Abbott's response to the Appraisal Consultation Document of ustekinumab for the treatment of psoriasis

Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) prepared by the Committee for the appraisal of ustekinumab for the treatment of psoriasis. Abbott's detailed comments following the executive summary are set out under section headings containing the questions NICE asks consultees to comment on for the ACD.

Executive Summary

- **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.**
- **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.**

1. 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 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.

2. 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-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[1] 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 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[2,3,4,5] - a double-blind, randomised, placebo-controlled trial in 1,212 patients.
- CHAMPION[6,7,8,9,10] - 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[11,12,13] (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 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 2.1.1.1 Probabilities of PASI 75 response estimated in meta-analysis of RCT data for adalimumab and ustekinumab

Treatment/ Study	PASI 75 rates from fixed effects meta analysis. Estimate [95% CI]	Weight in fixed effects meta-analysis	Estimated probability from the mixed treatment comparison submitted by Janssen Cilag.
Adalimumab 40mg eow			
REVEAL	71% [68%, 74%]	82%	
CHAMPION	81% [72%, 87%]	14%	
Gordon et al.	53% [38%, 68%]	4%	
Fixed effects pooled estimate	**71.5% [68.7%, 74.3%]**		**58.6%**
Ustekinumab 45 mg (among patients ≤ 100 kg)			
PHOENIX 1	74% [67%, 80%]	28%	
PHOENIX 2	73% [68%, 78%]	48%	
ACCEPT	72% [65%, 79%]	24%	
Fixed effects pooled estimate	**73.2% [69.7%, 76.7%]**		**74.7%**

Ustekinumab 90 mg (among patients > 100 kg)			
PHOENIX 1 PHOENIX 2 ACCEPT	69% [59%, 78%] 71% [63%, 79%] 65% [56%, 74%]	29% 40% 31%	
Fixed effects pooled estimate	**68.5% [63.3%, 73.6%]**		**68.7%**

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[14] 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 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.

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.

Table 2.1.2.1: Comparison of the probabilities of response in differing mixed treatment comparisons

	Mean Probability of response (%)			
	Woolacott et al[15]	**Infliximab STA**	**Adalimumab STA**	**Ustekinumab STA**
PASI 50				
Supportive care/ placebo	14%	14.3%	15%	13%
Efalizumab 1mg/kg	55%	55.6%	54%	51%
Infliximab	93%	94%	94%	93%
Adalimumab	-	-	86%	**81%**
PASI 75				
Supportive care/ placebo	3%	4%	5%	4%
Efalizumab 1mg/kg	27%	29%	29%	26%
Infliximab	79%	81%	81%	80%
Adalimumab	-	-	67%	**59%**
PASI 90				
Supportive care/ placebo	0%	0.5%	1%	1%
Efalizumab 1mg/kg	8%	9.4%	10%	8%
Infliximab	52%	54%	55%	54%
Adalimumab	-	-	37%	**30%**

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 2.1.2.2: Re-run of the mixed treatment comparison based on Woolacott's original model using fixed effects and including the ustekinumab clinical trial results

Treatment	Probability of a Response		
	Mean	2.50%	97.50%
PASI 50 Response			
Supportive Care	13.9%	12.1%	15.9%
Etanercept 50 mg BIW	77.1%	73.5%	80.9%
Etanercept 25 mg BIW	63.1%	57.4%	69.0%
Efalizumab 1 mg/kg	52.9%	48.6%	57.2%
Infliximab 5 mg/kg	93.3%	91.1%	95.3%
Methotrexate	59.1%	47.2%	69.3%
Ciclosporin 5 mg/kg/day	76.5%	57.3%	89.0%
Ciclosporin 3 mg/kg/day	58.5%	42.4%	74.3%
Adalimumab 40 mg EOW	86.2%	82.6%	89.1%
Ustekinumab 45 mg	89.9%	87.3%	92.3%
Ustekinumab 90 mg	86.9%	83.3%	90.2%
PASI 75 Response			
Supportive Care	4.3%	3.6%	5.2%
Etanercept 50 mg BIW	54.5%	49.9%	59.6%
Etanercept 25 mg BIW	38.4%	32.8%	44.6%
Efalizumab 1 mg/kg	28.8%	25.3%	32.7%
Infliximab 5 mg/kg	80.8%	76.3%	85.2%
Methotrexate	34.6%	24.1%	45.0%
Ciclosporin 5 mg/kg/day	54.5%	32.7%	72.5%
Ciclosporin 3 mg/kg/day	34.4%	20.5%	50.9%
Adalimumab 40 mg EOW	67.7%	62.1%	72.6%
Ustekinumab 45 mg	74.0%	69.5%	78.5%
Ustekinumab 90 mg	68.8%	63.2%	74.5%
PASI 90 Response			
Supportive Care	0.6%	0.5%	0.8%
Etanercept 50 mg BIW	25.4%	21.7%	29.8%
Etanercept 25 mg BIW	14.3%	11.1%	18.2%
Efalizumab 1 mg/kg	9.1%	7.4%	11.1%
Infliximab 5 mg/kg	53.9%	47.7%	60.6%
Methotrexate	12.2%	6.9%	18.3%
Ciclosporin 5 mg/kg/day	26.2%	11.1%	42.8%
Ciclosporin 3 mg/kg/day	12.3%	5.5%	22.7%
Adalimumab 40 mg EOW	37.7%	32.0%	43.0%
Ustekinumab 45 mg	44.9%	39.6%	50.6%
Ustekinumab 90 mg	38.9%	33.0%	45.3%

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[16]. 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 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 2.1.3.1. PASI 75 Response Rates in M02-528 among Moderate-to-Severe Patients and All Randomised Patients

Patient Population/Treatment Arm	PASI 75 Response Rate at Week 12
Moderate-to-Severe Patients* (Gordon et al.)	
Adalimumab EOW (N=26)	69%
Placebo (N=18)	0%
All Randomised Patients (Gordon et al.)	
Adalimumab EOW (N=45)	53%
Placebo (N=52)	4%

*Moderate-to-severe psoriasis defined by baseline PASI ≥ 10 and baseline DLQI > 10.

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 2.1.3.2: Re-run of the mixed treatment comparison used in the adalimumab STA submission with a fixed effects model and excluding the adalimumab Gordon et al study

Treatment	Probability of a Response		
	Mean	2.50%	97.50%
PASI 50 Response			
Supportive Care	13.9%	12.2%	16.0%
Etanercept 50 mg BIW	77.0%	73.4%	80.8%
Etanercept 25 mg BIW	63.0%	57.2%	69.0%
Efalizumab 1 mg/kg	52.9%	48.7%	57.2%
Infliximab 5 mg/kg	93.3%	91.2%	95.2%
Methotrexate	60.7%	48.5%	70.9%
Ciclosporin 5 mg/kg/day	77.9%	58.8%	89.9%
Ciclosporin 3 mg/kg/day	58.4%	42.5%	74.2%
Adalimumab 40 mg EOW	87.3%	83.8%	90.1%
Ustekinumab 45 mg	89.8%	87.3%	92.3%
Ustekinumab 90 mg	86.9%	83.3%	90.2%
PASI 75 Response			
Supportive Care	4.3%	3.6%	5.2%
Etanercept 50 mg BIW	54.4%	49.7%	59.5%
Etanercept 25 mg BIW	38.2%	32.7%	44.6%
Efalizumab 1 mg/kg	28.8%	25.3%	32.6%
Infliximab 5 mg/kg	80.7%	76.5%	85.0%
Methotrexate	36.2%	25.1%	46.7%
Ciclosporin 5 mg/kg/day	56.3%	34.1%	73.9%
Ciclosporin 3 mg/kg/day	34.2%	20.6%	50.8%
Adalimumab 40 mg EOW	69.6%	63.8%	74.4%
Ustekinumab 45 mg	74.0%	69.5%	78.6%
Ustekinumab 90 mg	68.8%	63.2%	74.5%
PASI 90 Response			
Supportive Care	0.6%	0.5%	0.8%
Etanercept 50 mg BIW	25.3%	21.7%	29.6%
Etanercept 25 mg BIW	14.2%	11.0%	18.1%
Efalizumab 1 mg/kg	9.1%	7.5%	11.1%
Infliximab 5 mg/kg	53.8%	48.0%	60.3%
Methotrexate	13.1%	7.4%	19.7%
Ciclosporin 5 mg/kg/day	27.7%	11.7%	44.7%
Ciclosporin 3 mg/kg/day	12.2%	5.5%	22.5%
Adalimumab 40 mg EOW	39.7%	33.6%	45.2%
Ustekinumab 45 mg	44.8%	39.5%	50.6%
Ustekinumab 90 mg	38.9%	33.1%	45.2%

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%.

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 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 reflects these revised cost-effectiveness estimates for ustekinumab versus adalimumab.

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 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.

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.[17,18] 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.

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 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[19,20]. 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 2.4.1. ACR Response Rates in Clinical Trials of Adalimumab and Ustekinumab for PsA

Week 12 Response	Gottlieb et al. (2009)		ADEPT	
	Ustekinumab 90/63mg EW week 0-3 (N=76)	Placebo (N=70)	Adalimumab 40 mg EOW (N=151)	Placebo (N=162)
ACR 20 (%)	42.1	14.0	57.6	14.2
ACR 50 (%)	25.0	7.0	36.4	3.7
ACR 70 (%)	10.5	0.0	19.9	0.6
Median reduction in HAQ	0.25	0	0.375	0

Of note, the ustekinumab dosing regimen used in the Phase II trial published by Gottlieb et al. was more aggressive compared to the 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 life[21], Abbott considers that the Janssen-Cilag model underestimates the true ICER of ustekinumab versus adalimumab among patients with moderate-to-severe psoriasis.

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.

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.

Table 2.5.1.1 Mean Costs reported in manufacturer submission

	Adalimumab	Ustekinumab	Incremental cost (adalimumab vs. ustekinumab)
Deterministic analysis	£4,660	£4,615	£45
Probabilistic analysis	£4,536	£4,579	-£43

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.

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.

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.

3. 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 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.

4. 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.

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National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Ustekinumab for the treatment of moderate to severe psoriasis

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by **Janssen-Cilag**. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Acknowledgement and Undertaking Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. You must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

May 2009

Issue 1 Probabilities of response for PASI 50, 75 and 90 are incorrect and inconsistent with other similar analyses

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
As outlined in section 1 of Abbott's response to the ACD, the probabilities of response for PASI 50, 75 and 90 for adalimumab do not appear to have been based on all of the available evidence, and are therefore incorrect and inconsistent with other similar analyses	Re-run MTC using all available efficacy inputs for adalimumab Abbott has repeated the mixed treatment comparison conducted by Janssen-Cilag to all of the available evidence for adalimumab (see section 2.1.2 of Abbott's response to the ACD for further details). The weight based Winbugs output included in the ustekinumab cost-effectiveness model were replaced with the weight based Winbugs outputs from this MTC and the cost-effectiveness analysis was re-run. The Winbugs output used in this analysis is provided in the excel spreadsheet included in Abbott's response.	ustekinumab vs adalimumab: £97,155 per QALY ustekinumab vs supportive care: £30,331 per QALY

Issue 2 The phase II Gordon study should not have been included in the MTC

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
As outlined in section 2.1.3 of Abbott's response to the ACD, Janssen-Cilag included a phase II study of adalimumab (Gordon et al.) 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	Re-run MTC excluding Gordon The MTC described above was re-run with the Gordon study removed. The Winbugs output used in this analysis is provided in the excel spreadsheet included in Abbott's response.	ustekinumab vs adalimumab: £186,868 per QALY ustekinumab vs supportive care: £30,362 per QALY

estimation of comparative effectiveness of ustekinumab compared to adalimumab. less severe psoriasis population than is being considered in this appraisal		

Issue 3 The proportion of patients assumed to weigh >100kg is unlikely to represent the weight mix of the target population

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
As outlined in section 2.3 of Abbott's response to the ACD, the mix of patients in the <100kg and >100kg weight categories is unlikely to represent the weight mix of patients in the moderate to severe psoriasis population. The manufacturer failed to adequately investigate the impact of the weight mix assumption in sensitivity analysis	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). The model was therefore re-run using this weight mix. This amendment was conducted in the same version of the model in which the incorrect adalimumab response rates were corrected (as outlined in issue 1).	ustekinumab vs adalimumab: £114,277 per QALY ustekinumab vs supportive care: £30, 451 per QALY

Issue 4 The 16 week stopping rule used in the manufacturer submission is not in line with the ustekinumab license

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
As outlined in section 2.2 of Abbott's response to the ACD, the ustekinumab licence indicates that consideration for stopping ustekinumab should be given for patients not responding at 28 weeks	In line with the product license, the model was re-run assuming 3 doses of ustekinumab during the trial period (week 0, week 4 and week 16). This amendment was conducted in the same version of the model in which the incorrect adalimumab response rates were	ustekinumab vs adalimumab: £452,081 per QALY ustekinumab vs supportive care: £35,025 per QALY

Dermatologists are most likely to consider the 28 week stopping rule in the licence when making their treatment decisions	corrected (as described in issue 1).	

Issue 5 Treatment response is not included in the probabilistic sensitivity analysis (PSA)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
As a result of their PSA, the manufacturer submission reported that ustekinumab was the only biologic to be cost-effective (p30 manufacturer submission). Given that the 95% confidence intervals for ustekinumab 45mg and adalimumab overlap, this conclusion lacks face validity. Although the manufacturer submission states that the probability of PASI 50, 75 and 90 response is included in the probabilistic sensitivity analysis, it appears that this is not in fact the case. Since treatment effectiveness is a key input into any cost-effectiveness model, failure to include this variable in the PSA is a major flaw in the analysis.	In order to test the hypothesis that treatment response rates are not included in the PSA, the other variables included in the PSA (weight adjustment and utilities) were set to equal the deterministic value. On the Parameters worksheet, cells C10, C62, C63, and C66-C69 were set equal to the corresponding cell in column D. The Run PSA button on the “Main” worksheet was then selected.	The MCResultsWe worksheet shows the results of the 10,000 Monte Carlo simulations. In this analysis, the costs and QALYs for each of the treatment options are exactly the same in each simulation. This analysis therefore indicates that treatment effectiveness is not included in the PSA. The only variables included are therefore weight adjustment (which as indicated in section 2.5.3 of Abbott’s response to the ACD has not been varied within a meaningful range), and the utilities.

(please cut and paste further tables as necessary)