an estimate of the relationship between PASI response rates and changes in DLQI score from the PHOENIX-1 and PHOENIX-2 trials mapped to EQ-5D scores. This mapping shows that patients with higher PASI response show better improvements in health related quality of life, e. g. a higher utility gain with a PASI 90 than with a PASI 75. Evidence from other sources are contrary to this assumption, and support the assumption, that the biggest gain in utility is achieved up to a PASI 75.	Comment noted. The utility estimates used in the psoriasis appraisals suggest that the biggest relative gain in HRQOL is for people with a PASI 75% response. For PASI response categories <50%, 50-75%, 75-90% and >90%, the assessment report for TA103 includes the following utility estimates 0.05, 0.17, 0.19 and 0.21 (all patient data). For the ustekinumab appraisal the values were 0.04, 0.17, 0.22, and 0.25. No changes made to the FAD.
Wyeth Pharmaceuticals	The ICER for ustekinumab compared with etanercept 25 mg given intermittently (assuming 88% of the cost of continuous etanercept) was £27,105 per QALY gained. The cost of intermittent etanercept is 73.9% of the cost of continuous etanercept, not 88% (£6,878 vs. £9.295).	Comment noted. The Committee considered the frequency of administration of intermittent etanercept. The Committee was aware of the estimates of intermittent etanercept costs used in other psoriasis appraisals including those in TA103 (etanercept and efalizumab) and TA146 (adalimumab). The Committee also heard from clinical specialists that people may receive etanercept continuously or have very short re-

Commentator	Comment	Response
		treatment intervals. It considered that there is variation in the administration of etanercept. See FAD section 4.8.
Wyeth Pharmaceuticals	The manufacturer also varied the assumptions about the cost and efficacy of intermittent etanercept. The cost of intermittent compared with continuous etanercept was changed from the base-case estimate of 88% to 74% (the figure used in TA103) and to 98%. Using an assumption of 74%, the ICER for ustekinumab compared with intermittent etanercept 25 mg increased from £27,105 to £68,339 per QALY gained. The figure of 74% should be used, based on the difference between £6,878 for intermittent etanercept and £9.295 for continuous etanercept, which is 73.9%. Therefore the ICER for ustekinumab compared with the NICE recommended dose for etanercept is more likely to be £68,339 per QALY gained.	Comment noted. The Committee considered the frequency of administration of intermittent etanercept. The Committee was aware of the estimates of intermittent etanercept costs used in other psoriasis appraisals including those in TA103 (etanercept and efalizumab) and TA146 (adalimumab). The Committee also heard from clinical specialists that people may receive etanercept continuously or have very short re-treatment intervals. It considered that there is variation in the administration of etanercept. See FAD section 4.8.
Wyeth Pharmaceuticals	The ERG noted that in the mixed treatment comparison, data from the weight-based dosing analysis of ustekinumab were taken from a subgroup of the trial data, whereas for the comparator trials data for all patients were used. This leads probably to an underestimation of the effectiveness of the comparators used.	Comment noted. The Committee recognised the issues raised concerning the mixed treatment comparison and took these into account when making its decision. See FAD section 4.7.
Wyeth Pharmaceuticals	The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ustekinumab, having considered evidence on the nature of the condition and the value placed on the benefits of ustekinumab by people with psoriasis, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources. The British Association of Dermatologists draft Guidelines for Biological Interventions for Psoriasis 2009 state that in light of limited patient exposure, ustekinumab should be reserved for use in patients with severe psoriasis who fulfil the stated disease severity criteria AND where anti-TNF therapy has failed or is contra-indicated. Therefore, and given the wealth of data on safety and efficacy available for anti-TNF therapies, the Appraisal Committee should follow the BAD and restrict the use of ustekinumab only to those patients who fulfil the	Comment noted. The Committee discussed the sequential use of agents and decided that it could not make a specific recommendation on the use of ustekinumab after the failure of TNF inhibitors because no evidence for its use in this position had been placed before the Committee. See FAD section 4.9.

Commentator	Comment	Response
	stated disease severity criteria AND where anti-TNF therapy has failed or is contra-indicated.	
Wyeth Pharmaceuticals	The Appraisal Committee heard from the clinical specialists that there are currently no treatments that they considered to be effective for people whose psoriasis does not respond adequately to the tumour necrosis factor (TNF) inhibitors (that is, adalimumab, infliximab and etanercept). In addition, with the withdrawal of efalizumab there are no treatment options for people in whom TNF inhibitors are contraindicated, such as people with heart failure or demyelinating disease. The Appraisal Committee should follow the BAD and restrict the use of ustekinumab only to those patients who fulfil the stated disease severity criteria AND where anti-TNF therapy has failed or is contra-indicated.	Comment noted. The Committee discussed the sequential use of agents and decided that it could not make a specific recommendation on the use of ustekinumab after the failure of TNF inhibitors because no evidence for its use in this position had been placed before the Committee. See FAD section 4.9.
Wyeth Pharmaceuticals	The Committee heard from the clinical specialists that ustekinumab is a new drug that has been given to far fewer people than the other biological therapies, and therefore its long-term safety profile is less certain. Therefore, and given the wealth of data on safety and efficacy available for anti-TNF therapies, the Appraisal Committee should follow the BAD and restrict the use of ustekinumab only to those patients who fulfil the stated disease severity criteria AND where anti-TNF therapy has failed or is contra-indicated.	Comment noted. The Committee discussed the sequential use of agents and decided that it could not make a specific recommendation on the use of ustekinumab after the failure of TNF inhibitors because no evidence for its use in this position had been placed before the Committee. See FAD section 4.9.
Wyeth Pharmaceuticals	The Committee heard from the clinical specialists that biological therapies for psoriasis, including etanercept, are usually used on a continuous basis in clinical practice. Even as Wyeth has submitted to obtain a license, including intermittent and continuous treatment options, treatment will still be initiated with intermittent treatment, and only patients in whom it will be necessary will receive continuous treatment with etanercept. Current market research suggests that approximately 74% of patients receive etanercept intermittently. Therefore, intermittent etanercept is the right comparator.	Comment noted. The Committee considered the frequency of administration of intermittent etanercept. The Committee was aware of the estimates of intermittent etanercept costs used in other psoriasis appraisals including those in TA103 (etanercept and efalizumab) and TA146 (adalimumab). The Committee also heard from clinical specialists that people may receive etanercept continuously or have very short re-treatment intervals. It considered that there is variation in the administration of etanercept. See FAD section 4.8.

Commentator	Comment	Response
Wyeth Pharmaceuticals	The Committee also heard from the clinical specialists that the cost of £288 per day for an inpatient stay, as assumed in the model, may be too low. The cost for a rheumatological infusion is £407. Therefore the true cost of ustekinumab may have been underestimated in the current appraisal.	Comment noted. £288 is the cost of an inpatient stay for a person requiring hospitalisation because they have had an inadequate response to their psoriasis treatment. This cost figure does not relate specifically to the costs of ustekinumab treatment. Ustekinumab is given subcutaneously and is not associated with an infusion cost. No changes made to the FAD.
Wyeth Pharmaceuticals	The Committee was aware that the clinical specialists had indicated that ustekinumab may be used after a person's psoriasis has failed to respond to TNF inhibitors. The Committee noted that the manufacturer had provided no detailed evidence of clinical effectiveness and no cost-effectiveness evidence for this subgroup. Approximately 40–50% of people in the PHOENIX trials had previously tried a biological therapy such as a TNF inhibitor and therefore agreed that the estimates of clinical effectiveness were based on a population that included a reasonable proportion of people who had tried biological therapies before. Therefore, and given the wealth of data on safety and efficacy available for anti-TNF therapies, the Appraisal Committee should follow the BAD and restrict the use of ustekinumab only to those patients who fulfil the stated disease severity criteria AND where anti-TNF therapy has failed or is contra-indicated.	Comment noted. The Committee discussed the sequential use of agents and decided that it could not make a specific recommendation on the use of ustekinumab after the failure of TNF inhibitors because no evidence for its use in this position had been placed before the Committee. See FAD section 4.9.
Wyeth Pharmaceuticals	It is proposed that the guidance on this technology is considered for review together with the review of other drugs for the treatment of psoriasis 'Etanercept and efalizumab for the treatment of adults with psoriasis (NICE technology appraisal guidance 103), 'Infliximab for the treatment of adults with psoriasis (NICE technology appraisal guidance 134) and 'Adalimumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 146). The Institute would particularly welcome comments on this proposal. Wyeth supports this proposal.	Comments noted, no changes to the FAD required.

Commentator	Comment	Response
Schering-Plough Ltd	Schering-Plough is concerned that the recommendations do not appear to have taken into account the comments made by clinicians and the ERG regarding this appraisal. Additionally, Schering-Plough is concerned that the ACD does not clarify how the recommendations for ustekinumab should be interpreted in the context of anti-TNF guidance. The ACD appears to position a new non anti-TNF treatment alongside existing anti-TNFs without any attempt to guide clinicians in respect of choosing between the different treatment options. Comments are set out below in response to the questions raised by the Institute.	Comment noted. The Committee discussed the sequential use of agents and decided that it could not make a specific recommendation on the use of ustekinumab after the failure of TNF inhibitors because no evidence for its use in this position had been placed before the Committee. See FAD section 4.9.
Schering-Plough Ltd	**Do you consider that all of the relevant evidence has been taken into account?** Schering-Plough considers that all of the relevant evidence has been presented however the ACD does not appear to reflect the comments made by the ERG and clinicians.	Comment noted. The Committee discussed the sequential use of agents and decided that it could not make a specific recommendation on the use of ustekinumab after the failure of TNF inhibitors because no evidence for its use in this position had been placed before the Committee. See FAD section 4.9.
Schering-Plough Ltd	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** There are a number of issues with respect to interpreting the evidence which have been commented on below. <u>Clinical effectiveness</u> Point 4.4, page 16, ACD document Schering-Plough agrees with the clinical specialists' opinions that since far fewer patients have received ustekinumab compared to anti-TNFs and since there is therefore a lack of long term safety data, ustekinumab should be prescribed more cautiously than comparator therapies. Ustekinumab has only been used in around 2,500 patients compared to an anti-TNF such as infliximab for which	Comment noted. The Committee discussed the sequential use of agents and decided that it could not make a specific recommendation on the use of ustekinumab after the failure of TNF inhibitors because no evidence for its use in this position had been placed before the Committee. See FAD section 4.9.

Commentator	Comment	Response
	there is approximately 1.3 million patient years of experience. Additionally, Schering-Plough considers that the opinion of the British Association of Dermatologists (BAD) is crucial in contributing to NICE guidance in order to provide the safest care for psoriasis patients in the UK. The BAD guidelines, which we understand are due to be published in August 2009, are likely to differ significantly from the ACD guidance and therefore Schering-Plough is concerned that the overall consensus of clinicians has not been taken into account when producing the guidance for ustekinumab. The current ACD guidance does not appear adequately to have taken account of the wider context of the psoriasis therapy area in which anti-TNF treatment options are available with well established safety profiles, and where a treatment with an alternative mode of action recommended by the Institute – efalizumab – was withdrawn due to concerns about safety.	
Schering-Plough Ltd	Point 4.6, page 17, ACD document Schering-Plough is concerned that the methods for extracting data for the weight-based subgroup analysis were not explored further. In particular the way in which data was extracted may have resulted in the randomisation of the trial being violated. Due to the uncertainty in the weight-based dosing subgroup analysis, the use of the data in the mixed treatment comparison results in the efficacy comparisons being uncertain. Schering-Plough believes that this is likely to have an impact on the cost effectiveness results as the clinical effectiveness of ustekinumab compared to the comparitors is made using a mixed treatment comparison which does not compare the same patient populations. All patients in the clinical trials of the comparator therapies are compared to subgroups extracted from the ustekinumab trial, the methods for which are unclear.	Comment noted. The Committee recognised the issues raised concerning the mixed treatment comparison and took these into account when making its decision. See FAD section 4.7.
Schering-Plough Ltd	<u>Cost effectiveness</u> Point 4.8, page 18, ADC document	Comment noted. The Committee recognised the issues raised concerning the mixed

Commentator	Comment	Response
	Schering-Plough would like to stress the comments made by the ERG that no formal analysis of the subgroups have been undertaken. The methods used to extract data in order to carry out subgroup analysis of the weight based dosing may not have been explored sufficiently in order to reliably inform the economic model and therefore may not be appropriate for the analysis. This is of particular relevance as the ERG found that the cost effectiveness of ustekinumab was sensitive the choice of patient-level efficacy data. Although Schering-Plough agrees that the model is robust, due to the uncertainties in the data informing the model, Schering Plough believe it would be premature to issue guidance without the uncertainty in the analysis being addressed further.	treatment comparison and took these into account when making its decision. See FAD section 4.7.
Schering-Plough Ltd	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** Schering-Plough believes that the NICE guidelines should be in line with the British Association of Dermatologists views in order to clarify which treatments clinicians should use.	Comment noted. The Committee discussed the sequential use of agents and decided that it could not make a specific recommendation on the use of ustekinumab after the failure of TNF inhibitors because no evidence for its use in this position had been placed before the Committee. See FAD section 4.9.
Schering-Plough Ltd	**Are there any equality related issues that need special consideration that are not covered in the ACD?** Schering-Plough has concerns about the uncertainty of the PAS and how this would impact patients over 100kg following a NICE review and the resultant cost implications to the NHS.	Comment noted. The Department of Health considered that the PAS was appropriate for use by the NHS and its incorporation into the cost effectiveness analyses was considered by the Committee. The PAS will not be withdrawn without discussion with NICE and the Department of Health. Any review of the guidance would take into account the continuing availability of the PAS. No changes made to the FAD.
Schering-Plough Ltd	Point 8.2, page 23, ACD document Schering-Plough welcomes the proposed review of all psoriasis treatments however is concerned that there is no date stated for the	Comment noted. The guidance on ustekinumab will be considered for review in January 2010, at the same time as guidance

Commentator	Comment	Response
	review. However the discussion in section 8.2 is not clear on how it relates to the existing proposal that NICE communicated to stakeholders on December 22nd 2008, stating that "the Institute's Guidance Executive has decided to recommend that the reviews of all the guidance should be combined and updated as a multiple technology appraisal. This appraisal should be planned into the work programme as soon as possible. We hope to begin working on this appraisal early next year depending on available resources. We will be in touch again once timelines are set." Schering-Plough has been working on the assumption that an MTA will commence imminently, however the ACD appears to indicate that a review will not now be considered until towards the end of 2009 at the earliest, presumably with guidance following during 2011. Schering-Plough requests clarification from the Institute regarding this issue.	on other psoriasis treatments TA103 (etanercept and efalizumab), TA134 (infliximab) and TA146 (adalimumab). See FAD section 8.
Schering-Plough Ltd	In summary, Schering-Plough is concerned about the methods used to extract data for the weight based subgroups from the ustekinumab trials and the way in which the subgroups have been compared to whole patient populations in the mixed treatment comparison have informed a robust model. Schering Plough believes the uncertainty in the clinical efficacy of ustekinumab compared to anti-TNFs from the mixed treatment comparison would have fed into the cost effectiveness evidence. In addition due to the clinicians concerns regarding patient safety, Schering-Plough believes that ustekinumab should be available for patients who are contraindicated to anti-TNFs which would be in line with the consensus with the British Association of Dermatologists.	Comments noted, see responses above.
Abbott Laboratories	<u>Executive Summary</u> • The probabilities of PASI 50, 75 and 90 responses for adalimumab from the mixed treatment comparison presented by the manufacturer do not appear to have been based on all of the available data, and are therefore incorrect and inconsistent with other similar analyses. These incorrect effectiveness estimates have been used throughout the economic evaluation and need to be amended to provide an accurate assessment of the cost-effectiveness of ustekinumab vs. current treatment options.	Comments noted, see responses to individual comments below.

Commentator	Comment	Response
	• The manufacturer included a phase II study of adalimumab in their mixed treatment comparison which not only did not meet their own inclusion criteria, but was also conducted in a less severe psoriasis population than is being considered in this appraisal. The inclusion of this study biases the estimation of comparative effectiveness of ustekinumab compared to adalimumab. • The mix of patients in the <100kg and >100kg categories is not adequately justified and appears to present an optimistic cost-effectiveness estimate for ustekinumab. • The cost-effectiveness of ustekinumab appears to be highly dependent on whether a third dose is given at week 16 and the available data indicate that use in line with a 28-week stopping rule as per the licence is not cost effective. • Abbott considers that the provisional recommendations are currently unsound because of concerns over the robustness of the estimated cost effectiveness of ustekinumab versus adalimumab based on suspected data input errors in the mixed treatment comparison. Abbott requests that a detailed assessment by the ERG or Decision Support Unit is conducted for the reasons as to why lower estimates of effectiveness for adalimumab have been ascertained from this mixed treatment comparison. Abbott requests that when the Committee prepares its final recommendations that any confirmed data errors are amended in the revised recommendations to accurately reflect the cost-effectiveness of ustekinumab vs. all the current treatment options for severe psoriasis.	
Abbott Laboratories	**Do you consider that all of the relevant evidence has been taken into account?** Abbott does not consider that all the relevant evidence has been taken into account. In particular, it appears that Janssen-Cilag did not use the full set of available PASI response outcomes for adalimumab in their model. Table 6.6.2a of the manufacturer submission (page 63) indicates that PASI 50, PASI 75, and PASI 90 response rates were collected when reported. However several key	Comment noted. The Committee discussed the issues raised concerning the possible underestimation of the efficacy of adalimumab in the mixed treatment comparison and took these into account when making its decision. See FAD sections 4.7, 4.18.

Commentator	Comment	Response
	clinical efficacy outcomes for adalimumab are missing from this table including: • PASI 90 response rates for the adalimumab-treated and placebo-treated patients in the CHAMPION trial, and for placebo-treated patients in the M02-528 trial; and • PASI 50 response rates for adalimumab-treated and placebo-treated patients in CHAMPION and REVEAL, and for placebo-treated patients in M02-528. The reason for this omission is unclear, as PASI 50 and PASI 90 response outcomes from adalimumab trials were essential parameters for their model and were reported in the publicly-available Abbott submission to NICE (Abbott MS, pp. 63-71). The exclusion of these key data increases the uncertainty around the reported clinical efficacy estimates for adalimumab, as the evidence synthesis performed by Janssen-Cilag would need to apply imputation methods or other techniques to deal with the missing PASI 50 and PASI 90 data for patients in these clinical trials. Abbott believes that these inaccuracies need to be addressed in order to provide a more robust view of the cost-effectiveness of ustekinumab in comparison to current treatment options for patients with severe psoriasis. Abbott's concerns have been outlined in question 2 below.	
Abbott Laboratories	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** *2.1 The probabilities of response for PASI 50, 75 and 90 for adalimumab are incorrect and inconsistent with other similar analyses* In section 3.9 of the ACD (page 9), the details of the mixed treatment comparison used by the manufacturer to estimate the relative effectiveness of ustekinumab and the relevant comparators is discussed. This section states that the probability of response defined as at least a PASI 75 improvement was 59% for adalimumab. On page 78 of the manufacturer submission, Janssen-	Comments noted. The Committee discussed the issues raised concerning the possible underestimation of the efficacy of adalimumab in the mixed treatment comparison and took these into account when making its decision. See FAD sections 4.7, 4.18.

Commentator	Comment	Response
	Cilag attempts to qualify the reason why the estimated probability of response for adalimumab is lower than reported in the Abbott submission for TA146 as being because inappropriate WinBUGs code was used. On page 135 of the manufacturer submission, Janssen-Cilag goes on to state: "In the analysis presented in this submission, the fixed effect baseline has been used in preference as it does not require the strong assumption of exchangeability of baseline rates between studies required by the random effects baseline model. As a result of this change, in combination with the inclusion of additional studies in the mixed treatment comparison, the estimated efficacy rates among the comparators differ from those estimated in previous mixed treatment comparison analyses. Most notably, the estimated PASI 75 for adalimumab decreased from 67% in the adalimumab submission to 59% in this submission." Abbott requested Appendix 10 of the manufacturer submission, which contains the WinBUGs code and input values, to verify the data used to generate the probability of response estimates in the mixed treatment comparison. As outlined in section 1, Abbott believes that key clinical efficacy data for adalimumab was excluded from the mixed treatment comparison. Abbott was informed that this appendix was commercial in confidence and therefore could not verify the inputs, but instead has supplied evidence to show that the 59% probability of at least a PASI 75 response that Janssen-Cilag estimated is incorrect. The clinical data supporting at least a 67% probability of PASI 75 response are outlined in subsection 2.1.1. A comparison of all the previous mixed treatment comparisons in this area is presented in sub-section 2.1.2. This comparison shows that it is only the probability of responses for adalimumab that have changed considerably, which is inconsistent with using a different model and is more likely to be due to the omission of key data from the analysis. The impact of including the Gordon study of adalimumab, which does not meet Janssen-Cilag's study inclusion criteria for the mixed treatment comparison, is discussed in sub-section 2.1.3. Finally, the impact that the incorrect probability of	

Commentator	Comment	Response
	response for adalimumab has on the cost-effectiveness of ustekinumab vs. adalimumab is outlined in sub-section 2.1.4.	
	2.1.1 Clinical evidence for the PASI 75 response rate for adalimumab Adalimumab has been evaluated in two large placebo-controlled phase III trials for the treatment of psoriasis: • REVEAL - a double-blind, randomised, placebo-controlled trial in 1,212 patients. • CHAMPION - a double-blind, randomised, active (vs. methotrexate) and placebo-controlled, multinational trial in 271 patients. In REVEAL, 814 patients received 80 mg adalimumab at week 0, 40 mg adalimumab at week 1, and then 40mg adalimumab every other week; 398 patients received placebo. At week 16, 70.9% of patients administered adalimumab achieved at least a PASI 75 response compared to 6.5% in the placebo arm. In CHAMPION, 271 patients were randomised to receive either adalimumab, methotrexate or placebo in a 2:2:1 ratio. At week 16, 79.6% of patients administered adalimumab achieved at least a PASI 75 response from baseline, compared to 35.5% and 18.9% for the methotrexate and placebo arms, respectively. Section 3.9 of the ACD states that etanercept 50mg BIW and etanercept 25 mg BIW have a probability of PASI 75 response at week 12 of 52% and 39%, respectively. Abbott concedes that it is not possible to directly compare the effectiveness of etanercept and adalimumab when there are no head-to-head trials, however the three etanercept phase III trials in Woolacott's HTA of etanercept and efalizumab (with similar baseline characteristics to REVEAL) had a PASI 75 response rate of 34.0%, 34.2% and 29.8% for the 25mg etanercept BIW at week 12, and 49.4% and 49.5% for the 50mg etanercept BIW at week 12. Abbott considers that the results of the manufacturer's mixed treatment comparison lack face validity as adalimumab and etanercept have estimated probabilities of response for PASI 75 of 59% and 52%, respectively, when the results for the two large phase III adalimumab trials show that the	Comment noted. The Committee discussed the issues raised concerning the possible underestimation of the efficacy of adalimumab in the mixed treatment comparison and took these into account when making its decision. See FAD sections 4.7, 4.18.

Commentator	Comment	Response
	PASI 75 response rates are 70.9% and 79.6% and for 50mg etanercept BIW they are 49.4% and 49.5%. In order to summarise the effectiveness of adalimumab and ustekinumab a conventional fixed effects meta-analysis was conducted using the meta command in STATA software. In order to enable a comparison of the results with Janssen-Cilag's mixed treatment comparison, a phase II adalimumab trial (Gordon et al) was also included in this meta-analysis since it was included in Janssen-Cilag's analysis. Table 2.1.1.1 provides the PASI 75 response rates resulting from this meta-analysis. ***TABLE PROVIDED BUT NOT REPRODUCED HERE*** These data indicate that there is a large discrepancy between the adalimumab results from the conventional fixed effects meta-analysis and the results from the mixed treatment comparison submitted by Janssen Cilag. Similar discrepancies between the two analyses would be expected for PASI 50 and PASI 90 response rates. The discrepancy observed in table 2.1.1.1 is reinforced by recently published results from the BELIEVE study, a double-blind, randomised, phase III trial comparing adalimumab monotherapy vs. adalimumab + topical treatment (Calcipotriol/betamethasone) in 730 patients. The BELIEVE study was conducted to reflect daily clinical practice of treating severe psoriasis patients. In this respect inclusion criteria reflected national clinical and reimbursement guidelines, and patients with prior anti-TNF and other biologic experiences were allowed. Baseline PASI scores (19.5) were similar to those in REVEAL and the ustekinumab trials PHOENIX 1 and 2. A total of 730 patients were randomised in a 1:1 ratio to receive either adalimumab + vehicle control, or adalimumab + calcipotriol/betamethasone. At week 16, 71% of the adalimumab monotherapy group achieved at least a PASI 75 response and 65% of the adalimumab + topical treatment group also achieved at least a PASI 75 response. The results from BELIEVE suggest that adalimumab is an effective treatment of severe	

Commentator	Comment	Response
	psoriasis in patients who have failed multiple prior systemic therapies. The BELIEVE study could not be included in the meta-analysis as it was not a placebo controlled trial. However, given that both the meta analysis and the BELIEVE study estimate that around 71% of patients administered adalimumab achieve at least a PASI 75 response at week 16, Abbott considers that the estimated 59% probability of response from the mixed treatment comparison for adalimumab is incorrect.	
Abbott Laboratories	*2.1.2 Comparison of the previous mixed treatment comparisons* Janssen-Cilag states that as a result of using a fixed effects model and the inclusion of additional studies in the mixed treatment comparison, that the estimated efficacy rates among the comparators differ from those estimated in previous mixed treatment comparisons. Abbott accepts that the inclusion of the ACCEPT study will alter the probability of response for etanercept. However, no additional trials over and above those included in the previous mixed treatment comparisons were included in the ustekinumab analyses for the following agents: supportive care, infliximab, efalizumab or adalimumab. As such, the probability of response for these drugs should not differ too much between the different mixed treatment comparisons given that the same trials are used in each comparison to estimate the probability of response. Table 2.1.2.1 shows the probability of response from all the mixed treatment comparisons for those drugs that had no additional trials included in the ustekinumab analyses. Any of the estimates that differ by more than 5 percentage points have been highlighted. As can be seen from the table, the only probabilities that have differed by more than 5 percentage points are in the ustekinumab mixed treatment comparison for adalimumab. Abbott considers it odd that in the adalimumab single technology appraisal the mixed treatment comparison yielded very similar results to the previous two MTCs using the same methodology, and yet Janssen-Cilag's analysis resulted in similar results for supportive care, efalizumab and infliximab, but such large discrepancies for adalimumab.	Comment noted. The Committee discussed the issues raised concerning the possible underestimation of the efficacy of adalimumab in the mixed treatment comparison and took these into account when making its decision. See FAD sections 4.7, 4.18.

Commentator	Comment	Response
	TABLE PROVIDED BUT NOT REPRODUCED HERE Abbott has recreated the fixed effects mixed treatment comparison based on the Woolacott et al. code and the methodology described in the manufacturer submission. Data for weight based cohorts of ustekinumab treated patients in PHOENIX 1, PHOENIX 2, and ACCEPT was extracted from the manufacturer submission. The results are detailed in Table 2.1.2.2. It is clear to see from the results that at week 16 the probability of PASI 75 response for 40mg adalimumab is higher than reported in Janssen-Cilag analysis, but consistent with previous analyses. ***TABLE PROVIDED BUT NOT REPRODUCED HERE***	
Abbott Laboratories	*2.1.3 Impact of including the Gordon phase II study of adalimumab* On Page 16 of the Evaluation report, the ERG discuss the manufacturer's inclusion and exclusion criteria for the selection of studies for the systematic review and the mixed treatment comparison. Any study which has one or more arms of less than 50 participants was one of the exclusion criteria stipulated in the submission. The phase II Gordon study has one arm of 46 patients, yet Janssen-Cilag included this trial in the mixed treatment comparison estimating the probability of response for adalimumab. Abbott also included this trial in the mixed treatment comparison carried out for TA146 in order to be conservative. However, the problem with including this study is that it included patients with affected BSA ≥5% to enroll, and did not apply any minimum PASI, PGA or DLQI requirements at baseline. In a post-hoc analysis, Gordon et al. evaluated PASI 75 rates among the subset of M02-528 patients meeting the British Association of Dermatology (BAD) criteria for moderate-to-severe psoriasis Gordon et al. report that 42.2% and 65.4% of patients in the adalimumab every other week (EOW) and placebo cohorts of this study did not meet the BAD specifications for moderate-to-severe disease, respectively. Results from this study indicate that the overrepresentation of these less	Comment noted. The Committee discussed the issues raised concerning the possible underestimation of the efficacy of adalimumab in the mixed treatment comparison and took these into account when making its decision. See FAD sections 4.7, 4.18.

Commentator	Comment	Response
	severe psoriasis patients contributed to the lower response rates for adalimumab EOW observed in this trial compared to those observed in REVEAL or CHAMPION. Table 2.1.3.1 presents the considerably higher PASI 75 response rates demonstrated by adalimumab EOW patients in the moderate-to-severe psoriasis subgroup, compared to those observed for the entire adalimumab EOW cohort in Gordon et al. ***TABLE PROVIDED BUT NOT REPRODUCED HERE*** These data indicate that the inclusion of the Gordon study for patients of all levels of severity biases the estimation of comparative effectiveness for ustekinumab compared to adalimumab. Furthermore Janssen-Cilag state that trials with arms of less than 50 participants should not be included in the mixed treatment comparison. Abbott has re-run the mixed treatment comparison carried out for TA146 to estimate the probability of response for adalimumab excluding the Gordon study of lower severity patients. ***TABLE PROVIDED BUT NOT REPRODUCED HERE*** The results from the mixed treatment comparison excluding the Gordon et al. study show that the probability of at least a PASI 75 response for adalimumab increases from 68% to 70%.	
Abbott Laboratories	*2.1.4 Impact on the cost-effectiveness estimate of ustekinumab vs. adalimumab* Abbott considers that the incorrect estimates for the effectiveness of adalimumab have a critical impact on the ICER for ustekinumab vs. adalimumab. In section 3.15 of the ACD (Page 11) it states that adalimumab is dominated by ustekinumab. Yet all the data so far point to the fact that there has been an error in the input values used to generate the WinBUGs output that has led to a PASI 75 probability of response for adalimumab being 59% rather than 68% (alongside lower estimates for PASI 50 and PASI 90 response rates). If the correct probability of response for adalimumab is used	Comment noted. The Committee discussed the issues raised concerning the possible underestimation of the efficacy of adalimumab in the mixed treatment comparison and took these into account when making its decision. See FAD sections 4.7, 4.18.

Commentator	Comment	Response
	in the Janssen-Cilag economic model (68% rather than 59%), Abbott considers that ustekinumab will no longer dominate adalimumab and that ustekinumab will no longer be a cost effective use of NHS resources when compared incrementally to adalimumab. It is unclear why input values for the comparator drugs in the mixed treatment comparison have been marked commercial in confidence and included in additional appendices given that these form the basis of the cost-effectiveness estimates, and the trials and HTA reports on which these estimates are based have been published in full. To conclude, Abbott requests that the ustekinumab model be re-run with the correct probabilities of response for adalimumab and that the content of the final appraisal determination	
Abbott Laboratories	*2.2 Use of 16 week stopping rule for ustekinumab* In Section 1.2 of the ACD (Page 3), it states that ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16-weeks after starting treatment. In addition, in section 4.14 of the ACD the Committee noted that treatment response should be measured at 16 weeks for ustekinumab, rather than 12 weeks as defined for etanercept in TA103. However, on page 13 of the Evaluation Report, the ERG acknowledge that for ustekinumab the model uses 12 week trial data to reflect 16 week response rates, and it is assumed that the efficacy of ustekinumab does not decline between 12 weeks and 16 weeks. On page 109 of the manufacturer submission, Janssen-Cilag explains that: “The efficacy for ustekinumab at 16 weeks is assumed to be the same as at 12 weeks as per the primary outcome measure in the trials. We applied the 12-week efficacy in the analysis to accurately reflect the costs associated with the first two injections.” The primary endpoint for all three ustekinumab trials was measured at week 12, but the posology section of the SmPC states that consideration for discontinuation should be given in patients who have shown no response up to 28 weeks of treatment. Given the licence refers to a stopping rule at 28 weeks it is important to consider the cost-effectiveness of ustekinumab when the week 16 dose is administered in all patients, as dermatologists are most likely	Comment noted. The response to treatment should be assessed at 16 weeks before a third dose has been administered. This has been clarified in the FAD. See FAD section 4.19.

Commentator	Comment	Response
	to consider the 28 week stopping rule in the licence when making their treatment decisions. The inclusion of a week 16 dose will increase the cost of treatment for non-responders by £2,147. The impact of including this dose on the ICER for ustekinumab vs. standard care and vs. adalimumab should be assessed incorporating the results of Abbott's revised mixed treatment comparison incorporating ustekinumab data.	
Abbott Laboratories	*2.3 Patient weight mix* The mix of patients in the <100kg and >100kg categories is not adequately justified and appears to present an optimistic cost-effectiveness estimate for ustekinumab. In the base case analysis performed by Janssen-Cilag, cost-effectiveness estimates for ustekinumab are derived as a weighted average of the 45 mg and 90 mg doses under the assumption that 80% of patients receive ustekinumab 45 mg and 20% receive ustekinumab 90 mg, according to the estimated proportion of patients weighing >100 kg. However, the Janssen-Cilag submission does not provide adequate justification for the use of an 20% versus 80% breakdown of patients >100 kg versus ≤100 kg, which has significantly lower percentage of high weight patients compared to the patient mix reported in ustekinumab trials. To justify the 20% versus 80% patient mix, the submission indicates that the "estimate of the percentage of psoriasis patients who are over 100kg varies from 17% to 20% based on two database studies both conducted in the UK" (Janssen-Cilag MS, pg. 23). As a note, Abbott has not been provided with the corresponding Appendices 5 and 6 of the submission describing these observational studies as they have been marked commercial in confidence. However, we consider that these population-based analyses of psoriasis patients are unlikely to yield reliable estimates of the appropriate weight mix of the target population of ustekinumab and adalimumab, mainly due to the difficulty of identifying the relevant subset of psoriasis patients with moderate-to-severe disease activity in claims data. It is well-documented that patients with more severe psoriasis are at a greater risk for obesity than patients with mild psoriasis.	Comment noted. The Committee recognised that the proportion of patients >100kg in the trials was 30% not 20% as was used in the model. However, it considered that changing this assumption had minimal impact on cost effectiveness estimates. See FAD section 4.11.

Commentator	Comment	Response
	Thus, within the target population of moderate-to-severe psoriasis patients indicated for biologics, the true percentage of patients over 100 kg is very likely to be higher than the 17% to 20% measured within a general psoriatic population, but more consistent with the patient mix presented in ustekinumab trials. In the pooled population from PHOENIX 1, PHOENIX 2, and ACCEPT, 30.3% of patients weighed more than 100 kg at baseline (Janssen-Cilag Clarification Response, pg. 1). Therefore, a higher proportion of patients weighing over 100 kg appears to be a reasonable assumption given the reported baseline characteristics for patients enrolled in clinical trials of ustekinumab. It is notable that the Janssen-Cilag submission failed to consider a sensitivity analysis based on the patient mix in the ustekinumab trials, and also limited the univariate sensitivity analysis of the patient mix to one direction: an even lower of proportion of high weight patients (i.e., 6% and 17%; Janssen-Cilag MS, pg. 133). Since ustekinumab's response rate is higher in low-weight patients on 45 mg than high weight patients on 90 mg (74.7% vs. 68.7% for PASI 75; see Janssen-Cilag Excel Model), it is not surprising that this unconventional single direction sensitivity analysis in the Janssen-Cilag submission yielded even more favourable and, to our view, biased effectiveness and cost-effectiveness estimates for ustekinumab. To conclude, Abbott contends that the ustekinumab model should be re-run with a 30.3% proportion of patients in the >100kg category as minimising the proportion of patients in the >100kg category has an important impact on the estimated effectiveness and cost-effectiveness of ustekinumab versus adalimumab.	
Abbott Laboratories	*2.4 Adalimumab effectiveness on psoriatic arthritis comorbidity* One of the limitations of all the economic analyses to date is that treatment effect is only considered according to PASI response. It could be argued that improvements in the PASI score are not an ideal proxy for treatment response, particularly for patients with concomitant psoriatic arthritis (PsA) (approximately 18%-30% of psoriasis patients) where improvements in arthritis symptoms would	Comment noted. NICE can only make recommendations within the marketing authorisation. Ustekinumab is licensed for the treatment of plaque psoriasis. The appraisal has considered the cost effectiveness of ustekinumab for the treatment of plaque psoriasis and not psoriatic arthritis. No

Commentator	Comment	Response
	be expected with anti-TNF agents such as adalimumab, but not necessarily with other psoriasis treatments. The prevalence of PsA in the pooled population of PHOENIX 1, PHOENIX 2, and ACCEPT is 28% (Janssen-Cilag MS, pp. 33-34). Therefore, a comprehensive estimate of cost-effectiveness for ustekinumab versus comparator treatments for moderate-to-severe psoriasis would need to account for the differing effects of these therapies on PsA-related health utility. Psoriasis patients with PsA suffer from joint pain, stiffness, and reduced mobility, in addition to the physical discomfort and disfigurement caused by skin lesions. Health utility in this patient subgroup cannot be solely derived from DLQI, which largely reflects the impact of skin lesion on quality of life, because they are likely to show incremental utility gains from reductions in PsA severity. Efficacy measures indicating reduction in PsA severity and improvement in PsA-related quality of life, including American College of Rheumatology (ACR) and Health Assessment Questionnaire (HAQ) scores, would need to be factored into the model in order to account for differences in the effect of comparator treatments on PsA symptoms. If these efficacy measures were considered in health utility, the cost-effectiveness of ustekinumab relative to adalimumab would decrease. Table 2.4.1 below summarises the efficacy of ustekinumab and adalimumab on ACR response and HAQ scores reported in key clinical trials of either therapy among patients with PsA. At week 12, the rate of ACR 20 response was 15.5 percentage points higher among adalimumab-treated patients compared to ustekinumab-treated patients. The median reduction in HAQ at week 12 was greater by 0.125 points in adalimumab-treated patients, indicating additional improvement of symptoms on a scale of 0 to 3. ***TABLE PROVIDED BUT NOT REPRODUCED HERE*** Of note, the ustekinumab dosing regimen used in the Phase II trial published by Gottlieb et al. was more aggressive compared to the	changes to the FAD made.

Commentator	Comment	Response
	dosages used for psoriasis in PHOENIX 1, PHOENIX 2 or ACCEPT. In Gottlieb et al., PsA patients received ustekinumab 90mg or 63 mg every week for four weeks from week 0 to week 3, while patients in the three psoriasis trials received 90 mg or 45 mg at weeks 0 and 4 and then every 12 weeks thereafter. Thus, the week 12 ACR response rates reported for ustekinumab in Gottlieb et al. are based on twice the cumulative number of ustekinumab doses as recommended for psoriasis and do not include evidence of ACR response for the 45mg ustekinumab dose. ACR 20, 50 and 70 response rates may have been lower if the ustekinumab dosing regimen studied in the manufacturer's psoriasis submission was used. Given evidence of the greater efficacy of adalimumab to alleviate PsA symptoms compared to ustekinumab, as well as the high prevalence of PsA within the target population for the current submission and the substantial impact of PsA symptoms on quality of life21 , Abbott considers that the Janssen-Cilag model underestimates the true ICER of ustekinumab versus adalimumab among patients with moderate-to-severe psoriasis.	
Abbott Laboratories	*2.5 Issues relating to sensitivity analyses conducted* Although the manufacturer's submission reports that ustekinumab dominates adalimumab in the deterministic base case model, a detailed review of the cost-effectiveness analysis indicates that the apparent dominance of ustekinumab over adalimumab is not robust and that uncertainty has not been properly characterised in the model.	Comment noted. The Committee noted comments on the potential limitations of the probabilistic sensitivity analyses but considered that the overall approach to modelling adopted by the manufacturer was appropriate. See FAD section 4.10.
Abbott Laboratories	*2.5.1 Deterministic results for mean costs are contradicted by mean costs from Probabilistic Sensitivity Analysis* The mean costs of adalimumab and ustekinumab resulting from the deterministic analysis are reported in table 7.3.1 of the manufacturer submission. The deterministic analysis indicates that adalimumab is associated with an additional £45 when compared with ustekinumab. However, according to the probabilistic results reported in table 7.3.3 of the manufacturer submission, adalimumab is found to be associated with cost savings of £43 when compared to ustekinumab.	Comment noted. The Committee noted comments on the potential limitations of the probabilistic sensitivity analyses but considered that the overall approach to modelling adopted by the manufacturer was appropriate. See FAD section 4.10.

Commentator	Comment	Response
	TABLE PROVIDED BUT NOT REPRODUCED HERE Since the probabilistic analysis (PSA) results are based on 10,000 Monte Carlo simulations, these results should be considered to be more robust than the deterministic results. The conclusion reached by Janssen-Cilag that "ustekinumab is cheaper on average than adalimumab" (p127 Manufacturer Submission) cannot therefore be supported by the data presented in the manufacturer's submission.	
Abbott Laboratories	*2.5.2 Key parameters do not appear to vary in Probabilistic Sensitivity Analysis* The ERG report states that only three variables are stochastic in the PSA: utilities, treatment response and the proportion of people above 100kg (ERG report p74). The ERG acknowledged that as a result of the exclusion of several important variables, the PSA is inappropriate and does not show the true uncertainty of the model. However, the results of the Monte Carlo simulation do not even appear to fully represent the uncertainty in these three variables. In particular, Abbott has noticed that the costs associated with all treatments other than ustekinumab are the same in each of the 10,000 trials (MCResultsWe worksheet). Although costs have not been included as a stochastic variable in the PSA, treatment response rates have been included. Since the cost of visits is applied only to non-responders, the total cost associated with each treatment would be expected to change as the probability of non-response changes. It therefore appears that treatment response rates are not varied in the probabilistic sensitivity analysis.	Comment noted. The Committee noted comments on the potential limitations of the probabilistic sensitivity analyses but considered that the overall approach to modelling adopted by the manufacturer was appropriate. See FAD section 4.10.
Abbott Laboratories	*2.5.2 Key parameters do not appear to vary in Probabilistic Sensitivity Analysis* The ERG report states that only three variables are stochastic in the PSA: utilities, treatment response and the proportion of people above 100kg (ERG report p74). The ERG acknowledged that as a result of the exclusion of several important variables, the PSA is inappropriate and does not show the true uncertainty of the model. However, the results of the Monte Carlo simulation do not even	Comment noted. The Committee noted comments on the potential limitations of the probabilistic sensitivity analyses but considered that the overall approach to modelling adopted by the manufacturer was appropriate. See FAD section 4.10.

Commentator	Comment	Response
	appear to fully represent the uncertainty in these three variables. In particular, Abbott has noticed that the costs associated with all treatments other than ustekinumab are the same in each of the 10,000 trials (MCResultsWe worksheet). Although costs have not been included as a stochastic variable in the PSA, treatment response rates have been included. Since the cost of visits is applied only to non-responders, the total cost associated with each treatment would be expected to change as the probability of non-response changes. It therefore appears that treatment response rates are not varied in the probabilistic sensitivity analysis.	
Abbott Laboratories	*2.5.3 The patient weight mix is not varied over a sufficiently wide range* Although the proportion of patients >100kg was one of the two variables included in the PSA, the standard error for this weight adjustment was only 0.05. This means that 95% of the time, the proportion of patients with weight >100kg was between 20.4% and 19.6%. When compared with the 30.3% of patients weighing >100kg in the pooled population from PHOENIX 1, PHOENIX 2, and ACCEPT, the meaningfulness of such sensitivity analysis is questionable. Given the concerns raised by the ERG, and the issues outlined above, Abbott feels that the PSA outputs do not represent the uncertainty in the cost effectiveness of ustekinumab versus standard care and versus adalimumab.	Comment noted. The Committee recognised that the proportions of patients >100kg in the trials was 30% not 20% as was used in the model. However, it considered that changing this assumption had minimal impact on cost effectiveness estimates. See FAD section 4.11.
Abbott Laboratories	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** Abbott considers that the provisional recommendations are currently unsound because of concerns over the robustness of the estimated cost effectiveness of ustekinumab versus adalimumab based on suspected data input omissions in the mixed treatment comparison. Abbott requests that a detailed assessment by the ERG or Decision Support Unit is conducted for the reasons as to why a lower estimate of effectiveness for adalimumab has been ascertained from this mixed treatment comparison. Abbott asks that when the Committee	Comment noted. The Committee discussed the issues raised concerning the possible underestimation of the efficacy of adalimumab in the mixed treatment comparison and took these into account when making its decision. See FAD sections 4.7, 4.18.

Commentator	Comment	Response
	prepares its final recommendations that any confirmed data omissions are amended in the revised recommendations to accurately reflect the cost-effectiveness of ustekinumab vs. all the current treatment options for severe psoriasis.	
Abbott Laboratories	**Are there any equality related issues that may need special consideration?** Abbott is not aware of any equity related issues that may need special consideration in the preliminary recommendations.	Comments noted, no changes to the FAD required.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	2	In para 2.2 it should read injection site erythema, not infection site	Comments noted. The FAD has been amended accordingly.
NHS Professional 1	4	In hospital-based clinical practice, the PASI 10 and DLQI 10 standard for defining severe psoriasis is widely used and is at about the right level. As laid out above, the availability of an agent with a different mode of action to the anti-TNF group will be important, particularly in the long term management of severe psoriasis. Many of these severe patients require long term, even life-long therapy with systemic agents. Usually by the time they reach the biologicals, they have been treated with oral immunsuppressive and cytotoxic agents (MTX, CyA, hydroxycarbamide, fumarates) and often have developed contraindications to continued therapy - impaired renal or hepatic function. It seems likely that over long periods, it will be necessary to have a range of comparable but different therapeutic agents from which to choose. Ustekinumab is highly efficacious and will be a really valuable addition because of the different mechanism of action.	Comments noted, no changes to the FAD required.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional 1	6	There is an increasing trend to treating severe and even moderate psoriasis with combination therapy, e.g. combining low doses of two or even 3 drugs to get better control with fewer side effects. Therefore trials of combination therapies using ustekinumab and methotrexate, retinoids, hydroxycarbamide etc, should be udertaken.	Comments noted, no changes to the FAD made.