NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Technology appraisals

Trabectedin

Patient access scheme submission

1 October 2009

PHARMA MAR, S.A.

POLÍGONO INDUSTRIAL LA MINA

AVDA. DE LOS REYES, 1

28770 COLMENAR VIEJO

MADRID – SPAIN

1. DETAILS OF THE PATIENT ACCESS SCHEME

1.1. Please provide the title of the appraisal for which the patient access scheme applies

Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

1.2. Please provide any background details and the rationale for developing the patient access scheme

PharmaMar have proposed this scheme in response to the possibility that Yondelis® (trabectedin) may not be recommended by NICE on grounds of cost-effectiveness. PharmaMar considers Yondelis to be of substantial benefit to soft tissue sarcoma patients. In the Consultation Document (ACD) the Appraisal Committee "agree that trabectedin provided an improvement in the treatment of advanced soft tissue sarcoma and that it was likely that trabectedin would increase overall survival by more than 3 months". PharmaMar is therefore proposing this scheme as a means of making it available to these patients who would otherwise have limited treatment options. We further note that, in the ACD (Paragraph 4.13), the Committee concluded that trabectedin meets the criteria for being a life-extending, end-of-life treatment.

1.3. Please state whether the scheme is financially based or outcome based

The scheme is financially based.

1.4. Please provide specific details about the patient population that the scheme applies to.

As part of this patient access scheme, PharmaMar propose to make Yondelis available to all patients with advanced soft tissue sarcoma who have failed treatment with ifosfamide and anthracyclines, or who are unsuited to receive these agents.

1.5. Please provide details of when the scheme will apply to the population specified above and why?

The scheme will apply to patients who require more than 5 cycles of trabectedin. The rationale for selecting this scheme is to achieve acceptable cost-effectiveness outcomes. The expected costs to the NHS will be substantially reduced compared with previous estimates and patient access to treatment will be unaffected. The criteria will be easily measured by monitoring the number of treatments that patients receive.

1.6. What proportion of the population in 1.4 is expected to meet the scheme criteria specified in 1.5?

In the Pivotal Phase II STS-201 trial, 41% of patients received more than 5 cycles of trabectedin, and so would be eligible to receive additional free cycles of Yondelis as part of the patient access scheme. The three pooled phase II non comparative studies including non L-sarcoma patients reported that 28% of patients received more than 5 cycles of trabectedin.

1.7. Please explain how the NHS will be rebated through the Patient Access Scheme

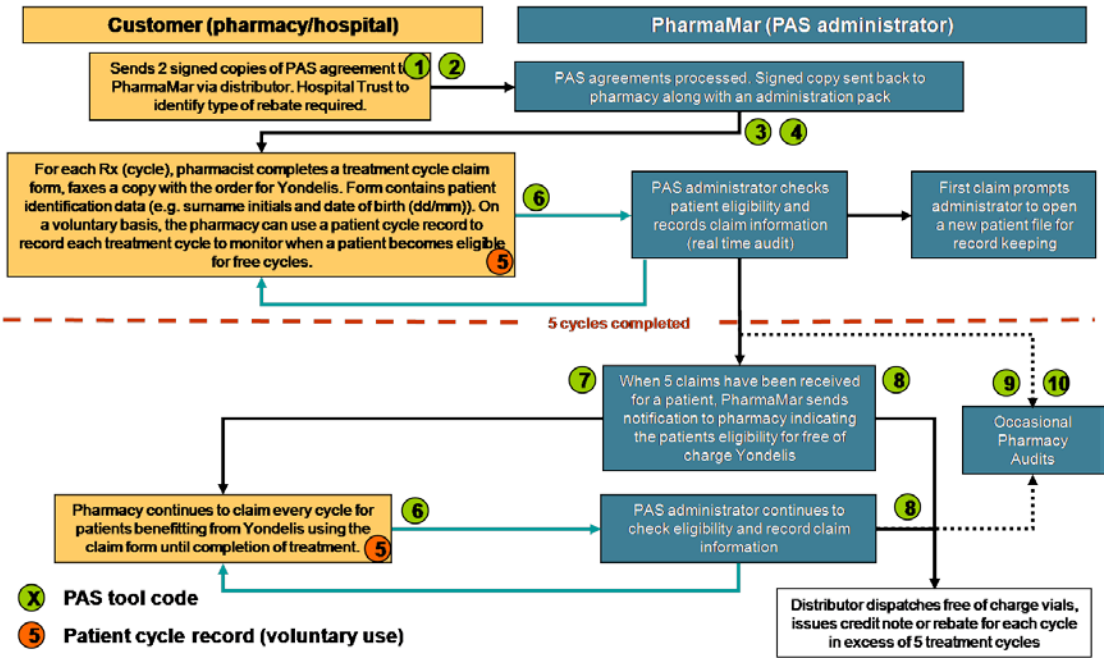
Participating NHS Hospital Trusts would order Yondelis in the same way as they would if there were no scheme except that they will asked to send treatment cycle claim forms to PharmaMar's distributor with each order. The treatment cycle claim forms will be sent by the pharmacy with the product order or within two to three months of each order. The usage of Yondelis by the hospital will be rebated in the form of free stock. For credit notes/cash rebates the claim form can be sent on a quarterly basis.

1.8. Please provide details of how the scheme will be administered. Please specify any additional data or information that may need to be collected, explaining when this will be done and by whom.

For each treatment cycle administered to a patient eligible for Yondelis, a PAS authorised person completes a treatment cycle claim form and faxes a copy with the order for Yondelis. The form contains anonymised patient data (e.g. surname, initials and date of birth (dd/mm)). When a patient has received 5 cycles of Yondelis, PharmaMar would send notification to pharmacy indicating the patient's eligibility for free of charge Yondelis. The pharmacy continues to claim every cycle for patients benefitting from Yondelis using the claim form until completion of treatment. A t the discretion of the institution, Yondelis would be rebated in the form of free stock, as a rebate via credit note or by transfer of funds back to the institute.

On a voluntary basis, the pharmacy can use a patient cycle record to record each treatment cycle to monitor when a patient becomes eligible for free cycles.

1.9. Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.



1.10. Please provide details of the duration of the scheme

PharmaMar commit to continuing with the scheme until NICE conducts a scheduled review of its appraisal of Yondelis for the treatment of soft tissue sarcoma.

1.11. Are there any equity or equality issues relating to the patient access scheme bearing in mind current legislation and any issues identified during the course of the appraisal? If so how have these been addressed?

No equity or equality issues have been identified.

1.12. If available please list any scheme agreement forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents. Please include copies in the appendix.

Tool	Description	Purpose
1	Introductory letter to hospitals/pharmacies	This would be sent to hospital pharmacies to describe the scheme and encourage participation
2	Agreement (contract with hospitals)	This would be sent to hospital pharmacies with the introductory letter. It outlines the terms and conditions of the scheme and pharmacy's rebate preference. A signed Agreement triggers participation in the scheme.
3	PAS binder (Administration Pack)	This would be sent to pharmacies. It contains materials to help manage the PAS (i.e. 4, 5 and 6).
4	PAS Guide for pharmacies	This informs pharmacies of how the scheme works, what records to keep, how to make claims and what PharmaMar will do when claims are received, and the audit process
5	Treatment cycle record	This can be used on a voluntary basis by pharmacies to keep a record of each patient's treatment history.
6	Treatment cycle claim form	The treatment cycle claim form is sent to the distributor with product orders preferably or within 2-3 months of product orders for each cycle. For credit notes/cash rebates the claim form can be sent on a quarterly basis. Cycles are counted and after cycle 5 PharmaMar authorises free drug delivery (or credit note/ rebate).
7	Notification of free drug eligibility	A letter/ e-mail will be sent to the pharmacy to inform them that patient with surname initials and date of birth dd/mm is eligible for free of charge Yondelis.
8	Rebate instructions to distributor	This is used by PharmaMar to instruct their distributor to authorise supply of free drug (or alternatives) to pharmacies.
9	Audit process instructions	Audits will be performed occasionally to ensure the scheme is working as intended. This tool instructs auditors on how to audit a pharmacy.
10	Audit checklist	Checklist for use in the audit.

2 COST-EFFECTIVENESS

2.1 Methodological approach

2.1.1 Please provide details of how the patient access scheme has been incorporated into the analysis

The patient access scheme has been incorporated into the cost-effectiveness analysis by assigning a lower cost to for free cycles of treatment. The first 5 cycles of chemotherapy are assigned full cost, including the acquisition cost of Yondelis. Cycle 6 and subsequent cycles are assigned the cost of administration of a cycle so chemotherapy and of the cost of dexamethasone but the acquisition of Yondelis in these cycles is assumed to be zero.

In the PAS, an additional administrative cost per cycle was included for the pharmacist to fill out the Treatment Cycle Form. A one-off cost for training a pharmacist to operate the scheme was also applied.

2.1.2 If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. Please provide details of how this has been done. No other changes should be made to the model.

The analysis has been conducted on a version of the cost-effectiveness analysis that incorporates all responses to the ERG recommendations and concerns raised by the appraisal committee. This model resolves structural problems in the original model that assigned Best Supportive Care a lower utility on initiation into the model than patients receiving Yondelis. The model assumes that utility is equal in the progression free and progressed health state. When patients die a utility decrement associated with a month of progressed disease is applied in the model to account for the sudden deterioration in health reported to be observed in late stage soft tissue sarcoma.

2.1.3 Please provide details of any additional patient-related costs incurred by implementing the patient access scheme (see table 1). The costs should be provided for the intervention with and without the patient access scheme.

Table 1: Patient related costs for the intervention with and without the patient access scheme

	Intervention without PAS		Intervention with PAS	
	Unit cost (£)	Total cost per cycle per patient	Unit cost (£)	Total cost per cycle per patient
Cycles 1-5				
Intervention acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring tests	319.61*	319.61*	319.61*	319.61*
Diagnostic tests				
Appointments				
Other costs: Dexamethasone	1.98:1.00 (2mL:1mL)	4.96	1.98:1.00 (2mL:1mL)	4.96
Total patient related costs per cycle		[redacted]		[redacted]
Cycles >=6				
Intervention acquisition	[redacted]	[redacted]	Nil	Nil
Monitoring tests	319.61*	319.61*	319.61*	
Diagnostic tests				
Appointments				
Other costs: Dexamethasone	1.98:1.00 (2mL:1mL)	4.96	1.98:1.00 (2mL:1mL)	4.96
Total patient related costs per cycle		[redacted]		324.57
Total per patient **undiscounted**		[redacted]		[redacted]&

PAS: Patient Access Scheme; *NHS Reference Costs, item SB12Z; & Based on mean of 3.48 cycles per patient at full price; and 3.51 cycles free.

The scheme will operate by allowing patients to receive free cycles of Yondelis after 5 paid cycles have been administered. The total cost per patient therefore depends on the number of cycles received. In the pivotal study, patients received a mean of 6.99 cycles of trabectedin. Of these, 3.48 cycles were administered to patients who were receiving their first to fifth cycles of trabectedin. The reminder (a mean of 3.51 cycles per patient) were administered to patients how ere receiving their 6th or subsequent cycle of trabectedin.

2.1.4 Please use table 2 to list any operational costs related to the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). Please give the reference source of these costs. Please refer to section 6.2 of the 'Specification for manufacturer/sponsor submission of evidence'

PharmaMar will provide all materials, forms and documents to operate the scheme, and will provide training to staff in oncology centres to teach them how to complete the forms.

The operational cost of the scheme to the NHS will therefore be limited to the staff time required to be trained to operate the scheme and time required to fill in and dispatch the forms.

Table 2: Operational costs relating to patient access scheme

	Calculation of cost	Reference source
Stock management	Nil	Not applicable
Admin of claims forms	£8 per cycle given	PSSRU (2008) Cost per hour of hospital pharmacist p140. Assumed that it will take 15 minutes to complete and return the form for each cycle given.
Staff training to administer scheme	£32 / hour * 3 staff * 1 hour / person = £96 / centre 7.8 patients per centre = £12.30 per patient	PSSRU (2008) Cost per hour of hospital pharmacist p140. It is assumed that for each centre 3 staff undergo one hour of training each to administer the scheme. It is estimated that in the first year 78 patients would be eligible for trabectedin distributed across 10 centres, for an average of 7.8 patients per centre. The cost per centre of training staff is divided between patients expected to be seen. Costs in subsequent years may be lower if the number of patients treated per site increases
Other costs		
Total operational costs	£12.30 per patient plus £8 per cycle	

2.2 Summary results

Base case analysis

2.2.1 Please present the cost-effectiveness results as follows:

• table 4 (sic) should summarise the results for the intervention without the patient access scheme

• table 5 (sic) should summarise the results for the intervention with the patient access scheme

Table 3: Base case cost effectiveness without patient access scheme

	Intervention (without PAS)	Usual care
Intervention acquisition cost (£)	[redacted]	£0
Other costs (£)	£5,559	£1,965
Total costs (£)	[redacted]	£1,965
Difference in total costs (£)		[redacted]
LYG	1.529	0.710
LYG difference		0.819
QALYs	0.98	0.449
QALY difference		0.535
ICER (£)		£50,747

[a] trabectedin cost only, cost of cycles given in year 2 or later discounted at 3.5% to be consistent with model results

Table 4: Base case cost effectiveness with patient access scheme

	Intervention (without PAS)	Usual care
Intervention acquisition cost (£)	[redacted]	£0
Other costs (£)	£5,5,14	£1,965
Total costs (£)	[redacted]	£1,965
Difference in total costs (£)		[redacted]
LYG	1.529	0.710
LYG difference		0.819
QALYs	0.98	0.449
QALY difference		0.535
ICER (£)		£28,712

[a] trabectedin cost only, all paid cycles occur in year 1

2.2.2 Please present the incremental results as follows:

- table 6 (sic) should summarise the results without the patient access scheme
- table 7 (sic) should summarise the results with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 5: Base case incremental results without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALY	ICER vs baseline (QALYs)	ICER inc. (QALYs)
Yondelis	[redacted]	1.529	0.98	[redacted]	0.819	0.535	50,747	50,845
Best Supportive care	1,965	0.710	0.449					

Table 6: Base case incremental results with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALY	ICER vs baseline (QALYs)	ICER inc. (QALYs)
Yondelis	[redacted]	1.529	0.98	[redacted]	0.819	0.535	28,712	28,712
Best Supportive care	1,965	0.710	0.449					

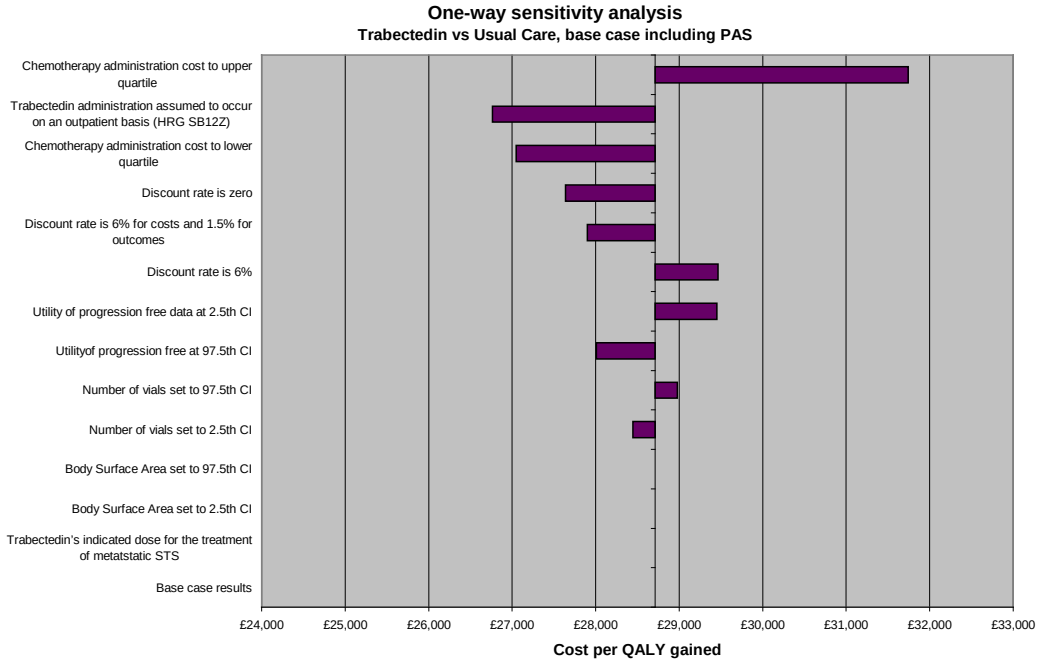
Sensitivity analyses

2.2.3 Please present deterministic sensitivity analysis results as described for the main submission. Consider using tornado diagrams.

Table 7: results of one way sensitivity analysis

Description	Incremental costs	Incremental Life years	Incremental QALYs	ICER - QALYs
Base case results	[redacted]	0.819	0.534	£28,712
Discount rate is zero	[redacted]	0.856	0.559	£27,637
Discount rate is 6%	[redacted]	0.795	0.519	£29,463
Discount rate is 6% for costs and 1.5% for outcomes	[redacted]	0.840	0.548	£27,901
Trabectedin's indicated dose for the treatment of metastatic STS	[redacted]	0.819	0.535	£28,712
Number of vials set to 2.5th CI	[redacted]	0.819	0.535	£28,446
Number of vials set to 97.5th CI	[redacted]	0.819	0.535	£28,979
Body Surface Area set to 2.5th CI	[redacted]	0.819	0.535	£28,712
Body Surface Area set to 97.5th CI	[redacted]	0.819	0.535	£28,712
Trabectedin administration assumed to occur on an outpatient basis (HRG SB12Z)	[redacted]	0.819	0.535	£26,763
Chemotherapy administration cost to lower quartile	[redacted]	0.819	0.535	£27,050
Chemotherapy administration cost to upper quartile	[redacted]	0.819	0.535	£31,740
Utility of progression free data at 2.5th CI	[redacted]	0.819	0.521	£29,452
Utility of progression free at 97.5th CI	[redacted]	0.819	0.548	£28,009

Figure 1: one way sensitivity analysis



2.2.4 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

1.13. Probabilistic sensitivity analysis

Figure 2: Cost effectiveness acceptability curve

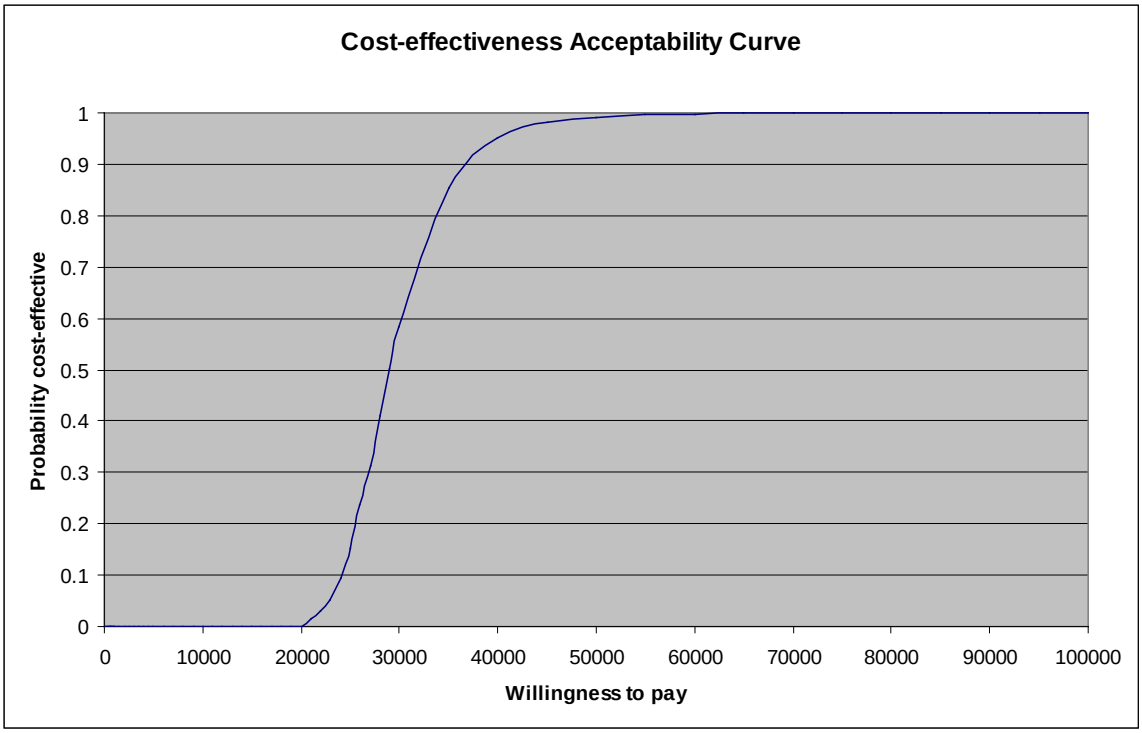


Figure 3: Scatter plot

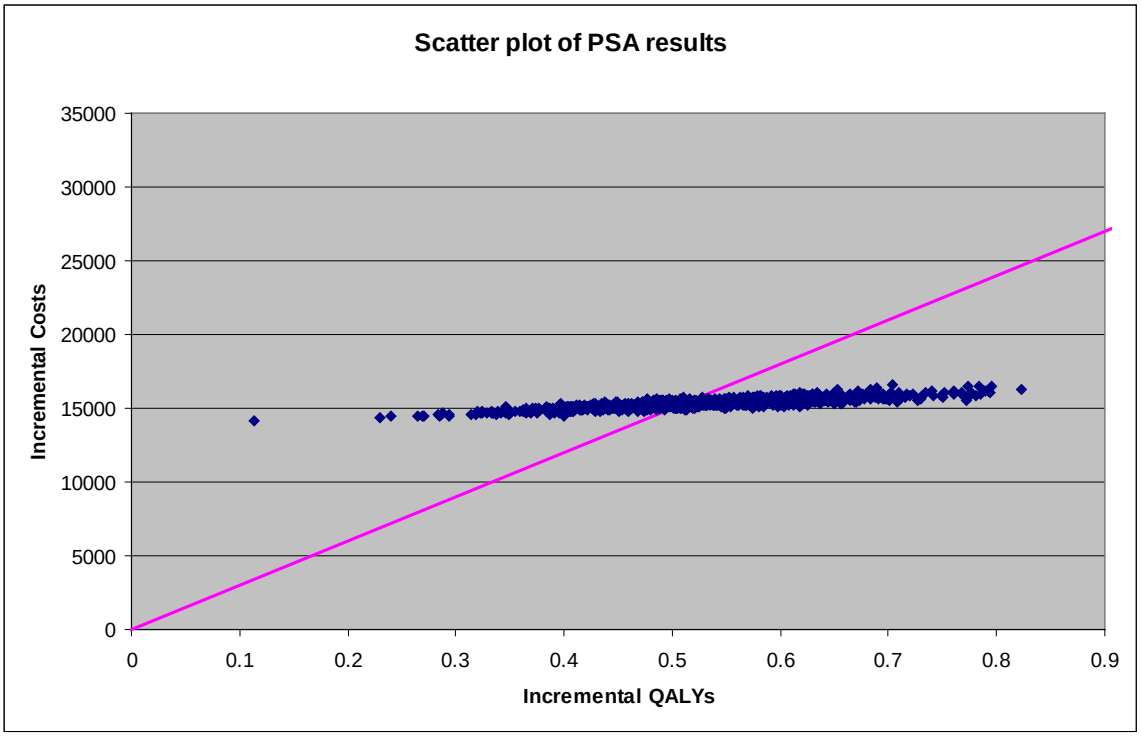


Table 8: Net Benefit Analysis

	Willingness to pay = £20,000		Willingness to pay = £30,000	
	Expected net benefit	**Probability CE**	**Expected net benefit**	**Probability CE**
Yondelis	£2,250.70	0.001	£12,030	0.585
Best Supportive Care	£6,988.47	0.999	£11,464	0.415

2.2.5 Please present scenario analysis results as described for the main submission.

Table 9: Results of scenario analysis

Scenario	Without PAS	With PAS
Base case	£50,747	£28,712
Differential utility estimates for progression free and progressed disease	£56,884	£32,184
Differential utility estimate with linear decline in Best Supportive Care arm	£60,948	£34,484
Pooled analysis of non comparative phase II studies that include non-L-sarcoma patients.	£45,646	£35,524

2.2.6 If any of the criteria on which the patient access scheme depends can be determined by the Appraisal Committee (for example, choice of measure, level of response, duration of treatment), please present the results of scenario analyses using any other criteria.

The ACD states that, in the opinion of the Appraisal Committee, trabectedin in soft tissue sarcoma meets criteria for consideration under NICE guidance as a life-extending, end of life therapy. We have therefore performed an assessment using end of life considerations. This follows the methods for NICE analyses conducted in other appraisals.

Table 10: Results of analysis including end of life criteria

Scenarios	Incremental costs (£)	Incremental life-year gained	Incremental QALYs (original)	ICER (original, £/QALY)	Incremental QALYs (max)*	ICER (max QALY)	Relative Weights			
							Original QALY		Max QALY	
							20000	30000	20000	30000
No PAS, base case	[redacted]	0.819	0.535	50,747	0.69615	38,993	2.54	1.69	1.95	1.30
PAS, base case	[redacted]	0.819	0.535	28,712	0.69615	22,061	1.44	0.96	1.10	0.74
No PAS, pooled analysis	[redacted]	0.556	0.363	45,646	0.4726	35,032	2.28	1.52	1.75	1.17
PAS, pooled analysis	[redacted]	0.556	0.363	35,524	0.4726	27,264	1.78	1.18	1.36	0.91

* Assuming maximum utility of 0.85, population mean for age group 45-54 from Kind et al. UK population norms for EQ-5D, CEHE discussion paper 172. Median age on entry to study STS-01 was 53 years.

3. APPENDICES

3.1 If available, please include patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, and patient information documents.