ERG review of the PAS submission of ustekinumab for treating active psoriatic arthritis by the manufacturer

Produced by CRD and CHE Technology Assessment Group

Authors Stephen Rice, Research Fellow in Health Economics, CRD
Joanne O'Connor, Research Fellow in Health Economics, CRD
Nerys Woolacott, Senior Research Fellow, CRD

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1 Introduction

Following the publication of the NICE Technology Appraisal Guidance 313, that stated that,

"Ustekinumab (given by itself or with another drug called methotrexate) is not recommended for active psoriatic arthritis when treatment with non-biological disease-modifying anti-rheumatic drugs (or DMARDs) has not worked well enough.",

the manufacturer (Janssen) made a Patient Access Scheme (PAS) submission to NICE. The ERG was requested by NICE to review the submission. The ERG's critique of this PAS submission is presented in this short report.

The ERG has identified that the changes in the new PAS economic models included:

- A reduced price for 90 mg ustekinumab
- Adjustments according to the NICE Appraisal Committee's preferred assumptions as detailed in the TA Guidance 313

These are presented and critiqued below.

2 PAS Implementation

2.1 PAS Price of 90 mg ustekinumab

The manufacturer (Janssen) proposes that the price of 90 mg ustekinumab (two 45 mg vials) for adults with active psoriatic arthritis who weigh more than 100 kg should be the same as that of a single 45 mg ustekinumab vial. This reduces the cost of 90 mg from £4,294 to £2,147 per year.

The ERG notes that 24.2% of the anti-TNF alpha naïve patients and 35.6% of the anti-TNF alpha experienced patients were assumed to weigh > 100 kg in the respective models. These percentages were derived from the PSUMMIT trials. Because the proportion of patients weighing greater than 100 kg is higher in the anti-TNF alpha experienced patient model, the price change should have a greater effect on the anti-TNF alpha experienced patient model results than the anti-TNF alpha naïve patient results.

2.2 Administration costs

The costs associated with the operation of the PAS are presented in Table 1. Treatment-related costs associated with the PAS are presented in Table 2.

Table 1: Costs associated with the implementation and operation of the patient access scheme (PAS), Table 4, P16 PAS MS

	Calculation of cost	Reference source
Stock management	£0	No additional cost incurred due to the patient access scheme
Administration of claim forms	£4	PSSRU, Unit Costs of Health and Social Care 2012 (page 218). Hourly wage for hospital pharmacist £24 * 10 additional minutes to administer the patient access scheme
Staff training	£0	The relevant staff are likely to be already familiar with the patient access scheme for the psoriasis indication
Tracking of supplies	£0	This activity is conducted by the homecare provider
Other costs	£15	PSSRU, Unit Costs of Health and Social Care 2012 (page 235). Hourly wage for consultant (medical) £91 * 10 additional minutes to obtain patient consent and to administer the patient access scheme
Audit	£12	PSSRU, Unit Costs of Health and Social Care 2012 (page 218). Hourly wage for hospital pharmacist £24 * 30 minutes to audit (if needed)
Total implementation and operation costs	£31	Total cost per psoriatic arthritis patient who receives ustekinumab
PSSRU: Personal and Social Services Research Unit		

Table 2: Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS), Table 5, P17 PAS MS

	Calculation of cost	Reference source
Providing intervention	£0	N/A
Monitoring tests	£0	N/A
Diagnostic tests	£0	N/A
Appointments	£0	N/A
Other costs	£2	PSSRU, Unit Costs of Health and Social Care 2012 (page 225). Hourly wage for hospital nurse £20 * 5 additional minutes to administer the patient access scheme per patient
Other [add more rows as necessary]	£0	N/A
Total treatment-related costs	£2	
PSSRU: Personal and Social Services Research Unit		

The manufacturer did not include these PAS associated costs in the model, stating they are immaterial. It is not clear to the ERG if the costs listed in Tables 1 and 2 are per injection or incurred less frequently. At most, assuming the operational costs are per injection (and with injections being administered 4.33 times per year on average), the total cost per year for a patient weighing >100 kg is £33*4.33 = £142.89. It was assumed that 24.2% of the anti-TNF naïve patients and 35.6% of the anti-TNF alpha experienced patients were > 100 kg. Averaged out over all the patients, the cost is £34.60 per anti-TNF naïve patient and £50.87 per anti-TNF experienced patient. If £142.89 is added to the cost of treating ustekinumab patients >100 kg then the ICER for ustekinumab compared to conventional management increases by around £500. Therefore, the ERG agrees that these costs are immaterial relative to the £2,147 per year cost of either dose of ustekinumab and so it does not have a significant impact on the cost-effectiveness of ustekinumab.

3 Model changes based on NICE Appraisal Committee's preferences

The manufacturer submitted three models:

- anti-TNF alpha naïve patients
- anti-TNF alpha experienced patients
- sequencing model

Anti-TNF alpha naïve patient and anti-TNF alpha experienced patient models were both included in the original manufacturer's submission. The ERG included a simple sequencing model in their ERG report in order to include other anti-TNFs as treatment comparators rather than just conventional

management following withdrawal from anti-TNF treatment. The sequencing model in the manufacturer's PAS submission is the sequencing model included in the ERG report.

3.1 How the PAS models relate to the previous models

The ERG has produced several versions of the three submitted PAS models incorporating incremental changes in previous models, correcting errors and incorporating the preferred assumptions of the NICE Appraisal Committee. A summary of the model versions produced in chronological order with the changes made with respect to the previous models is presented in Table 3.

The PAS submission model builds on the Final model described in Table 3, which is the ERG corrected model with the adjustment made to the golimumab 100 mg cost input. The base case model in this PAS submission includes two adjustments to the Final model:

- The PAS price for 90 mg ustekinumab for patients > 100 kg
- Incorporation of an effect of conventional management on skin symptoms

Table 3: The model versions produced in chronological order with the changes made with respect to the previous models.

Models by population and sequence	Model versions over time				
	Original	Updated*	ERG corrected**	Final***	PAS****
Anti-TNF alpha naïve	-	Phototherapy costs removed + PASI costs adjusted for inflation properly + Different probability distributions	Same as Updated + Revised (higher) baseline HAQ and PASI scores	Same as Updated + Revised (higher) baseline HAQ and PASI scores + Cost for golimumab 100mg revised upwards	Same as ERG corrected + Cost for golimumab 100mg revised upwards + PAS reduced price for ustekinumab 90 mg for patients >100 kg + Incorporated effect of conventional management on PASI skin outcome
Anti-TNF alpha experienced	-	Phototherapy costs removed + PASI costs adjusted for inflation properly + Different probability distributions	Same as Updated + Revised (higher) baseline HAQ and PASI scores	Same as Updated + Revised (higher) baseline HAQ and PASI scores	Same as ERG corrected + Cost for golimumab 100mg revised upwards + PAS reduced price for ustekinumab 90 mg for patients >100 kg + Incorporated effect of conventional management on PASI skin outcome
Sequential†	NA	NA	Used the ERG corrected model assumptions, + first biologic failure due to inefficacy + ERG estimates for 2nd-line clinical effectiveness for anti-TNFs + Ustekinumab 2nd-line effectiveness data from PSUMMIT2 only	NA	Same as ERG corrected + Cost for golimumab 100mg revised upwards + PAS reduced price for ustekinumab 90 mg for patients >100 kg + Incorporated effect of conventional management on PASI skin outcome for 1st-line treatment only*****

*The Updated model was produced by the manufacturer in response to the points for clarification
**The ERG corrected model was presented in Section 6 of the ERG report. This was not referred to in the FAD
***The Final model was produced by the manufacturer during the consultation period in response to the ACD
****The PAS model was produced by the manufacturer after the publication of the FAD in the PAS submission
*****The ERG sequencing model assumed that only PsARC outcomes would change for 2nd-line treatment. The manufacturer claims this is conservative for ustekinumab
†Different sequencing scenarios were produced. The one presented here was the scenario the NICE Committee found most useful

3.2 Changes made based on NICE Appraisal Committee preferred assumptions

In TA Guidance 313, it is stated that the NICE Appraisal Committee expressed a desire for different scenarios to be evaluated and for preferred assumptions to be incorporated. These included:

1) The effect of conventional management on skin symptoms (4.13, TA313)
2) Treatment response should have been assessed at the same time point for the ustekinumab comparison with conventional management (4.15, TA313)
3) 40 year time horizon preferable (4.16, TA313)
4) Sequential analysis with (a) TNF alpha inhibitor failed because of lack of efficacy, and (b) clinical data taken directly from the PSUMMIT2 trial (4.19, TA313)
5) An assessment of worsening HAQ-DI during ustekinumab or anti-TNF treatment (4.12, TA313)

Of the above, in their PAS submission the manufacturer incorporated (1) the effect of conventional management on skin symptoms, (2) assessed treatment response at the same time point (24 weeks) for the ustekinumab comparison with conventional management in a sensitivity analysis, and (4) the preferred sequential analysis.

3.3 The effect of conventional management on skin symptoms (PASI)

Skin-related outcomes for ustekinumab and anti-TNFs in the previous models were modelled using PASI scores and these are translated into QALYs. In this model, skin-related outcomes for conventional management are modelled in the same way. The PASI score of a patient was the baseline score minus the change from baseline, with the change from baseline the average of the PASI change for PASI75 responders and non-responders.

The PASI 75 response rates were derived from the PASI 50, PASI 75 and PASI 90 response rates. The response rates and the change from baseline scores were different for the anti-TNF alpha naive and experienced populations.

The PASI scores for the patients that withdrew from treatment onto conventional management in the PAS model were also revised from the Final model. In the Final model, the PASI score for the patients that withdrew from treatment rebounded to baseline. In the PAS model, the PASI score was also calculated according to the formula given above. The average PASI score of a patient that had withdrawn from treatment to conventional management was not the same as the average PASI score of a patient in the conventional management strategy because 12 week conventional management PASI response rates were used in the conventional management strategy whereas 24 week

conventional management response rates were used in the anti-TNF alpha and ustekinumab strategies. The effect of this differed according to the population because different response rates and PASI change from baseline estimates differed between the populations. For the anti-TNF alpha naive population, the average PASI score for a patient withdrawn to conventional management from treatment was slightly higher (i.e. worse) than the average of a patient in the conventional management strategy. For the anti-TNF alpha experienced population, the average PASI score for a patient withdrawn to conventional management from treatment was slightly lower (i.e. better) than the average of a patient in the conventional management strategy. As shown in section 4, this meant that the introduction of an effect of conventional management on skin-related outcomes slightly improved the cost-effectiveness of ustekinumab compared to conventional management in the anti-TNF alpha experienced population.

The ERG does not think that it is likely that the average PASI score of a patient withdrawn to conventional management from treatment would be less (i.e. better) than the average PASI score of a patient on conventional management. However, ensuring the average PASI scores are the same for patients on conventional management in each strategy by using 12 week response rates only increases the ICER of ustekinumab compared to conventional management by roughly £300-400. The Alternative model introduced in section 3.5 assumes 24 week response rates for conventional management in each strategy.

The ERG considers the modelling of the effect of conventional management on skin-related outcomes mostly to be reasonable. The effect of incorporating the effect of conventional management on skin symptoms on the results compared to the results of a previous model is presented in Section 4.

3.4 Sequential model

The population of the sequential model was anti-TNF alpha experienced patients. The baseline PASI score included in the PAS submission was the same as that included in the anti-TNF alpha experienced patient model. However, the PASI response rates included in the sequential model were those included in anti-TNF alpha naïve patient model. This was based on an ERG simplifying assumption made in Section 6 of the ERG report, and the ERG considers this to be appropriate. In the anti-TNF alpha experienced patient model the PASI response rates were obtained from the PSUMMIT2 trial. In general, the ERG considers the results of the sequential model to be highly uncertain.

3.5 ERG analyses

In order to provide some context for the results of the manufacturer's PAS submission, the ERG presents the results of the following analyses:

1) the Final model, with and without the PAS price
2) a model closer to the NICE Appraisal Committee's preferred assumptions with a 40 year time horizon and response at 24 weeks for both ustekinumab and conventional management, hereafter referred to as the *Alternative* model

For the assessment of worsening HAQ-DI during ustekinumab or anti-TNF treatment, the ERG notes the lack of data to inform the analysis; the model changes required are too involved for the ERG to undertake given the time available.

The Final model is presented to allow the effect of the PAS, independent of the inclusion of PASI in conventional management to be assessed. The Alternative model is presented to allow the effect of the PAS to be assessed on a model that includes as many as possible of the Alternative assumptions and scenarios.

The ERG found three errors in the original manufacturer's model (Final model), which were carried through to the models in the PAS submission and four errors specific to the PAS submitted models. These errors are listed in Appendix 6.1 and the code changes required listed in Appendix 6.2. The ERG therefore produced corrected as well as uncorrected Final model results and PAS submission model results. The Alternative model incorporates the corrections.

4 Results

In this section the uncorrected and corrected manufacturer's PAS submission results are presented, the uncorrected and corrected Final model results are presented, and the results of an Alternative model closer to the NICE Appraisal Committee's preferred assumptions (as identified by the ERG from TA Guidance 313) an incorporating the corrections are presented. A few of the model errors end up cancelling each other out, but there is a considerable impact on the absolute costs and an effect on absolute QALYs. The errors tended to underestimate cost and QALYs associated with the outcomes, hence the most effective treatments were disadvantaged by the errors. It is the underestimate of the HAQ state-related costs that mostly explains the change in absolute costs, and it is the underestimate of QALYs associated with each health state in year two that mostly explains the change in absolute QALYs. Correcting these errors causes the ICER for ustekinumab compared to conventional management to reduce significantly, but ustekinumab becomes less cost-effective compared to the more effective anti-TNF alpha treatments.

The NICE Appraisal Committee considered the incremental cost-effectiveness ratios for four populations for which there was some evidence. These are presented in Table 4 along with the most appropriate comparator according to the NICE Appraisal Committee and the principal model that was

used in addition to the results of manufacturer and ERG sensitivity analyses. The results for these populations will be highlighted.

Table 4: Populations considered for ustekinumab by the NICE Committee, the most appropriate comparators and the model used

Population for ustekinumab	Most appropriate comparator	Model used
anti-TNF alpha naïve, anti-TNF alpha indicated (4.18, TA313)	Anti-TNFs	anti-TNF alpha naïve patient
anti-TNF alpha naïve, anti-TNF alpha contraindicated (4.19, TA313)	Conventional management	anti-TNF alpha naïve patient
anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions (4.20, TA313)	Anti-TNFs	sequencing
anti-TNF alpha experienced, anti-TNFs as a class have failed (4.21, TA3131)	Conventional management	anti-TNF alpha experienced patient

4.1 The manufacturer's results

4.1.1 Uncorrected results

The manufacturer produced deterministic results for the models with and without the PAS price and probabilistic sensitivity analysis results for the models with the PAS price. All of the following results are from probabilistic sensitivity analyses, except for the sequencing model results to be consistent with the original ERG report. In general, the probabilistic ICERs were in the range £1,000 to £2,000 greater than the deterministic ICERs. The full incremental cost-effectiveness results and the pairwise results compared to conventional management for the manufacturer's model excluding the PAS for the anti-TNF alpha naïve population are presented in Table 5. The results for ustekinumab with the PAS price are reported on a separate line. The results for the anti-TNF alpha experienced population are presented in Table 6. The results of the sequencing model are presented in Table 7.

Table 5: Anti-TNF alpha naïve patients: incremental cost-effectiveness analysis for the uncorrected Manufacturer's model excluding the PAS and the individual results for ustekinumab with the PAS

Technologies	Total		Incremental		ICER (cost per QALY) (£)	ICER vs. conv. Mngmt (£)
	Costs (£)	QALYs	Costs (£)	QALYs		
Conventional management strategies	25,916	4.67				
Adalimumab	60,251	6.25	ED	ED	ED	21,786
Ustekinumab	65,913	6.1	Dominated	Dominated	Dominated	28,014
Etanercept	67,235	6.73	41,319	2.06	20,058	20,092
Golimumab	67,898	6.65	Dominated	Dominated	Dominated	21,180
Infliximab	128,279	6.9	61,044	0.18	347,532	45,860
Ustekinumab (PAS)	59,105	6.09	33,135	1.43	ED	23,164
Probability ustekinumab is most cost-effective at £30,000: 0 (no PAS) 0 (PAS)						
ED: extendedly dominated						

Table 6: Anti-TNF alpha experienced patients: incremental cost-effectiveness analysis for the uncorrected Manufacturer's model excluding the PAS and the individual results for ustekinumab with the PAS

Technologies	Total		Incremental		ICER (cost per QALY) (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Conventional management strategies	30,022	2.84			
Ustekinumab	72,891	4.10	42,875	1.26	33,993
Ustekinumab (PAS)	62,724	4.08	32,700	1.27	25,675
Probability ustekinumab is most cost-effective at £30,000: 0.18 (no PAS) 0.85 (PAS)					

Table 7: Sequencing model: the cost-effectiveness of ustekinumab with and without the PAS given different first-line treatments for the uncorrected manufacturer's model

	Incremental ICER of ustekinumab with the following treatment as first-line treatment (£)			Pairwise ICER vs conventional management (£)
Model	Golimumab	Adalimumab	Etanercept	
Without PAS	37,222	37,222	35,481	33,467
With PAS	25,921	25,921	25,921	25,921

The ICERs for ustekinumab for the populations identified in TA Guidance 313 are collated in Table 8.

Table 8: ICERs for ustekinumab for the populations considered for ustekinumab by the NICE Appraisal Committee

Population for ustekinumab	Most appropriate comparator	Model used	ICER
anti-TNF alpha naïve, anti-TNF alpha indicated	Anti-TNFs	anti-TNF alpha naïve patient	Dominated (no PAS), ED (PAS) P(CE)=0 with PAS
anti-TNF alpha naïve, anti-TNF contraindicated	Conventional management	anti-TNF alpha naïve patient	£28,014 (no PAS), £23,164 (PAS)
anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions	Anti-TNFs	sequencing	£35,481 (no PAS), £25,921 (PAS)
anti-TNF alpha experienced, anti-TNFs as a class have failed	Conventional management	anti-TNF alpha experienced patient	£33,993 (no PAS), £25,657 (PAS) P(CE)=0.85 with PAS
ED, extendedly dominated; P(CE), the probability of ustekinumab being the most cost-effective treatment at the £30.000 threshold			

For the anti-TNF alpha naïve, anti-TNF alpha indicated population, ustekinumab is dominated without the PAS price and extendedly dominated with the PAS price (Table 19). For the anti-TNF alpha naïve, anti-TNF alpha contraindicated population, the ICER for ustekinumab is £28,014 without the PAS price and £23,164 with the PAS price (Table 19). For the anti-TNF alpha experienced who have withdrawn from anti-TNFs due to lack of efficacy or adverse reactions population, the ICER for ustekinumab is £35,481 without the PAS price and £25,921 with the PAS price (Table 21). For the anti-TNF alpha experienced, in whom anti-TNFs as a class have failed population, the ICER for ustekinumab is £33,993 without the PAS price and £25,657 with the PAS price (Table 20). The ERG re-emphasises the uncertainty surrounding the results of the sequencing model. The probability that ustekinumab is cost-effective at the £30,000 threshold is 0.85 with the PAS price for the anti-TNF alpha experienced population but 0 for the anti-TNF alpha naïve population.

The manufacturer reproduced all of the scenarios from the original submission conducting incremental and pairwise cost-effectiveness analyses. Please see the manufacturer's PAS submission for the full results. In summary, for the anti-TNF naïve alpha patient model, the pairwise ICER results compared to conventional management ranged from £23,786 to £35,768 without the PAS price to £21,411 to £29,580 with a PAS price. For the anti-TNF experienced alpha patient model, the pairwise ICER results compared to conventional management ranged from £27,035 to £44,113 without the PAS price to £23,229 to £33,578 with a PAS price. For the sequencing model, the pairwise ICER results compared to conventional management ranged from £28,263 to £48,435 without the PAS price to £25,311 to £37,591 with a PAS price.

4.1.2 ERG corrected results

The full incremental cost-effectiveness results and the pairwise results compared to conventional management for the manufacturer's model excluding the PAS for the anti-TNF alpha naïve population are presented in Table 9. The results for ustekinumab with the PAS price are reported on a separate line. The results for the anti-TNF alpha experienced population are presented in Table 10. The results of the sequencing model are presented in Table 11.

Table 9: Anti-TNF alpha naïve patients: incremental cost-effectiveness analysis for the corrected Manufacturer's model excluding the PAS and the individual results for ustekinumab with the PAS

Technologies	Total		Incremental		ICER (cost per QALY) (£)	ICER vs. Mngmt (£)
	Costs (£)	QALYs	Costs (£)	QALYs		
Conventional management strategies	61,446	4.90	-	-	-	-
Adalimumab	89,716	6.68	ED	ED	ED	15,909
Ustekinumab	95,842	6.49	Dominated	Dominated	Dominated	21,605
Etanercept	96,680	7.25	35,234	2.35	14,993	15,027
Golimumab	97,438	7.14	Dominated	Dominated	Dominated	16,103
Infliximab	157,379	7.45	60,698	0.20	299,615	37,660
Ustekinumab with PAS	88,472	6.49	ED	ED	ED	17,008
Probability ustekinumab is most cost-effective at £30,000 for full analysis: 0 (no PAS) 0 (PAS). Probability ustekinumab is most cost-effective at £30,000 compared to conv. mgmnt: 0.91 (no PAS) 0.98 (PAS)						
ED: extendedly dominated						

Table 10: Anti-TNF alpha experienced patients: incremental cost-effectiveness analysis for the corrected Manufacturer's model excluding the PAS and the individual results for ustekinumab with the PAS

Technologies	Total		Incremental		ICER (cost per QALY)
	Costs	QALYs	Costs	QALYs	
Conventional management strategies	67,422	3.03			
Ustekinumab	105,578	4.44	38,156	1.41	27,052
Ustekinumab (PAS)	94,618	4.44	27,196	1.41	19,284
Probability ustekinumab is most cost-effective at £30,000: 0.77 (no PAS) 0.97 (PAS)					

Table 11: Sequencing model: the cost-effectiveness of ustekinumab with and without the PAS given different first-line treatments for the corrected manufacturer's model

	Incremental ICER of ustekinumab with the following treatment as first-line treatment (£)			Pairwise ICER vs conventional management (£)
Model	Golimumab	Adalimumab	Etanercept	
Without PAS	35,698	35,698	33,553	25,404
With PAS	19,702	19,702	18,429	18,171

The ICERs for ustekinumab for the populations identified in TA Guidance 313 are collated in Table 12.

Table 12: ICERs for ustekinumab for the populations considered for ustekinumab by the NICE Appraisal Committee

Population for ustekinumab	Most appropriate comparator	Model used	ICER
anti-TNF alpha naïve, anti-TNF alpha indicated	Anti-TNFs	anti-TNF alpha naïve patient	Dominated (no PAS), ED (PAS) P(CE)=0 with PAS
anti-TNF alpha naïve, anti-TNF contraindicated	Conventional management	anti-TNF alpha naïve patient	£21,605 (no PAS), £17,008 (PAS) P(CE)=0.98 with PAS
anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions	Anti-TNFs	sequencing	£33,553 (no PAS), £18,429 (PAS)
anti-TNF alpha experienced, anti-TNFs as a class have failed	Conventional management	anti-TNF alpha experienced patient	£27,052 (no PAS), £19,284 (PAS) P(CE)=0.97 with PAS
ED, extendedly dominated; P(CE), the probability of ustekinumab being the most cost-effective treatment at the £30.000 threshold			

For the anti-TNF alpha naïve, anti-TNF alpha indicated population, ustekinumab is dominated without the PAS price and extendedly dominated with the PAS price (Table 9). For the anti-TNF alpha naïve, anti-TNF alpha contraindicated population, the ICER for ustekinumab is £21,605 without the PAS price and £17,008 with the PAS price (Table 9). For the anti-TNF alpha experienced who have withdrawn from anti-TNFs due to lack of efficacy or adverse reactions population, the ICER for ustekinumab is £33,553 without the PAS price and £18,429 with the PAS price (Table 11). For the anti-TNF alpha experienced, in whom anti-TNFs as a class have failed population, the ICER for ustekinumab is £27,052 without the PAS price and £19,284 with the PAS price (Table 10). The ERG re-emphasises the uncertainty surrounding the results of the sequencing model. The probability that ustekinumab is cost-effective at the £30,000 threshold is 0.97 with the PAS price for the anti-TNF alpha experienced population but 0 for the anti-TNF alpha naïve population.

4.2 The effect of the PAS price on the Final model

4.2.1 Uncorrected Final model

The full incremental cost-effectiveness results and the pairwise results compared to conventional management for the Final model excluding the PAS for the anti-TNF alpha naïve population are presented in Table 13. The results for ustekinumab with the PAS price are reported on a separate line. The results for the anti-TNF alpha experienced population are presented in Table 14. The results of the sequencing model are presented in Table 15.

Table 13: Anti-TNF alpha naïve patients: incremental cost-effectiveness analysis for the uncorrected Final model excluding the PAS, and the individual result for ustekinumab with the PAS

Technologies	Total		Incremental		ICER (cost per QALY) (£)	ICER vs. conv. Mngmt (£)
	Costs (£)	QALYs	Costs (£)	QALYs		
Conventional management strategies	33,069	4.62				-
Adalimumab	64,471	6.39	ED	ED	ED	17,763
Ustekinumab	70,280	6.20	Dominated	Dominated	Dominated	23,567
Etanercept	72,216	6.93	39,146	2.31	16,969	16,969
Golimumab	72,931	6.84	Dominated	Dominated	Dominated	17,948
Infliximab	134,840	7.12	62,624	0.20	320,055	40,665
Ustekinumab (PAS)	62,713	6.20	ED	ED	ED	18,762
Probability ustekinumab is most cost-effective at £30,000: 0 (no PAS) 0 (PAS)						

Table 14: Anti-TNF alpha experienced patients: cost-effectiveness of ustekinumab compared to conventional management with and without the PAS for the uncorrected Final model

Technologies	Total		Incremental		ICER (cost per QALY) (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Conventional management strategies	36,022	2.81			
Ustekinumab	77,294	4.19	41,272	1.39	29,784
Ustekinumab (PAS)	66,063	4.20	30,040	1.39	21,668
Probability ustekinumab is most cost-effective at £30,000: 0.589 (no PAS) 0.94 (PAS)					

Table 15: Sequencing model: the cost-effectiveness of ustekinumab with and without the PAS given different first-line treatments for the uncorrected Final model

	Incremental ICER of ustekinumab with the following treatment as first-line treatment (£)			Pairwise ICER vs conventional management (£)
Model	Golimumab	Adalimumab	Etanercept	
Without PAS	32,824	37,851	32,824	27,469
With PAS	21,449	21,449	20,330	19,991

The ICERs for ustekinumab for the populations identified in TA Guidance 313 are collated in Table 16.

Table 16: ICERs for ustekinumab for the populations considered for ustekinumab by the NICE Committee

Population for ustekinumab	Most appropriate comparator	Model used	ICER
anti-TNF alpha naïve, anti-TNF alpha indicated	Anti-TNFs	anti-TNF alpha naïve patient	Dominated (no PAS), ED (PAS) P(CE)=0 with PAS
anti-TNF alpha naïve, anti-TNF alpha contraindicated	Conventional management	anti-TNF alpha naïve patient	£23,567 (no PAS), £18,762 (PAS)
anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions	Anti-TNFs	sequencing	£32,824 (no PAS), £20,330 (PAS)
anti-TNF alpha experienced, anti-TNFs as a class have failed	Conventional management	anti-TNF alpha experienced patient	£29,784 (no PAS), £21,668 (PAS) P(CE)=0.94 with PAS
ED, extendedly dominated; P(CE), the probability of ustekinumab being the most cost-effective treatment at the £30.000 threshold			

For the anti-TNF alpha naïve, anti-TNF alpha indicated population, ustekinumab is dominated without the PAS price and extendedly dominated with the PAS price (Table 13). For the anti-TNF alpha naïve, anti-TNF alpha contraindicated population, the ICER for ustekinumab is £23,567 without the PAS price and £18,762 with the PAS price (Table 13). For the anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions population, the ICER for ustekinumab is £32,824 without the PAS price and £20,330 with the PAS price (Table 15). For the anti-TNF alpha experienced, anti-TNFs as a class have failed population; the ICER for ustekinumab is £29,784 without the PAS price and £21,668 with the PAS price (Table 14). The probability that ustekinumab is cost-effective at the £30,000 threshold is 0.94 with the PAS price for the anti-TNF alpha experienced population but 0 for the anti-TNF naïve population.

4.2.2 ERG corrected Final Model

The full incremental cost-effectiveness results and the pairwise results compared to conventional management for the Final model excluding the PAS for the anti-TNF alpha naïve population are presented in Table 17. The results for ustekinumab with the PAS price are reported on a separate line. The results for the anti-TNF alpha experienced population are presented in Table 18. The results of the sequencing model are presented in Table 19.

Table 17: Anti-TNF alpha naïve patients: incremental cost-effectiveness analysis for the corrected Final model excluding the PAS, and the individual result for ustekinumab with the PAS

Technologies	Total		Incremental		ICER (cost per QALY)	ICER vs. conv. Mngmt
	Costs	QALYs	Costs	QALYs		
Conventional management strategies	62,813	4.83	-	-	-	-
Adalimumab	90,944	6.63	ED	ED	ED	15,614
Ustekinumab	96,970	6.44	Dominated	Dominated	Dominated	21,262
Etanercept	97,761	7.19	34,948	2.36	14,808	14,792
Golimumab	98,477	7.09	Dominated	Dominated	Dominated	15,816
Infliximab	158,423	7.40	60,662	0.21	295,037	37,229
Ustekinumab (PAS)	89,620	6.44	ED	ED	ED	16,658
Probability ustekinumab is most cost-effective at £30,000 for full analysis: 0 (no PAS) 0 (PAS). Probability ustekinumab is most cost-effective at £30,000 compared to conv. mgmnt: 0.76 (no PAS) 0.98 (PAS)						

Table 18: Anti-TNF alpha experienced patients: cost-effectiveness of ustekinumab compared to conventional management with and without the PAS for the corrected Final model

Technologies	Total		Incremental		ICER (cost per QALY)
	Costs	QALYs	Costs	QALYs	
Conventional management strategies	67,914	2.99	-	-	-
Ustekinumab	106,113	4.40	38,200	1.40	27,238
Ustekinumab (PAS)	95,249	4.39	27,335	1.40	19,488
Probability ustekinumab is most cost-effective at £30,000: 0.76 (no PAS) 0.97 (PAS)					

Table 19: Sequencing model: the cost-effectiveness of ustekinumab with and without the PAS given different first-line treatments for the corrected Final model

	Incremental ICER of ustekinumab with the following treatment as first-line treatment (£)			Pairwise ICER vs conventional management (£)
Model	Golimumab	Adalimumab	Etanercept	
Without PAS	34,892	34,892	32,836	24,802
With PAS	19,196	19,196	17,980	17,691

The ICERs for ustekinumab for the populations identified in TA Guidance 313 are collated in Table 20.

Table 20: ICERs for ustekinumab for the populations considered for ustekinumab by the NICE Committee

Population for ustekinumab	Most appropriate comparator	Model used	ICER
anti-TNF alpha naïve, anti-TNF alpha indicated	Anti-TNFs	anti-TNF alpha naïve patient	Dominated (no PAS), ED (PAS) P(CE)=0 with PAS
anti-TNF alpha naïve, anti-TNF alpha contraindicated	Conventional management	anti-TNF alpha naïve patient	£21,262 (no PAS), £16,658 (PAS) P(CE)=0.98 with PAS
anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions	Anti-TNFs	sequencing	£32,836 (no PAS), £17,980 (PAS)
anti-TNF alpha experienced, anti-TNFs as a class have failed	Conventional management	anti-TNF alpha experienced patient	£27,238 (no PAS), £19,488 (PAS) P(CE)=0.97 with PAS
ED, extendedly dominated; P(CE), the probability of ustekinumab being the most cost-effective treatment at the £30.000 threshold			

For the anti-TNF alpha naïve, anti-TNF alpha indicated population, ustekinumab is dominated without the PAS price and extendedly dominated with the PAS price (Table 17). For the anti-TNF alpha naïve, anti-TNF alpha contraindicated population, the ICER for ustekinumab is £21,262 without the PAS price and £16,658 with the PAS price (Table 17). For the anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions population, the ICER for ustekinumab is £32,836 without the PAS price and £17,980 with the PAS price (Table 19). For the anti-TNF alpha experienced, anti-TNFs as a class have failed population; the ICER for ustekinumab is £27,238 without the PAS price and £19,488 with the PAS price (Table 18). The probability that ustekinumab is cost-effective at the £30,000 threshold is 0.97 with the PAS price for the anti-TNF alpha experienced population but 0 for the anti-TNF naïve population.

4.3 The effect of the PAS price on an Alternative model with the preferred assumptions of the NICE Committee

All the errors identified by the ERG have been corrected in the models to produce the results presented in this section.

The full incremental cost-effectiveness results and the pairwise results compared to conventional management for the Alternative model excluding the PAS for the anti-TNF alpha naïve population are presented in Table 21. The results for ustekinumab with the PAS price are reported on a separate line. The results for the anti-TNF alpha experienced population are presented in Table 22. The results of the sequencing model are presented in Table 23.

Table 21: Anti-TNF alpha naïve patient model: incremental cost-effectiveness analysis for the Alternative model excluding the PAS, and the individual result for ustekinumab with the PAS

Technologies	Total		Incremental		ICER (cost per QALY) (£)	ICER vs. conv. mgmt. (£)
	Costs (£)	QALYs	Costs (£)	QALYs		
Conventional management strategies	59,755	5.26	-	-	-	-
Adalimumab	88,573	6.71	ED	ED	ED	19,915
Ustekinumab	94,613	6.52	Dominated	Dominated	Dominated	27,699
Etanercept	95,514	7.27	35,759	2.01	17,791	17,809
Golimumab	96,273	7.16	Dominated	Dominated	Dominated	19,213
Infliximab	150,338	7.47	54,823	0.20	268,107	40,943
Ustekinumab with PAS	87,278	6.52	ED	ED	ED	21,857
Probability ustekinumab is most cost-effective at £30,000 for full analysis: 0 (no PAS) 0 (PAS). Probability ustekinumab is most cost-effective at £30,000 compared to conv. mgmnt: 0.7 (no PAS) 0.91 (PAS)						
ED: extendedly dominated						

Table 22: Experienced patient model: cost-effectiveness of ustekinumab compared to conventional management with and without the PAS for the Alternative model

Technologies	Total		Incremental		ICER (cost per QALY) (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Conventional management strategies	65,929	3.34	-	-	-
Ustekinumab	104,651	4.44	38,721	1.10	35,098
Ustekinumab (PAS)	93,745	4.44	27,816	1.10	25,292
Probability ustekinumab is most cost-effective at £30,000: 0.11 (no PAS) 0.84 (PAS)					

Table 23: Sequencing model: the cost-effectiveness of ustekinumab with and without the PAS given different first-line treatments for the Alternative model

	Incremental ICER of ustekinumab with the following treatment as first-line treatment (£)			Pairwise ICER vs conventional management (£)
Model	Golimumab	Adalimumab	Etanercept	
Without PAS	35,742	35,742	35,295	39,125
With PAS	**25,393**	**25,393**	**25,393**	**25,393**

The ICERs for ustekinumab for the populations identified in TA Guidance 313 are collated in Table 24.

Table 24: ICERs for ustekinumab for the populations considered for ustekinumab by the NICE Committee

Population for ustekinumab	Most appropriate comparator	Model used	ICER
anti-TNF alpha naïve, anti-TNF alpha indicated	Anti-TNFs	anti-TNF alpha naïve patient	Dominated (no PAS), ED (PAS) P(CE)=0 with PAS
anti-TNF alpha naïve, anti-TNF alpha contraindicated	Conventional management	anti-TNF alpha naïve patient	£27,699 (no PAS), £ 21,857 (PAS) P(CE)=0.91 with PAS
anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions	Anti-TNFs	sequencing	£35,295 (no PAS), £25,393 (PAS)
anti-TNF alpha experienced, anti-TNFs as a class have failed	Conventional management	anti-TNF alpha experienced patient	£35,098 (no PAS), £25,292 (PAS) P(CE)=0.84 with PAS
ED, extendedly dominated; P(CE), the probability of ustekinumab being the most cost-effective treatment at the £30.000 threshold			

For the anti-TNF alpha naïve, anti-TNF alpha indicated population, ustekinumab is dominated without the PAS price and extendedly dominated with the PAS price (Table 21). For the anti-TNF alpha naïve, anti-TNF alpha contraindicated population, the ICER for ustekinumab is £27,699 without the PAS price and £21,857 with the PAS price (Table 21). For the anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions population, the ICER for ustekinumab is £35,295 without the PAS price and £25,393 with the PAS price (Table 23). For the anti-TNF alpha experienced, anti-TNFs as a class have failed, the ICER for ustekinumab is £35,098 without the PAS price and £25,292 with the PAS price (Table 22). The probability that ustekinumab is cost-effective at the £30,000 threshold is 0.84 with the PAS price for the anti-TNF alpha experienced population but 0 for the anti-TNF alpha naïve population.

We explored the individual contributions of changing the time horizon to 40 years and changing the time of assessment of conventional management to 24 weeks from 12 weeks. For the anti-TNF alpha experienced patients, the pairwise ICER compared to conventional management for ustekinumab in the manufacturer's PAS submission model was £19,284. When the time horizon is adjusted to 40 years, this increases the ICER slightly to £19,301. However, when the assessment time for conventional management is changed to 24 weeks, this increases the ICER further to £25,292.

A 24 week time point of assessment rather than a 12 week assessment time point affects the results because different PsARC and PASI75 response rates are used. These response rates are assumed to persist for the remainder of the time horizon in the model, adjusting downwards over time due to mortality. The response rates were estimated from a mixed treatment comparison and are reported in Table 25. For the anti-TNF alpha experienced population, the PASI75 response rate is higher at 24

weeks than at 12 weeks. The PsARC response rate is lower. The net effect of a 24 week assessment time point is an increase in QALYs for conventional management. The ICER estimate appears sensitive to these values.

Table 25: PsARC and PASI75 response rates at 12 and 24 weeks for conventional management

	Response rates			
	Naive population		Experienced population	
	12 weeks	24 weeks	12 weeks	24 weeks
PsARC	[redacted]	[redacted]	29%	25.8%
PASI75	[redacted]	[redacted]	1.6%	3.2%

5 ERG summary

The ERG considers that the PAS implementation and the effect of conventional management on skin symptoms have been adequately modelled. On review of the TA Guidance 313 the ERG identified two additional NICE Appraisal Committee preferred assumptions that could have been implemented in the base case. These were the same assessment time point for conventional management as for ustekinumab (24 weeks) and a forty year time horizon to be consistent with previously published models.

In the manufacturer's model, the PAS price brings the ICER of ustekinumab down below the £30,000 threshold for each of the considered populations except for the anti-TNF naïve population, for which there was a 0 probability of ustekinumab being the most cost-effective treatment. A summary of the results for the corrected Final model, the manufacturer's model and the Alternative model with the PAS price is presented in Table 26. The difference between the results of the Manufacturer's model and the Final model in Table 26 shows that, with the addition of the effect of conventional management on skin symptoms, the ICER of ustekinumab increases slightly except for the anti-TNF alpha experienced, anti-TNFs as a class have failed population. This is due to the use of 24 week conventional management response rates for patients withdrawn to conventional management form treatment compared to 12 week conventional management response rates for patients starting on conventional management.

In the uncorrected models presented in Table 27, there was an increase in the ICER for ustekinumab when compared to conventional management when the effect of conventional management on skin symptoms was included, and increased further when the same 24 week assessment time point is used. Ustekinumab remained dominated by extension in every case in the anti-TNF alpha naive population.

The difference between the results of the Alternative model and the Manufacturer's model in Table 26 shows that, with a 40 year time horizon and the same assessment time point at 24 weeks for conventional management and ustekinumab, the ICER of ustekinumab increases. When a time horizon of 40 years is modelled without modelling the same assessment time point for conventional management and ustekinumab, the results do not change greatly. Most of the increase in the ICER is due to the same assessment point, but with the PAS price the ICER remained below £30,000/QALY for every population, except for the anti-TNF alpha naïve, anti-TNF alpha indicated population, for which ustekinumab was extendedly dominated.

The errors in the manufacturer's models substantially affect the absolute costs and QALYs, and the ICER for ustekinumab compared to conventional management reduces significantly as a result for all of the populations except for the anti-TNF alpha naïve, anti-TNF alpha indicated population, as the anti-TNF alpha treatments always dominate ustekinumab by extension.

Table 26: Summary of the results for the ERG corrected Final model, the manufacturer's PAS model and the Alternative model with the PAS price

Population for ustekinumab	Final Model (*with* PAS)	Manufacturer's PAS model (*with* PAS)	Alternative Model (*with* PAS)
anti-TNF alpha naïve, anti-TNF alpha indicated	Extendedly dominated	Extendedly dominated	Extendedly dominated
anti-TNF alpha naïve, anti-TNF contraindicated	£16,658	£17,008	£21,857
anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions	£17,980	£18,429	£28,281
anti-TNF alpha experienced, anti-TNFs as a class have failed	£19,488	£19,284	£ 25,292

Table 27: Summary of the results for the uncorrected Final model, the manufacturer's model and the Alternative model with the PAS price

Population for ustekinumab	Final Model (*with* PAS)	Manufacturer's PAS model (*with* PAS)	Alternative Model (*with* PAS)
anti-TNF alpha naïve, anti-TNF alpha indicated	Extendedly dominated	Extendedly dominated	Extendedly dominated
anti-TNF alpha naïve, anti-TNF contraindicated	£18,762	£23,164	£30,177
anti-TNF alpha experienced, withdraw from anti-TNF due to lack of efficacy or adverse reactions	£20,330	£25,921	£38,679
anti-TNF alpha experienced, anti-TNFs as a class have failed	£21,668	£25,657	£34,845

6 Appendices

6.1 Appendix 1- Model errors

There were inconsistencies in accounting for outcomes across the Markov model cycles within models and between models. The ERG found the following errors in the Final model and these also apply to the PAS submission model:

1) From year 2 onwards patients received only 12 weeks' worth of HAQ costs per cycle when the cycles are actually 1-year cycles. Since the first cycle was labelled 0 and the first four cycles were of 12 weeks duration each, this equates to cycle 4 onwards.
2) For year 2 only, only 12 weeks' worth of QALYs were applied when a full year of QALYs should have been applied.
3) Discounting started in year 3 (cycle 5) rather than year 2.

The following errors were identified in the PAS submission models only:

4) For patients receiving conventional management, MRU costs (consultation and diagnostic) were only incurred for patients who were PsARC responders, whereas in the Final model all patients on conventional management incurred these costs.
5) For patients on conventional management, when a patient died they continued to incur HAQ costs for the remaining cycles of the model up to the time horizon.
6) For year 2 only, only 12 weeks' worth of costs associated with PASI scores were applied when a full year of PASI-related costs should have been applied.
7) While (correctly) the original Final model calculated the patients in each health state in year 2 (from cycles 3 to 4) by accounting for the mortality risk associated with the fourth quarter of year 1, i.e. the mortality risk associated with 12 weeks, in the PAS submission model the mortality risk associated with one year was applied.

6.2 Appendix 2 – Model changes

6.2.1 To correct the HAQ scores per cycle

For the Final models,

Remove " /(365.25/7/12) from the end of the code

"Calcs_Ustekinumab!ED35:ED86",

and the same for every treatment except for conventional management, which should be

"Calcs_CMS!BT35:BT86",

For the PAS models, it is the same for each treatment except for CMS, which should be

“Calcs_CMS!CP35:CP86”,

6.2.2 Year 2 QALYs

For both the original Final models and PAS submission models:

For the QALY estimates in year 2, change end of code in Calcs_Ustekinumab!EP35:EV86”, to IF($B35>3,1,((12*7)/365.25))) from IF($B35>4,1,((12*7)/365.25))). Make the comparable changes for the other treatment strategies.

6.2.3 Discounting

To correct the discounting error in every Final and PAS model, the following changes were made:

In ‘Calcs_Ustekinumab!F35’

Change

=IF(ROUND(D31+$C35,0)>100,"",1/(1+p_Discount_Costs)^ROUNDDOWN(C35,0))

to

=IF(ROUND(D31+$C35,0)>100,"",1/(1+p_Discount_Costs)^ROUNDUP(C35,0))

Drag so that the change is made to “Calcs_Ustekinumab!F35:G86.

Repeat for every intervention.

6.2.4 Conventional management MRU costs

To correct the conventional management MRU costs,

In “Calcs_CMS!CO32:CO86”, change SUM(BU34:BV34) to SUM(BT34:BW34)

6.2.5 Conventional management HAQ costs

To correct the conventional management HAQ costs to avoid deceased incurring costs,

In “Calcs_CMS!CP33:CP86”, change SUM(BT34:BX34) to SUM(BT34:BW34)

6.2.6 Conventional management PASI cost in year 2

To correct the conventional management PASI cost in year 2,

In “Calcs_CMS!CQ35”,

Change

=IF(ROUND(D31+C35,0)>100,"",SUMPRODUCT(CG35:CJ35,BT35:BW35)*IF(Phototherapy_Choice="include",p_Cost_PASI_With_Photo,p_Cost_PASI_No_Photo)/(365.25/7/12))

to

=IF(ROUND(D31+C35,0)>100,"",SUMPRODUCT(CG35:CJ35,BT35:BW35)*IF(Phototherapy_Choice="include",p_Cost_PASI_With_Photo,p_Cost_PASI_No_Photo))

6.2.7 Mortality risk in cycle 3

To change the health state distributions in cycle 4 in order to account for the 12 week mortality risk of cycle 3,

In “Calcs_CMS!K35:O35” and for the other interventions

add /(365.25/7/12), for example

change

=IF(ROUND(D31+C35,0)>100,"",K34*(1-VLOOKUP(D34,Mortality_Range,6,FALSE)))

to

=IF(ROUND(D31+C35,0)>100,"",K34*(1-VLOOKUP(D34,Mortality_Range,6,FALSE)/(365.25/7/12)))