Schering-Plough Ltd
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW

Tel: 01707 363636
Fax: 01707 363690

Ms Natalie Bemrose
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

September 18th 2007

Dear Ms Bemrose

RE: Appraisal Consultation Document: Infliximab for the treatment of adults with psoriasis:

Schering-Plough welcomes the opportunity to comment on the Appraisal Consultation Document ("ACD") on infliximab for the treatment of adults with psoriasis. The Appraisal Committee's ("the Committee") preliminary recommendation is that it "*is minded not to recommend infliximab within its licensed indication for the treatment of adults with moderate to severe plaque psoriasis*".

Schering-Plough considers that this preliminary recommendation is unfair and perverse. We believe the Committee failed to take adequate account of important benefits associated with infliximab for patients with severe psoriasis in need of a more rapid and longer-lasting treatment response compared with other TNF-α inhibitors. Further, the Committee's interpretation of the evidence is inconsistent with technology appraisal number 103 on etanercept and efalizumab for the treatment of adults with psoriasis ("TA103").

Schering-Plough is pleased to note that the Committee appears to recognize that infliximab represents the most clinically effective treatment option for patients with severe psoriasis. Infliximab's clinical effectiveness translates into important and meaningful benefits to patients. Approximately two-thirds of patients (65.9%) treated with infliximab in the EXPRESS clinical trial achieved a Dermatology Life Quality Index score of 0 or 1, indicating that psoriasis had 'no effect' on their health related quality of life following treatment.[1] These data underscore the view that infliximab is the most effective treatment option and will deliver significant benefits to patients with severe psoriasis. Schering-Plough has modeled the benefits of infliximab compared to alternative biologic treatment options using an established framework that demonstrates infliximab to be cost-effective in severe psoriasis.

Since the Institute had already published guidance for the NHS in relation to the use of the biologics etanercept and efalizumab in psoriasis, Schering-Plough replicated the approach used by the independent assessment group for this appraisal. On this basis, infliximab was demonstrated to be a cost-effective treatment option for patients with severe psoriasis, defined as a Psoriasis Area Severity Index (PASI) score of 10 or more and a DLQI score of greater than 10. It is therefore Schering-Plough's view that the Committee's preliminary recommendation reflects an unreasonable interpretation of the evidence.

In response to the Appraisal Committee's requests for clarification, Schering-Plough has provided additional data as well as further clarification regarding its interpretation of both the decision-problem for

1 K. Reich, F.O. Nestle, K. Papp, Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. Br J Dermatol. 2006 Jun;154(6):1161-8.

this appraisal and the existing recommendations for biologics based on TA103. These additional data further establish the evidence base to demonstrate that biologic treatment should be targeted at patients with severe psoriasis where the benefits associated with treatment are greatest.

However, even in the absence of this additional data, Schering-Plough believes that the cost-effectiveness case for infliximab is compelling. Using the same model framework and utility data for patients with low quality of life and a high probability of being hospitalized, which informed a recommendation to use etanercept in patients with severe psoriasis, the incremental cost-effectiveness ratio for infliximab is approximately £26,095 per QALY. In light of this evidence, a recommendation not to use infliximab for patients with severe psoriasis would be inconsistent with previous guidance and perverse.

Schering-Plough believes that the evidence clearly supports a recommendation for infliximab in the treatment of severe psoriasis, as defined in accordance with the British Association of Dermatology Guidelines and the clinical literature i.e. PASI≥10 and DLQI>10. Infliximab is most widely used in clinical circumstances requiring rapid disease control[2] due to its very rapid onset of action and high response rate. These circumstances frequently relate to particular groups of patients with severe psoriasis e.g. those with rapidly progressing disease, highly visible psoriasis, nail psoriasis and those patients requiring hospitalisation. In order to preserve the ability of clinicians to target infliximab appropriately in these patient categories, alternative definitions of severity for the purposes of recommendations for infliximab should be avoided.

The Committee also recommended that the National Institute for Health and Clinical Excellence ("NICE") requests further clarification from Schering-Plough on three principal points. Our response to this request is set out below, together with our detailed response to the ACD and our comments on the Evidence Review Group ("ERG") report.

Schering-Plough requests that the Committee reconsiders its preliminary recommendations for infliximab in light of our responses to the ACD and ERG report and the further clarifications provided pursuant to its requests below. We do not believe that the current draft recommendations are in the best interests of patients with psoriasis, nor do they provide for efficient use of NHS resources. We are confident, however, that following a review of our responses that the Committee will establish guidance allowing adults with severe psoriasis to benefit from treatment with infliximab.

S-P's response is structured into three sections:

I. Issues for clarification
II. Response to ACD content
III. Comments on ERG report

2 Smith C.H., Anstey A.V., Barker J.N.W.N, Burden A.D., Chalmers R.J.G., Chandler D., Finlay A.Y., Grifitths C.E.M., Jackson K., McHugh N.J., McKenna K.E., Reynolds N.J., Ormerod A.D.. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. British Journal of Dermatology 2005 153, pp486–497.

I. ISSUES FOR CLARIFICATION

Utilities: The impact on cost effectiveness of infliximab compared with all relevant comparators of the use of alternative assumptions for the utilities assigned to the health states in the submitted economic model for the patient group defined as those with a PASI score of at least 10 and a DLQI score greater than 10. The utilities should be based on the short-form 36 (SF-36) data collected in the EXPRESS randomised controlled trial (RCT).

In Schering-Plough's original submission, estimates of cost-effectiveness for infliximab in psoriasis were derived using utility estimates from HODaR that had previously been used to support Guidance from the Institute for etanercept and efalizumab (TA103). It remains the view of S-P, as stated in our letter of clarification (June 5th 2007) that these utility estimates are in line with the Institute's 'reference case'. They are therefore the appropriate utility estimates to be used for this review. There are two principal reasons for this.

Firstly the utility estimates from the HODaR database were derived using the EQ-5D instrument which is explicitly stated to be the preferred approach in the Institute's Guide to the Methods of Technology Appraisal (Ref N0515). Section 5.3.5 states: *"It is well established that different classification systems do not give consistent utility values to the same health states and hence results from the use of different systems cannot always be compared. Given the comparative nature of the Institute's work and the need for consistency across appraisals, the Institute would ideally wish that all appraisals used the same system. Currently, the most appropriate choice in the UK appears to be the EQ-5D."*

Secondly, and as stated in the same section of the Methods Guide, the Institute is keen to pursue consistency in its work across appraisals. Given that utility estimates using EQ-5D supported the development of recommendations for etanercept and efalizumab in TA103, recommendations for infliximab in this Single Technology Appraisal would be best informed by comparable utility data.

Notwithstanding these points of concern, SF-36 data are available for infliximab in psoriasis from the EXPRESS clinical trial and as suggested in the ERG report and the ACD these data may be used to estimate utilities. In order to estimate utilities from the EXPRESS trial that are as close to the Institute's reference case as possible, SF-36 scores for patients at baseline and week 10 have been converted to EQ-5D utilities using a published algorithm.[3] EQ-5D utilities were mapped against DLQI and are presented as utility gains for each PASI response category in Table 1 below. Utility gains from HODaR as per Schering-Plough's original submission are presented alongside for comparison.

Table 1 Utility estimates

Gains in utility (se) by PASI response category				
PASI Response Category	All patients* (HODaR)	PASI≥10, DLQI>10 (EXPRESS)	4th Quartile DLQI* (HODaR)	4th Quartile DLQI** (EXPRESS)
<50	0.05 (0.01)	[redacted]	0.12 (0.03)	[redacted]
≥50 and <75	0.17 (0.04)	[redacted]	0.29 (0.06)	[redacted]
≥75 and <90	0.19 (0.04)	[redacted]	0.38 (0.08)	[redacted]
≥90	0.21 (0.05)	[redacted]	0.41 (0.09)	[redacted]
***severity not defined; **DLQI>18**				

In addition to estimating utilities from the EXPRESS trial, Schering-Plough has derived a pooled mean estimate, combining utility estimates from EXPRESS with those derived from HODaR. Given the shortcomings associated with using the SF-36, and notably the potential for a "floor effect", it would be

[3] Rowen D, Psarras F, Brazier J, and Roberts J. Mapping SF-36 onto the EQ-5D index: how stable is the relationship? Oral presentation at the 6th IHEA World Conference Copenhagen, July 8-11th, 2007.

appropriate to use the data from EXPRESS to supplement the evidence included in Schering-Plough's original submission rather than replace it.

Schering-Plough has used the available utility estimates from EXPRESS to re-calculate cost-effectiveness estimates for infliximab against all relevant comparators. These results are presented in Table 2 below alongside the original estimates from Schering-Plough's submission and estimates based on the pooled mean utilities.

Table 2 Incremental cost-effectiveness ratios (ICER) by base case (HODaR), EXPRESS and pooled mean estimates of utility gain for all relevant comparators

	Base case (Schering-Plough submission)		**EXPRESS (EQ-5D)**		**Pooled mean estimate**	
	All patients	4th quartile DLQI	PASI≥10, DLQI>10	4th quartile DLQI	PASI≥10, DLQI>10	4th quartile DLQI
supportive care	£40,281	£21,671	£37,169	£28,271	£37,752	£24,527
etanercept 25mg BIW intermittent	£62,032	£33,155	£55,739	£40,484	£56,559	£38,848
efalizumab 1mg/kg	£46,380	£24,947	£42,218	£30,776	£42,766	£29,402
etanercept 25mg BIW continuous	£48,887	£26,095	£43,927	£31,905	£44,574	£30,616
etanercept 50mg BIW	£2,860	£1,519	£2,563	£1,809	£2,617	£1,732
Principal comparator from manufacturer's submission is highlighted for clarity.						

The utility estimates from the EXPRESS clinical trial and their corresponding cost-effectiveness estimates confirm the overall trend reported in Schering-Plough's submission and in TA103. That is to say, treatment of patients with lowest baseline quality of life and high probability of hospitalization is most cost-effective. Using utility estimates from the EXPRESS clinical trial we estimate that the ICER (vs continuous etanercept) for infliximab in severe psoriasis (PASI≥10, DLQI>10) patients is £43,927. In line with TA103 and Schering-Plough's submission we have also estimated ICERs for patients with low baseline quality of life (4th quartile DLQI, DLQI>18) who are at highest risk of hospitalization. In this group the ICER is £31,905. Whilst the ICER for patients with low quality of life at baseline is somewhat higher than that estimated using HODaR utilities, consideration of the combined evidence from both sources suggests that infliximab is highly likely to be cost-effective for patients in this group.

It is important to consider why estimates of utility gain for patients with lowest baseline quality of life (4th quartile DLQI) observed in the EXPRESS clinical trial are generally lower than those observed in HODaR. Comparison of the distribution of baseline utility scores in the two sources suggests that the differences in utility gain may be explained to some extent by the presence of a floor effect in the SF-36 data and this warrants further investigation. The distribution of baseline utilities (EQ-5D) against DLQI reported in TA103 shows the presence of particularly low scores and 'extreme values' (i.e. <0) consistent with the view that the most severe psoriasis is associated with extreme impairment to quality of life.[4] In contrast, these low utility values at baseline are notably absent from the EXPRESS clinical trial data. The absence of low utility values in the EXPRESS trial may be explained by a number of factors. First, as noted above, the SF-36 has been reported to exhibit floor effects in a number of chronic diseases.[5,6] Secondly, whilst HODaR reflects the utilities of patients in real clinical practice, the EXPRESS clinical trial utilities reflect a population subject to specific inclusion and exclusion criteria.

[4] S.R. Feldman, K.B. Gordon, M. Bala, R. Evans, S.Li, L.T. Dooley, C. Guzzo, K. Patel, A. Menter and A.B. Gottlieb, Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo-controlled trial. British Journal of Dermatology 2005 152, pp 954–960.

[5] J A Freeman, J C Hobart, D W Langdon and A J Thompson Clinical appropriateness: a key factor in outcome measure selection: the 36 item short form health survey in multiple sclerosis J. Neurol. Neurosurg. Psychiatry 2000;68;150-156

The combined effect of both these factors is to significantly underestimate the utility gain on treatment where only utilities from the EXPRESS trial are relied upon. Therefore, Schering-Plough argues that cost-effectiveness estimates based on utility estimates from the EXPRESS clinical trial alone are likely to reflect an underestimation of the benefit of treating patients with severe psoriasis.

Infusion costs: The impact on the cost-effectiveness analysis of infliximab compared with all relevant comparators of increasing the costs of administering infliximab infusions to better reflect clinical practice. This should take account of the difference in cost between a standard outpatient appointment and an appointment for an infliximab infusion.

Our model was adjusted to take into account the costs of administration of etanercept and efalizumab, during the 'trial period', as per the York Assessment report. A range of infusion costs have been used for the cost of administering infliximab. We applied a cost of £78.20 per infusion was applied to the model as this was the cost of administering infliximab that was used in the York Assessment report for the use of etanercept and efalizumab for the treatment of psoriasis. We also applied a cost of £124 per infusion was also applied, as a higher value, as this is the cost that was used in the Assessment report for rheumatoid arthritis.[7] The ICERs for infliximab compared to all the standard comparators are presented in the Table 3 below.

Table 3 Incremental cost-effectiveness ratios for different administration costs (HODaR utilities)

	ICER 'all patients' (base case £65.02)	ICER 4th quartile DLQI (base case £65.02)	ICER 'all patients' (£78.20 per infusion)	ICER 4th quartile DLQI (£78.20 per infusion)	ICER 'all patients' (£124 per infusion)	ICER 4th quartile DLQI (£124 per infusion)
supportive care	£40,281	£21,671	£42,049	£22,615	£44,475	£23,920
etanercept 25mg intermittent	£62,032	£33,157	£62,645	£33,483	£66,952	£35,785
efalizumab 1mg/kg	£46,380	£24,947	£46,915	£25,235	£50,676	£27,258
etanercept 25mg continuous	£48,887	£26,095	£49,484	£26,448	£53,790	£28,750
etanercept 50mg	£2,860	£1,519	£3,744	£1,988	£9,953	£5,284

Table 4 Incremental cost-effectiveness ratios associated with different administration costs (EXPRESS utilities)

	ICER PASI≥10, DLQI>10 (£65.02 per infusion)	ICER 4th quartile DLQI (£65.02 per infusion)	ICER PASI≥10, DLQI>10 (£78.20 per infusion)	ICER 4th quartile DLQI (£78.20 per infusion)	ICER PASI≥10, DLQI>10 (£124 per infusion)	ICER 4th quartile DLQI (£124 per infusion)
supportive care	£38,016	£29,057	£38,783	£29,510	£41,020	£31,212
etanercept 25mg intermittent	£55,739	£40,484	£56,290	£40,884	£60,159	£43,695
efalizumab 1mg/kg	£42,218	£30,776	£42,705	£31,131	£46,128	£33,626
etanercept 25mg continuous	£43,927	£31,905	£44,464	£32,295	£48,333	£35,105
etanercept 50mg	£2,563	£1,809	£3,354	£2,368	£10,190	£6,294

In conclusion, Schering-Plough acknowledges that there is some uncertainty in relation to the cost associated with the administration of infusions. However, we would argue that the range of costs

[6] R Harper, JE Brazier, JC Waterhouse, et al. Comparison of outcome measures for patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. Thorax 1997;52;879-887

[7] A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness, West Midlands HTA Collaboration, October 2005.

presented here, which have been derived from previous independent technology appraisals, is an appropriate reflection of the real cost to the NHS associated with the delivery of infusions.

Furthermore, any uncertainty regarding the cost of administration of infusions should be considered in the context of the overall cost of infliximab to the NHS. As the Committee is aware, the NHS is increasingly required to be efficient in its use of resources. In relation to infliximab, this requirement is reflected by the practice of vial optimization, which aims to minimize the unnecessary waste of excess drug. Where vial optimization is in place, costs associated with infliximab are likely to be substantially lower than in the modeled scenarios presented, which assume whole vial units and wastage of any excess drug. Schering-Plough believes that the practice of vial optimization and attributable cost-savings are an important consideration alongside costs of administration.

The decision problem: The estimated cost-effectiveness, using the adjusted model resulting from the two previous bullet points, in a subgroup of patients with severity of disease equivalent to the 4th quartile dermatology life quality index (DLQI) population used in the submitted economic model. This should give consideration to the generalisability of the clinical results from the patient group defined as those with a PASI score of at least 10 and a DLQI score greater than 10 to the 4th quartile group.

In Schering-Plough's definition of the decision problem and subsequent submission, severe psoriasis was defined by PASI≥10 and DLQI>10, according to the definition in Guidance TA103 for etanercept and efalizumab for the treatment of psoriasis. Estimates of cost-effectiveness addressing this decision problem were presented using the 4th quartile DLQI population. Whilst we agree that the PASI≥10, DLQI>10 and 4th quartile DLQI populations are not identical, Schering-Plough considers this approach to be entirely consistent with that taken by the Committee for TA103, in which etanercept and efalizumab were considered unlikely to be cost-effective except for those patients with lowest baseline quality of life and high probability of hospitalisation (TA103 section 4.2.4.2).

In TA103 an ICER of £65,320 is presented for the 'all patient' population comparing etanercept 25mg BIW intermittent and supportive care. This ICER was derived using the 'all patient' utilities from HODaR. The results of alternative scenarios are described, including a scenario that *'considered both poor quality of life and hospitalisation for non-responders'.* This refers to scenario III in the York assessment report, page 151 (section 6.3.5), in which cost-effectiveness is estimated *'for patients with worst quality of life (4th quartile DLQI) at baseline and assuming patients not responding to therapy are hospitalised for 21 days per year'*. In this scenario the ICER for intermittent etanercept 25mg BIW was £14,460 per QALY gained (Psoriasis Review Addendum: Table 6.3.10). In section 4.3.5 of TA103 the Committee concluded *'it was unlikely that these interventions would be cost-effective except in people who had very poor quality of life and who would be likely to require hospital admission for treatment'.*

Our understanding is that the Committee's conclusions regarding scenarios where etanercept 25mg BIW intermittent was likely to be cost-effective relate explicitly to the evidence in terms of cost-effectiveness for the 4th quartile DLQI population. Having accepted that etanercept was likely to be cost-effective in patients with very poor quality of life and who would be likely to require hospital admission for treatment, the Committee made use of clinical expert opinion suggesting that these people (i.e. very poor quality of life and requiring hospital admission for treatment) would be those with severe disease as defined by a PASI≥10 and DLQI>10 (section 4.3.5 TA103). This definition of severity is the basis on which patients are selected for treatment with etanercept according to the Guidance in section 1.1 (TA103). On this basis Schering-Plough accordingly presented evidence for the cost-effectiveness of infliximab in patients with severe psoriasis (PASI≥10, DLQI>10) using utility estimates for the 4th quartile DLQI as reported in TA103.

Cost-effectiveness estimates for the 4th quartile DLQI population as well as the PASI≥10, DLQI>10 population are presented in Table 5 and Table 6 . Results are presented using base case, EXPRESS and pooled utility estimates, as well as adjusted infusion costs.

Table 5 Incremental cost-effectiveness ratios for different utility estimates (£78.20 administration costs)

£78.20 infusion cost	HODaR utilities		EXPRESS (EQ-5D)		Weighted average	
	All patients	4th quartile DLQI	PASI≥10, DLQI>10	4th quartile DLQI	PASI≥10, DLQI>10	4th quartile DLQI
supportive care	£42,049	£22,615	£38,783	£29,510	£39,394	£27,885
etanercept 25mg BIW intermittent	£62,645	£33,483	£56,296	£40,884	£57,118	£39,232
efalizumab 1mg/kg	£46,915	£25,235	£42,705	£31,131	£43,260	£29,741
etanercept 25mg BIW continuous	£49,484	£26,448	£44,464	£32,295	£45,118	£30,990
etanercept 50mg BIW	£3,744	£1,988	£3,354	£2,368	£3,426	£2,268

Table 6 Incremental cost-effectiveness ratios for different utility estimates (£124 administration costs)

£124 infusion cost	HODaR utilities		EXPRESS (EQ-5D)		Weighted average	
	4th quartile DLQI	All patients	4th quartile DLQI	PASI≥10, DLQI>10	PASI≥10, DLQI>10	4th quartile DLQI
supportive care	£23,920	£44,475	£31,212	£41,020	£41,667	£29,494
etanercept 25mg BIW intermittent	£35,785	£66,952	£43,695	£60,159	£61,044	£41,929
efalizumab 1mg/kg	£27,258	£50,676	£33,626	£46,128	£46,727	£32,125
etanercept 25mg BIW continuous	£28,750	£53,790	£35,105	£48,333	£49,044	£33,687
etanercept 50mg BIW	£5,284	£9,953	£6,294	£8,917	£9,106	£6,028

The Committee requested that Schering-Plough give consideration to the generalisability of the clinical results from the patient group defined as those with a PASI≥10 and DLQI>10 to the 4th quartile DLQI group.

The results of the EXPRESS II trial, reported by Menter et al (2007), include an assessment of PASI 75 response at week 10 by baseline severity of disease. Baseline severity of disease is characterised by PASI score and percentage BSA involvement. 76 percent of patients with baseline PASI score ≥20 achieved a PASI 75 response compared to 70.9 percent of those patients with a PASI score <20 at baseline. Baseline percentage BSA involvement had no effect on treatment response with 72.9 percent of patients achieving PASI 75 response across both categories of BSA, <30 percent and ≥30 percent.

Therefore, from the evidence presented by Menter et al, it would appear reasonable to assume equivalence in terms of treatment effect for patients in both the 4th quartile DLQI and the PASI≥10 and DLQI>10 populations.

Further evidence is available from the EXPRESS clinical trial. PASI response rates are presented in Table 7 and Table 8 below for all patients and for the 4th quartile DLQI group. These data show that the clinical results observed for the all patient population are highly generalisable to those achieved in the low baseline quality of life group (4th quartile) with highly similar response rates for all categories of PASI response between these patient groups.

Table 7 All patients PASI response rates

	Treatment Placebo		Infliximab	
PASI	n=77	%	n=301	%
<50	71	92%	27	9%
50-75	4	8%	32	91%
75-90	1	3%	70	80%
>90	1	1%	172	57%

Source: Express Clinical trial, Schering-Plough, data on file.

Table 8 4th quartile PASI response rates

	Treatment Placebo	Infliximab
PASI		
<50		
50-75		
75-90		
>90		

Source: Express Clinical trial, Schering-Plough, data on file.

Schering-Plough notes that in section 4.8 of the ACD, the Committee stated that it *"was not persuaded that this very severe subgroup [4th quartile DLQI] had been sufficiently defined (in terms of DLQI at baseline)".* The Committee also noted that *"it was not clear from the data submitted what DLQI score would be used in practice to identify the severely affected group".* Schering-Plough can confirm that the 4th quartile DLQI population in the EXPRESS clinical trial is defined by a minimum DLQI score of 18 at baseline. It should be noted that the baseline PASI score for this patient group in the EXPRESS clinical trial ranged from [redacted] and this range was observed consistently across the 'all patient' group.

The 4th quartile of the EXPRESS clinical trial appears to be the subgroup of the trial population that derives the greatest utility gains from treatment and importantly this finding is consistent with the HODaR dataset. However, patient level data indicate that utility gain is not adequately explained by baseline DLQI alone. This observation is characterized by patients with substantial utility gains across the range of baseline DLQI scores. Schering-Plough believes that these considerations are supportive of a recommendation for infliximab in severe psoriasis in accordance with the existing clinical definition, i.e. PASI≥10, DLQI>10. Infliximab is most widely used in clinical circumstances requiring rapid disease control due to its very rapid onset of action and high response rate. These circumstances frequently relate to particular groups of patients with severe psoriasis e.g. those with rapidly progressing disease, highly visible psoriasis, nail psoriasis and those patients requiring hospitalisation. An alternative recommendation, for example restricting infliximab to a particularly severe subgroup would not be in the best interests of clinicians or patients and would prevent infliximab being appropriately targeted at patients with the greatest potential to benefit. Schering-Plough urges the Committee to maintain a definition of severity that is consistent with TA103 and BAD Guidelines.

II. RESPONSE TO ACD CONTENT:

Schering-Plough does not consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence or that the preliminary views on the resource impact and implications for the NHS are appropriate. The provisional recommendations of the Appraisal Committee, in consequence, do not constitute a suitable basis for the preparation of guidance to the NHS.

Schering-Plough's comments on the ACD are as follows:

The Committee's interpretation of the evidence is inconsistent with TA103 and fails to recognize that infliximab is a cost-effective treatment option for patients with severe psoriasis.

The Committee did not take proper account of the evidence set out in Schering-Plough's submission with regards to the cost-effectiveness of infliximab in psoriasis. Schering-Plough's base case cost-effectiveness analysis was in accordance with the analysis that the York Assessment group used to identify a cost-effective subgroup of patients with psoriasis to be treated with biologics in their report for TA103.

This group of patients was identified by having the worst quality of life at baseline (4th quartile DLQI) and the highest probability of hospitalization for non-responders (21 days). No further description of the 4th quartile DLQI is available either in the Assessment report or TA103 (information on HODaR analysis was marked as commercial in confidence). On the basis of this analysis and having received testimony from clinical experts and consultees, the Committee decided to recommend etanercept for the treatment of patients with severe psoriasis, described as having a PASI≥10 and DLQI>10.

There was no further clarification given as to how this recommendation was derived. However, it is evident that the Committee considered that the subgroup of severe patients for which treatment with etanercept was cost-effective represented patients with a PASI≥10 and DLQI>10 and that this was a view that was informed by the 4th quartile DLQI population and expert opinion.

Following this interpretation of the previous Guidance (TA103), Schering-Plough provided an analysis to NICE that was in agreement with the work that had been performed previously. The scenario presented was for patients in the 4th quartile DLQI that also had the highest probability of being hospitalized if they did not respond to treatment. As in the previous appraisal, this severe population of patients with a high probability of hospitalization is assumed to represent patients with a PASI≥10 and DLQI>10. The Committee failed to interpret the data presented in the S-P submission in the same manner as it had done in TA103 and therefore the interpretation is misleading and unfair.

The Committee has failed to adequately consider the implications for NHS resources in developing its preliminary recommendations for infliximab.

The Committee's preliminary recommendation, that it is minded not to recommend infliximab, suggests that it has not adequately considered the implications for NHS resources of denying patients with severe psoriasis treatment with infliximab

Severe psoriasis has a profound effect on both the quality of life and functionality of patients. These patients tend to suffer from highly visible and rapidly progressing psoriasis and are in need of rapid and effective control of the disease. In the absence of treatment with infliximab these patients are likely to require hospital admissions for treatment and this will have a high impact on NHS resources.

The draft recommendations set out in the ACD are inconsistent with TA103, relying on a misinterpretation of the data, and would create significant unmet need for those patients with severe psoriasis in need of a rapid and longer-lasting response.

The ACD states in section 3.5 that the manufacturer did not provide specific reasoning for focusing on the 4th quartile group; however, the evidence suggested that this was in order to concentrate on patients with severe psoriasis.

Schering-Plough's submission for infliximab in psoriasis was informed to a large extent by the prior appraisal of etanercept and efalizumab for psoriasis (TA103). This approach was intentionally pragmatic in as much as it attempted to follow an established framework for both modeling of cost-effectiveness and decision making.

Whilst Schering-Plough was not party to the precise deliberations of the Committee during TA103, the available draft and final guidance as well as consultation documents provided clear evidence to support Schering-Plough's rationale in developing its submission for infliximab. As explained in detail earlier in this response, the 4th quartile group described as 'patients with low baseline quality of life' was clearly the group used to support the Committee's decision to recommend etanercept for the treatment of severe psoriasis, as defined by PASI≥10, DLQI>10.

Schering-Plough accepts that its explanation for the focus on 4th quartile DLQI was concise in its submission. However, the unarguably clear relationship between recommendations set out in TA103 and the 4th quartile population offer a more than adequate rationale. We are concerned that the Committee appears to have overlooked this rationale.

The ACD states in section 3.7 that the manufacturer did not present an ICER for infliximab compared with etanercept using the 'all patients' utilities.

Schering-Plough accepts that this was an omission. The ICER for infliximab compared with continuous etanercept is £41,351 when applying the 'all patients' utilities.

The Committee considered in section 4.4 of the ACD that the principal comparator should be etanercept given intermittently in line with NICE guidance. The Committee noted however, that according to clinical specialists, the patient experts, the manufacturer and the ERG, etanercept is given continuously in routine UK clinical practice. The Committee was therefore persuaded that continuous etanercept was an appropriate comparator.

Schering-Plough acknowledges the fact that the Committee has recognized the use of continuous etanercept in routine clinical practice. On this basis it seems difficult to support the Committee's position that the principal comparator should be etanercept given intermittently, notwithstanding the fact that this reflects NICE guidance. It is Schering-Plough's view that given the predominant use of continuous etanercept, as reflected in routine UK clinical practice, is the most appropriate principal comparator.

The Committee accepted, as reported in section 4.6 of the ACD that due to the absence of RCT evidence to demonstrate any clinical difference between intermittent and continuous etanercept that it was reasonable to assume, as had been done in TA103, that there was no difference in clinical outcomes between continuous and intermittent. The Committee was therefore persuaded that infliximab could be more clinically effective than intermittent etanercept or efalizumab.

Schering-Plough acknowledges that the Committee follows the logic established in TA103 in this particular instance in assuming that there is no difference in outcome between continuous and intermittent etanercept. Whilst currently unclear in the ACD, it is reasonable to assume that infliximab could also be more clinically effective than continuous etanercept.

The Committee considered the cost of administering infliximab in section 4.9. The Committee considered that the estimates for the cost of administration in Schering-Plough's submission were inappropriate.

Schering-Plough presented alternative estimates of cost-effectiveness based on additional scenarios for the cost of administering an infusion to reflect the uncertainty around this parameter in the economic model. Schering-Plough does not agree with the view as presented in the ACD that patients often need to spend at least half a day in hospital. It is Schering-Plough's understanding that allocating the cost of half a day in hospital would not reflect the cost to the NHS of delivering infusions with infliximab and would lead to unreliable estimates of cost-effectiveness. Alternative scenarios presented by Schering-Plough earlier in this response were derived from other independent published health technology appraisals involving infliximab.

The ACD states in section 4.10 that the manufacturer did not provide ICERs of infliximab versus efalizumab for those patients in whom etanercept would be contraindicated or who would be intolerant to etanercept.

Schering-Plough notes that these ICERs were not included in its submission. ICERs for infliximab versus efalizumab in this setting are presented in section I of this response.

Summary

Schering-Plough believes that the Committees preliminary recommendations for infliximab set out in the ACD are not based on a reasonable interpretation of the evidence. The preliminary recommendations do not constitute a suitable basis for the preparation of guidance for the NHS. Schering-Plough has demonstrated the clinical and cost-effectiveness of infliximab in patients with severe psoriasis in a manner consistent with a previous appraisal conducted by the Institute, namely TA103. It is for this reason that Schering-Plough believes it to be incumbent upon the Appraisal Committee to develop recommendations for infliximab that are consistent with TA103 both in terms of the interpretation of evidence and the subsequent description of the patient group for which treatment is recommended. In conclusion, infliximab should be available for patients with severe psoriasis, defined as PASI≥10 and DLQI>10.

III. COMMENTS ON ERG REPORT:

In this section of S-P's response, comments are provided in response to the key issues outlined by the Evidence Review Group in their report on S-P's submission. Rather than addressing all the narrative in relation to the S-P submission, comments are provided for the key summary points in the ERG report, namely the 'Areas of Uncertainty' section and the 'Key Issues' section.

In general the ERG provides a thorough and balanced review and critique of the S-P submission. Several areas of uncertainty arise and these relate in large part to the interpretation of evidence provided previously to the Institute in TA103 for etanercept and efalizumab. Where relevant, issues that are raised in common with the Committee's requests for clarification are cross-referenced to the detailed response to avoid repetition.

Areas of Uncertainty; ERG Report Pages 8-9	**Schering-Plough Comment**
The short intervention period of 10 weeks provides limited information about the longer term efficacy of infliximab.	Schering-Plough acknowledges this limitation. The best available clinical evidence for both infliximab and the relevant comparators assessed clinical outcomes of interest over relatively short intervention periods.
The relative risks calculated by the manufacturer have wide confidence intervals around all four point estimates for the primary outcome of PASI 75 achievement (and other outcomes), indicating a lack of certainty regarding the true effect.	Uncertainty around the primary outcome of PASI 75 achievement for infliximab and its comparators has been handled using conventional techniques in the economic evaluation. Therefore, this uncertainty is represented in the ICERs presented for infliximab.
No description of the principles, assumptions or methodology behind the indirect comparison were provided, making it difficult for the ERG to check either the model or the data. Despite asking the manufacturer for clarification, a number of areas remain unclear, such as where the data come from, which trials were included and which placebo groups were included for the pooled estimates.	Please see appendix for further details on the rationale behind the indirect comparison methodology.
A definition of moderate psoriasis was not provided by the MS, and neither were there any inclusion/exclusion criteria for the rating of severity of psoriasis to ensure patients were moderate to severe. The populations of the included infliximab trials were predominantly those with severe psoriasis. In addition, it is unclear what proportion of trial participants had previously been treated with systemic therapy. This causes concern over whether the participants included in the trials reflect those in the scope.	As can be seen from the small number of trials included in the submission, relevant, published trials in this field are limited which makes it difficult to establish a definitive evidence base which is relevant to the decision problem. The trials selected represent the best available data. As such we undertook to include all of the trials, along with summaries of their baseline patient characteristics, rather than excluding them on the basis of these characteristics.
The PASI is not an ideal measure of the severity of psoriasis in terms of measuring the impact on patients, but is often the best available outcome and is the measure used most in clinical trials. This raises questions regarding the relevance of the PASI outcome to patient experience in practice.	Similarly to the evidence base, the PASI score represents the best available patient outcome. Data involving this outcome have been successfully interpreted in previous NICE Committee meetings and by our assessment of minutes from these meetings, the outcome is the most relevant of any outcome commonly measured in trials.
There is uncertainty over the appropriate group to use in terms of QALY values. The base case presents values for 4th quartile DLQI patients. It is unclear precisely what the characteristics of patients were in this group.	*This point has been addressed earlier, in S-P's response to the points of clarification requested by the Committee.*
It was unclear how values for the number of inpatient days per year for a non-responder were derived. There was also uncertainty about the costs associated with inpatient care and the number of outpatient stays required for an individual on supportive care.	Length of stay for an inpatient admission was assumed to be 21 days. This is further supported by the Department of Health, Hospital Episode Statistics (2004/05) for psoriasis, which give a mean of 18.1 days. Dermatologists questioned across the UK supported that at least 21 days annually would be necessary to treat patients with severe psoriasis only being treated with supportive care. Hospitalisation ranged from [redacted] in centres across the UK, depending on the severity of disease [redacted].

[8] Woods A.L, Rutter K.J, Gardner L.S et al, Inpatient Management of Psoriasis: A multi-centre service review. Submitted;

Areas of Uncertainty; ERG Report Pages 8-9	Schering-Plough Comment
	Furthermore, as per the evidence presented in the York Assessment Report, length of stay for an inpatient admission was based on Department of Health, Hospital Episode Statistics (2002/03) for psoriasis, which gave a mean of 19.6 days. This statistic was supported by evidence from recent audits of two local hospitals, which had average lengths of stay of [redacted] respectively [redacted] In addition expert opinion in the UK stated that non-responders would be expected to attend the clinic for management of their symptoms, including changing of dressings. This was estimated to be at least an average of 3 clinic visits per week for 6 weeks on an annual basis. As there is no exact cost described by the NHS for the treatment of a severe psoriasis patient, a combination cost was used to best represent the costs associated with the treatment of a non-responder. The cost of an inpatient day was based upon two NHS Reference Cost categories. An average of the categories 'Elective inpatient HRG data, major dermatological conditions J39 (>69 or w cc) (>69 or w cc: aged over 69 or with comorbidities or complications)' and 'Elective inpatient HRG data, major dermatological conditions J40 (<70 or w/o cc)' was estimated, weighted by number of Finished Consultant Episodes. Prices relate to the year 2005/06. These costs were also used in the York Assessment report, which was used to inform the previous Guidance (TA103).
There may be greater variability in the cost effectiveness of treatment than presented in the sensitivity analyses in the manufacturer's submission.	Additional analyses have been included in Schering-Plough's response specifically around utility estimates and costs associated with infusions.
The drop out rate for patients who no longer respond may be underestimated in the model.	The ERG incorrectly assumes (page 48, section 4.4.1.2) that the 20 per cent drop out rate used in S-P's model was derived from the clinical trials. PASI 75 response rates were not used to estimate drop out rates. Rather, the rate that had previously been used in TA103 by the Assessment Group, and had been tested with clinical experts was applied in S-P's model.

Key Issues; ERG Report Page 9	Schering-Plough Comment
The trials of infliximab efficacy presented by the MS were placebo-controlled trials. No head-to-head studies were identified that directly compared infliximab to etanercept or efalizumab, the comparators stated in the scope. The manufacturer carried out an indirect comparison, but the ERG have reservations about the comparison regarding a lack of information presented and areas of uncertainty in relation to the included data. In addition, the ERG questions the appropriateness of pooling data that is statistically heterogeneous.	As Schering-Plough has indicated in its submission, statistically significant heterogeneity between infliximab trials was observed and therefore an indirect comparison, based on a random effects regression model, was more appropriate. Although S-P presented pooled estimates from a fixed-effects model in section 5.5 of the manufacturer submission, these were given for illustrative purposes. S-P used a Bayesian, random-effects modelling approach to meta-analysis as presented in the indirect comparison section of the STA submission. This approach was chosen to minimise the bias associated with a heterogeneous evidence base. This approach had previously been acceptable to the Appraisal Committee in TA103. S-P would argue that the pooled mean values, and their confidence intervals, from this analysis are valid and represent the best available evidence synthesis. A rationale for the analysis has been attached with our response for review (see appendix), which demonstrates the robustness of our estimates by way of a sensitivity analysis which explores the potential effect of the heterogeneous evidence base on the overall finding.
The ICER is highly sensitive to assumptions about the costs and frequency of inpatient stays for non responders of infliximab,	See earlier response to ERG regarding length of stay and costs.
It is unclear what severity of psoriasis was represented by the utility values presented in the MS. It is also unclear to what extent moderate psoriasis would be represented in the analysis presented in the MS	*This point, with regard to utility values in S-P's submission, has been addressed earlier, in S-P's response to the points of clarification requested by the Committee.* With regard to the extent of moderate psoriasis represented in the S-P submission, the majority of patients in the infliximab clinical trials had severe psoriasis (PASI≥10 and DLQI>10). Whilst included in the license for infliximab, moderate psoriasis was not represented in S-P's base case analysis (severe psoriasis). This was consistent with the scope for the appraisal, the decision problem, and the recommendations set out in TA103. A proportion of patients in the trials may fit a classification of moderate psoriasis (e.g. PASI<10, DLQI<=10). Whilst the 'all patient' utility scenario presented in S-P's submission is not specific to moderate psoriasis, and the precise definition of this patient population is not specified anywhere in TA103, this 'all patient' scenario gives the only available estimate of cost-effectiveness that approximates to the moderate psoriasis group.

APPENDIX

Rationale for meta-analysis methodology

The fixed effect model assumes that all studies in a meta-analysis come from a population with a fixed average effect size: studies in the meta-analysis are sampled from a population in which the average effect size is fixed (Hunter & Schmidt, 2000). The alternative assumption is that the average effect size in the population varies randomly from study to study: studies in a meta-analysis come from populations that have different average effect sizes, so, population effect sizes can be thought of as being sampled from a 'superpopulation' (Hedges, 1992). That is the underlying true treatment effect follows some distribution.

Statistically speaking, the main difference between fixed- and random-effects models is in the amount of error. In fixed-effects models there is error introduced because of sampling studies from a population of studies. This error exists in random-effects models but in addition there is error created by sampling the populations from a superpopulation. So, calculating the error of the mean effect size in random-effects models involves estimating two error terms, whereas in fixed-effects models there is only one error term.

There is theoretical (Field, 2003; National Research Council, 1992; Hunter & Schmidt, 2000) and empirical (Barrick & Mount, 1991) evidence that real-world data are likely to reflect the random-effects conceptualization (that is, studies come from populations in which the average effect size varies). However, Hedges and Vevea (1998) suggested that the choice of model depends not on the assumptions about the true state of the world, but on the type of inferences that the researcher wishes to make: with fixed-effect models inferences can be drawn only about the studies included in the meta-analysis whereas random effects models allow inferences that generalise beyond the studies included in the meta-analysis.

As a result of this and of the significant variability between effect sizes in the fixed effects model we considered a random effects model to be the most appropriate analysis. However this does not account or explain sources of hetereogeneity but is the more conservative option and is in line with the earlier work carried out by the CRD group in the appraisal of etanercept and efalizumab in psoriasis, allowing direct comparison with their analysis.

To investigate heterogeneity between the infliximab studies we performed a sensitivity analysis using the fixed effects model for the PASI 75 outcome. Excluding results from the smallest study, with the lowest RR, (Chaudhari et al) provided the best fit. In this case the pooled RR (95%CI) for infliximab is 28.99 (15.19, 55.33) (Q=1.776, df=2, p=0.411). Excluding the largest study, with the highest RR, (Menter et al) also improved model fitting but to a much lesser degree (RR 18.23 [8.45, 39.34], Q=5.26, df=2, p=0.072). However we decided on the conservative approach and did not exclude any study in the random-effects model conducted within the Bayesian framework. By excluding the results from Chaudhari et al we would be increasing the effect size of infliximab and potentially biasing results in its favour.

References

Barrick, M. R., & Mount, M. K. (1991). The big five personality dimensions and job performance: a meta-analysis. Personnel Psychology, 44, 1-26.

Field, A. P., & Hole, G. (2003). How to design and report experiments. London: Sage.

Hedges, L. V. (1992). Meta-Analysis. Journal of Educational Statistics, 17, 279-296.

Hedges, L. V. & Vevea, J. L. (1998). Fixed- and random-effects models in meta-analysis. Psychological Methods, 3, 486-504.

Hunter, J. E., & Schmidt, F. L. (2000). Fixed effects vs. random effects meta-analysis models: implications for cumulative knowledge in Psychology. International Journal of Selection and Assessment, 8, 275–292.

National Research Council (1992). Combining information: Statistical issues and opportunities for research. Washington, D.C.: National Academy Press.

Appendix 2 to accompany Schering-Plough response to ACD for infliximab in psoriasis

26th September 2007

Table 2 Incremental cost-effectiveness ratios (ICER) by HODaR (base case), EXPRESS and pooled mean estimates of utility gain for all relevant comparators (original model submitted; £65.02 administration cost)

	Base case (Schering-Plough submission)		**EXPRESS (EQ-5D)**		**Pooled mean estimate**	
	All patients	4th quartile DLQI	PASI≥10, DLQI>10	4th quartile DLQI	PASI≥10, DLQI>10	4th quartile DLQI
supportive care	£40,281	£21,671	£37,169	£28,271	£37,752	£24,527
etanercept 25mg BIW intermittent	£62,032	£33,155	£55,739	£40,484	£56,559	£38,848
efalizumab 1mg/kg	£46,380	£24,947	£42,218	£30,776	£42,766	£29,402
etanercept 25mg BIW continuous	£48,887	£26,095	£43,927	£31,905	£44,574	£30,616
etanercept 50mg BIW	£2,860	£1,519	£2,563	£1,809	£2,617	£1,732
Principal comparator from manufacturer's submission is highlighted for clarity.						

BASE CASE (SCHERING-PLOUGH SUBMISSION)

ICER 'all patients'

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.110	0.048	0.048	0.067	0.039
ICER vs. infliximab	N/A	£48,887	£62,032	£2,860	£46,380

ICER 4th quartile DLQI

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.205	0.089	0.089	0.124	0.073
ICER vs. infliximab	N/A	£26,095	£33,155	£1,519	£24,947

EXPRESS (EQ-5D)

ICER PASI≥10, DLQI>10 (£65.02 per outpatient visit)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.120	0.051	0.051	0.072	0.042
ICER vs. infliximab	N/A	£43,927	£55,739	£2,563	£42,218

ICER 4th quartile DLQI (£65.02 per outpatient visit)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.157	0.062	0.062	0.089	0.050
ICER vs. infliximab	N/A	£31,905	£40,484	£1,809	£30,776

POOLED MEAN ESTIMATE

ICER PASI≥10, DLQI>10 (£65.02 per outpatient visit-original model)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.118	0.050	0.050	0.071	0.041
ICER vs. infliximab	N/A	£44,574	£56,559	£2,617	£42,766

ICER 4th quartile DLQI (£65.02 per outpatient visit-original model)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.166	0.067	0.067	0.095	0.054
ICER vs. infliximab	N/A	£30,616	£38,848	£1,732	£29,402

Table 3 Incremental cost-effectiveness ratios for different administration costs (HODaR utilities)

	ICER 'all patients' (base case £65.02)	ICER 4th quartile DLQI (base case £65.02)	ICER 'all patients' (£78.20 per infusion)	ICER 4th quartile DLQI (£78.20 per infusion)	ICER 'all patients' (£124 per infusion)	ICER 4th quartile DLQI (£124 per infusion)
supportive care	£40,281	£21,671	£42,049	£22,615	£44,475	£23,920
etanercept 25mg intermittent	£62,032	£33,157	£62,645	£33,483	£66,952	£35,785
efalizumab 1mg/kg	£46,380	£24,947	£46,915	£25,235	£50,676	£27,258
etanercept 25mg continuous	£48,887	£26,095	£49,484	£26,448	£53,790	£28,750
etanercept 50mg	£2,860	£1,519	£3,744	£1,988	£9,953	£5,284

HODAR UTILITIES

£65.02 PER INFUSION (SCHERING-PLOUGH BASE CASE)

ICER 'all patients' (base case £65.02)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.110	0.048	0.048	0.067	0.039
ICER vs. infliximab	N/A	£48,887	£62,032	£2,860	£46,380

ICER 4th quartile DLQI (base case £65.02)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.205	0.089	0.089	0.124	0.073
ICER vs. infliximab	N/A	£26,095	£33,155	£1,519	£24,947

£78.20 PER INFUSION

ICER 'all patients' (£78.20 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.110	0.048	0.048	0.067	0.039
ICER vs. infliximab	N/A	£49,484	£62,645	£3,744	£46,915

ICER 4th quartile DLQI (£78.20 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.205	0.089	0.089	0.124	0.073
ICER vs. infliximab	N/A	£26,448	£33,483	£1,988	£25,235

£124 PER INFUSION

ICER 'all patients' (£124 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.110	0.048	0.048	0.067	0.039
ICER vs. infliximab	N/A	£53,790	£66,952	£9,953	£50,676

ICER 4th quartile DLQI (£124 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.205	0.089	0.089	0.124	0.073
ICER vs. infliximab	N/A	£28,750	£35,785	£5,284	£27,258

Table 4 Incremental cost-effectiveness ratios associated with different administration costs (EXPRESS utilities)

	ICER PASI≥10, DLQI>10 (£65.02 per infusion)	ICER 4th quartile DLQI (£65.02 per infusion)	ICER PASI≥10, DLQI>10 (£78.20 per infusion)	ICER 4th quartile DLQI (£78.20 per infusion)	ICER PASI≥10, DLQI>10 (£124 per infusion)	ICER 4th quartile DLQI (£124 per infusion)
supportive care	£38,016	£29,057	£38,783	£29,510	£41,020	£31,212
etanercept 25mg intermittent	£55,739	£40,484	£56,290	£40,884	£60,159	£43,695
efalizumab 1mg/kg	£42,218	£30,776	£42,705	£31,131	£46,128	£33,626
etanercept 25mg continuous	£43,927	£31,905	£44,464	£32,295	£48,333	£35,105
etanercept 50mg	£2,563	£1,809	£3,354	£2,368	£10,190	£6,294

EXPRESS UTILITIES

£65.02 PER INFUSION

ICER PASI≥10, DLQI>10 (£65.02 per outpatient visit)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.120	0.051	0.051	0.072	0.042
ICER vs. infliximab	N/A	£43,927	£55,739	£2,563	£42,218

ICER 4th quartile DLQI (£65.02 per outpatient visit)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,562	£1,531	£716	£4,439	£1,269
Total QALYs	0.157	0.062	0.062	0.089	0.050
ICER vs. infliximab	N/A	£31,905	£40,484	£1,809	£30,776

£78.20 PER INFUSION

ICER PASI≥10, DLQI>10 (£78.20 per outpatient visit)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.120	0.051	0.051	0.072	0.042
ICER vs. infliximab	N/A	£44,464	£56,290	£3,354	£42,705

ICER 4th quartile DLQI (£78.20 per outpatient visit)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.157	0.062	0.062	0.089	0.050
ICER vs. infliximab	N/A	£32,295	£40,884	£2,368	£31,131

£124 PER INFUSION

ICER PASI≥10, DLQI>10 (£124 per outpatient visit)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.120	0.051	0.051	0.072	0.042
ICER vs. infliximab	N/A	£48,333	£60,159	£10,190	£46,128

ICER 4th quartile DLQI (£124 per outpatient visit)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.157	0.062	0.062	0.089	0.050
ICER vs. infliximab	N/A	£35,105	£43,695	£6,294	£33,626

Table 5 Incremental cost-effectiveness ratios for different utility estimates (£78.20 administration costs-new model)

£78.20 infusion cost	HODaR utilities		EXPRESS (EQ-5D)		Pooled mean estimate	
	All patients	4th quartile DLQI	PASI≥10, DLQI>10	4th quartile DLQI	PASI≥10, DLQI>10	4th quartile DLQI
supportive care	£42,049	£22,615	£38,783	£29,510	£39,394	£27,885
etanercept 25mg BIW intermittent	£62,645	£33,483	£56,296	£40,884	£57,118	£39,232
efalizumab 1mg/kg	£46,915	£25,235	£42,705	£31,131	£43,260	£29,741
etanercept 25mg BIW continuous	£49,484	£26,448	£44,464	£32,295	£45,118	£30,990
etanercept 50mg BIW	£3,744	£1,988	£3,354	£2,368	£3,426	£2,268

78.20 PER INFUSION

HODAR UTILITIES

ICER 'all patients' (£78.20 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.110	0.048	0.048	0.067	0.039
ICER vs. infliximab	N/A	£49,484	£62,645	£3,744	£46,915

ICER 4th quartile DLQI (£78.20 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.205	0.089	0.089	0.124	0.073
ICER vs. infliximab	N/A	£26,448	£33,483	£1,988	£25,235

EXPRESS UTILITIES

ICER PASI≥10, DLQI>10 (£78.20 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.120	0.051	0.051	0.072	0.042
ICER vs. infliximab	N/A	£44,464	£56,296	£3,354	£42,705

ICER 4th quartile DLQI (£78.20 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.157	0.062	0.062	0.089	0.050
ICER vs. infliximab	N/A	£32,295	£40,884	£2,368	£31,131

POOLED MEAN ESTIMATE

ICER PASI≥10, DLQI>10 (£78.20 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.118	0.050	0.050	0.071	0.041
ICER vs. infliximab	N/A	£45,118	£57,118	£3,426	£43,260

ICER 4th quartile DLQI (£78.20 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,639	£1,571	£755	£4,478	£1,308
Total QALYs	0.166	0.067	0.067	0.095	0.054
ICER vs. infliximab	N/A	£30,990	£39,232	£2,268	£29,741

Table 6 Incremental cost-effectiveness ratios for different utility estimates (£124 administration costs-new model)

£124 infusion cost	HODaR utilities		EXPRESS (EQ-5D)		Pooled mean estimate	
	4th quartile DLQI	All patients	4th quartile DLQI	PASI≥10, DLQI>10	PASI≥10, DLQI>10	4th quartile DLQI
supportive care	£23,920	£44,475	£31,212	£41,020	£41,667	£29,494
etanercept 25mg BIW intermittent	£35,785	£66,952	£43,695	£60,159	£61,044	£41,929
efalizumab 1mg/kg	£27,258	£50,676	£33,626	£46,128	£46,727	£32,125
etanercept 25mg BIW continuous	£28,750	£53,790	£35,105	£48,333	£49,044	£33,687
etanercept 50mg BIW	£5,284	£9,953	£6,294	£8,917	£9,106	£6,028

£124 PER INFUSION

HODAR UTILITIES

ICER 'all patients' (£124 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.110	0.048	0.048	0.067	0.039
ICER vs. infliximab	N/A	£53,790	£66,952	£9,953	£50,676

ICER 4th quartile DLQI (£124 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.205	0.089	0.089	0.124	0.073
ICER vs. infliximab	N/A	£28,750	£35,785	£5,284	£27,258

EXPRESS UTILITIES

ICER PASI≥10, DLQI>10 (£124 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.120	0.051	0.051	0.072	0.042
ICER vs. infliximab	N/A	£48,333	£60,159	£8,917	£46,128

ICER 4th quartile DLQI (£124 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.157	0.062	0.062	0.089	0.050
ICER vs. infliximab	N/A	£35,105	£43,695	£6,294	£33,626

POOLED MEAN ESTIMATE

ICER PASI≥10, DLQI>10 (£124 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.118	0.050	0.050	0.071	0.041
ICER vs. infliximab	N/A	£49,044	£61,044	£9,106	£46,727

ICER 4th quartile DLQI (£124 per infusion)

	infliximab	etanercept 25mg continuous	etanercept 25mg intermittent	etanercept 50mg	efalizumab
Total cost	£4,906	£1,571	£755	£4,478	£1,308
Total QALYs	0.166	0.067	0.067	0.095	0.054
ICER vs. infliximab	N/A	£33,687	£41,929	£6,028	£32,125