YONDELIS® (TRABECTEDIN) FOR THE TREATMENT OF SOFT TISSUE SARCOMA

PHARMAMAR SINGLE TECHNOLOGY APPRAISAL SUBMISSION TO THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brandname: Yondelis
INN: Trabectedin
Therapeutic class: Antineoplastic agent , ATC code : L01CX01

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yondelis has been approved via the centralized procedure. Commission Decision: 17 September 2007

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

The approved indication is:

Treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Yondelis has been introduced in the UK on 11 October 2007. Clinical trials are ongoing in UK for other indications. Since its introduction, funding for Yondelis

has been requested by some doctors in the UK for the treatment of their STS patients.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Yondelis has obtained marketing authorization for all EU, incl Iceland, Norway and Liechtenstein.

Besides, it is approved in Korea and Macau. Ongoing in many other countries.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Yondelis has been evaluated by the SMC (final recommendation published 11 Aug 2008) and AWMSG (final report 13 August 2008) .

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

The pharmaceutical form of Yondelis is a powder for concentrate for solution for infusion. Yondelis is available in vials containing 0,25 mg or 1mg of trabectedin. Each outer carton contains one vial.

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The recommended dose is 1.5 mg /m2 body surface area, administered as an i.v infusion over 24 hours with a three week interval between cycles. Dose adjustments may be necessary during treatment. The median number of cycles administered in the pivotal trial has been 5 cycles.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The NHS list price is:

363 £ for the 0.25mg vial

1366 £ for the 1mg vial

1.10 What is the setting for the use of the technology?

Patients with advanced soft tissue sarcoma have to have failed anthracyclines and ifosfamide or be unsuited for the treatment with these agents.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

All patients must receive dexamethasone intravenously prior to Yondelis.

2 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with advanced metastatic soft tissue sarcoma after failure of anthracyclines and ifosfamide, or whom these agents are unsuitable	
Intervention	trabectedin	
Comparator(s)	Best supportive care	*There are no clinical trials that capture comparisons of trabectedin vs other agents nor versus best supportive care. Best investigators choice was not considered an option.*
Outcomes	Overall survival Progression-free survival Response rates (including stabilisation) Adverse effects of treatment Health-related quality of life	*Quality of life data is not available.*
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being	*PharmaMar has not conducted a cost effectiveness study of Yondelis as there are no other technologies to compare trabectedin against.*

	compared. Costs will be considered from a NHS and Personal Social Services Perspective.	
Subgroups to be considered	If evidence allows different histological types of STS with improved response to trabectedin or other non-standard chemotherapy regimens will be considered as subgroups. Details of the components of best supportive care should be clearly described. Guidance will be issued in accordance with the marketing authorisation. Trabectedin may be continued if disease stabilisation is achieved in the absence of disease progression	
Special considerations, including issues related to equity or equality	Special consideration should be given as to whether the appraisal of trabectedin in GIST and rhabdomyosarcomas should be carried out given that these conditions follow different treatment protocols	*GIST has been excluded in the pivotal study with Yondelis*.

Section B

3 Executive summary

Background

Soft tissue sarcomas (STS) are relatively rare tumours affecting adults with an estimated incidence of 0.4 cases per 10,000 population in the European Union.

STS constitute a heterogeneous group of malignancies arising in extraskeletal connective tissues. Leiomyosarcoma and liposarcoma account for approximately 40-50% of all STS. Approximately 50% of patients present with or develop advanced or metastatic disease. Chemotherapy is the only active available systemic therapy for these patients and its goal is palliative.

At present, established first-line treatment options for advanced or metastatic STS consist of doxorubicin and ifosfamide in mono-therapy or in combination regimens. No effective therapies are currently approved or are generally accepted once conventional chemotherapy with doxorubicin and ifosfamide has failed. Consequently, the primary comparator for this analysis is best supportive care.

Trabectedin

Yondelis (Trabectedin) has approval from the European Commission for use in the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. It is a natural marine tetrahydroisoquinoline compound with antitumour properties and is now produced by chemical synthesis. It binds to the N2 position of guanine in the minor groove of deoxyribonucleic acid (DNA) bending it towards the major groove, a unique property in the class of DNA-binding agents. Trabectedin has a complex transcription-targeted mechanism of action. It inhibits activated gene transcription without modifying constitutive expression and interacts with the transcription-coupled nucleotide excision repair system. Trabectedin has considerable cytotoxic activity against a variety of cancer cells in vitro in the pM to nM range, and inhibits tumour growth in various xenograft models, both sensitive and resistant to standard anticancer agents.

The recommended dose for trabectedin is 1.5mg/m^2 to be administered over 24 hours every 3 weeks. Trabectedin comes in vials of 250mg and 1mg at a cost of £363.00 and £1366.00 respectively.

Clinical Effectiveness

The key clinical evidence comes from a Phase II pivotal randomised trial. Patients with Liposarcomas and leiomyosarcomas (L-sarcomas) were randomly assigned to receive either 1.5 mg/m^2 administered as a 24-hour IV infusion every 21 days (q3wk 24-h regimen) or 0.58 mg/m^2 administered as a 3-hour IV infusion on days 1, 8 and 15 of a 28-day cycle (qwk 3-h regimen). The primary endpoint of the trial was time to progression. A median TTP of 2.3 months was observed in the qwk 3-h arm versus 3.7 months in the q3wk 24-h arm. TTP rates at 3 months were 53.4% (q3wk 24-h) versus 45.1% (qwk 3-h) and the corresponding TTP rates at 6 months were 37.2% versus 27.3%. Three secondary endpoints were collected: progression free survival (PFS); overall survival (OS); best overall response (BSR). PFS was significantly prolonged in patients randomised to receive the q3wk 24-h regimen (median 3.3 months vs. 2.3 months). Median survival was 13.9 months (95% CI: 12.5-18.6) for the q3wk 24-h regimen and 11.8 months (95% CI: 9.9-14.9) for the qwk 3-h regimen (p=0.1985).

Supportive clinical evidence is provided from three non-comparative phase II trials in patients with L-sarcomas and non-L-sarcomas.

Economic Evaluation

A cost-effectiveness analysis has been conducted to assess the cost per life year gained and cost-per-QALY of trabectedin compared with Best Supportive Care from the NHS perspective. Costs and outcomes are generated from a Markov model comprising four health states: Progression free; progressed disease following trabectedin; progressed disease following ifosfamide and anthracycline; death. The chosen health states are commonly used in advanced and metastatic oncology models to capture the differential costs and quality of life. The health state distribution between progression free, progressive disease and death suitably incorporates time to progression primary endpoint, and overall survival secondary endpoint of the STS-201 clinical trial.

The model assumes a decreasing rate of progression and mortality as estimated from the Weibull distribution. The model assumes that patients receiving best supportive care start the model in a progressed disease health

state. Overall survival for the comparator arm is estimated from EORTC data from the point where patients have failed either ifosfamide or other chemotherapies. The model adopts utility data from studies in advanced lung cancer patients as a proxy for STS.

The base case model results are detailed below:

	Trabectedin	Best Supportive Care	Difference
Total costs	£26,140	£1,311	£24,829
Total life years	1.61	0.64	0.97
Total QALYs	0.86	0.30	0.56
Cost per life year			**£25,539**
Cost per QALY			**£44,567**

Budget impact for the NHS

The budget impact examines the cost of trabectedin in second-line treatment after failed combined ifosfamide and anthracycline, and third-line treatment after failed ifosfamide and anthracycline monotherapy and estimates the future cost of STS based on the expected uptake of trabectedin over the next 5 years. The current cost of treating second and third-line STS is estimated from a cost of illness study.

The annual budget impact over 5 years ranges from £1,688,014 in year 1 to £4,322,323 in year 5.

Conclusion

Trabectedin offers a valuable treatment opportunity for advanced STS patients who have failed all other approved active treatments. Trabectedin is well tolerated and has shown to be life-extending in patients who otherwise have a short life-expectancy. The results of the cost-effectiveness analysis suggest that trabectedin is cost-effective at high willingness to pay thresholds. Trabectedin has an incremental life years gained of approximately 1 year compared with best supportive care.

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Soft tissue sarcomas (STS) are relatively rare tumours affecting mainly adults with an estimated incidence and prevalence of 0.4 and 2 cases respectively per 10,000 population in the European Union (EU) (1;2).

STS constitute a heterogeneous group of malignancies arising in extraskeletal connective tissues (muscle, fat, fibrous tissue, blood vessels, or other mesenchymally-derived tissues). Frequent histopathologic types of STS are leiomyosarcoma and liposarcoma, which account for approximately 40-50% of all STS (3), followed by malignant fibrohystiocytoma, synovial sarcoma, rhabdomyosarcoma and angiosarcoma. Gastrointestinal stromal tumour (GIST) is not the subject of this appraisal, since a specific and effective therapy, namely imatinib, is available for these patients, and trabectedin has no activity in GIST (4).

Current treatment options for STS include surgery, radiotherapy and chemotherapy (5). Surgery is the standard treatment and the only hope for cure for patients with resectable disease. Radiotherapy is used in patients with lesions not amenable to surgery, generally with palliative intent. STS are generally incurable when the tumour cannot be eradicated by surgery.

Approximately 50% of patients present with or develop advanced or metastatic disease. Chemotherapy is the only active available systemic therapy for these patients and its goal is palliative. Despite available chemotherapy, the prognosis of these patients is very poor, with an estimated median survival of 8-13 months since the start of first-line anthracycline-based cytotoxic therapy, as shown in randomised trials performed over the last three decades (6-9). This poor prognosis has not improved over this period. These patients not only have a short life expectancy, but also are debilitated by their sarcoma, generally a bulky disease that results in complications such as pain, intestinal obstruction and other symptoms leading to end-stage organ failure and death.

At present, established first-line treatment options for advanced or metastatic STS consist of doxorubicin and ifosfamide in mono-therapy or in combination regimens (5). These are the only agents considered active, with objective

response rates [complete response (CR) plus partial response (PR)] in the 15-20% range in first-line therapy. Combination chemotherapy or dose intensification efforts have failed to improve survival of STS patients (10). No effective therapies are currently approved or are generally accepted once conventional chemotherapy with doxorubicin and ifosfamide has failed. Dacarbazine is considered active by some oncologists although it is scarcely administered as single-agent, but usually combined with other antitumour agents.

Despite numerous clinical trials, including those performed by major organisations such as the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) in Europe and the National Cancer Institute (NCI) cooperative groups in the USA, no new active agents have been registered or convincingly identified in pretreated STS patients for more than 20 years. The median survival for patients who have failed prior treatment with anthracyclines and ifosfamide is in the range of 6 months.

There is therefore an urgent and significant need for additional agents with efficacy in these tumours, and which can provide clinical benefit to patients with STS after failure of standard anthracycline and ifosfamide-based therapy.

4.2 What was the rationale for the development of the new technology?

Complete surgical resection of the metastases is only feasible in a small minority of cases, systemic chemotherapy being the main treatment modality for STS patients with metastatic disease. Despite available chemotherapy, many patients will experience progression of the STS despite the use of these agents. No effective therapies are currently approved or are generally accepted once conventional chemotherapy has failed.

Trabectedin demonstrated activity against several human cancer cell lines and xenografts (including sarcomas) with minimal or no cross-resistance to several conventional chemotherapeutic agents (11-13). Objective tumour responses and prolonged tumour stabilisations were obtained in patients with STS in the phase I clinical trials and these were considered of great interest by the investigators. These encouraging preclinical and clinical results showing trabectedin activity in STS resistant to available anticancer drugs suggested the value of a clinical development programme with this agent in this rare type of cancer.

4.3 What is the principal mechanism of action of the technology?

Yondelis (trabectedin), formerly known as ecteinascidin 743 (ET-743), is a natural marine tetrahydroisoquinoline compound with antitumour properties first isolated from the Caribbean tunicate Ecteinascidia turbinata, a colony-forming tunicate that grows in coastal temperate seas. It is now produced by chemical synthesis. Although the complete mechanism of action of trabectedin has not yet been completely elucidated, data obtained to date show some unique features for the mechanisms of this agent. Trabectedin binds to the N2 position of guanine in the minor groove of deoxyribonucleic acid (DNA) bending it towards the major groove, a unique property in the class of DNA-binding agents.

Trabectedin has a complex transcription-targeted mechanism of action. It inhibits activated gene transcription without modifying constitutive expression and interacts with the transcription-coupled nucleotide excision repair system. Trabectedin is 20 to 150 times more active in cells with loss of poly ADP-ribose polymerase (PARP) function, contrary to that observed with other chemotherapeutic agents such as doxorubicin and the platinum-based agents, in which loss of PARP results only in a 2 to 3 times increased sensitivity. Trabectedin induces slow progression through S and G2/M phases of the cell cycle and p53-independent apoptosis. Trabectedin has considerable cytotoxic activity against a variety of cancer cells in vitro in the pM to nM range, and inhibits tumour growth in various xenograft models, both sensitive and resistant to standard anticancer agents.

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

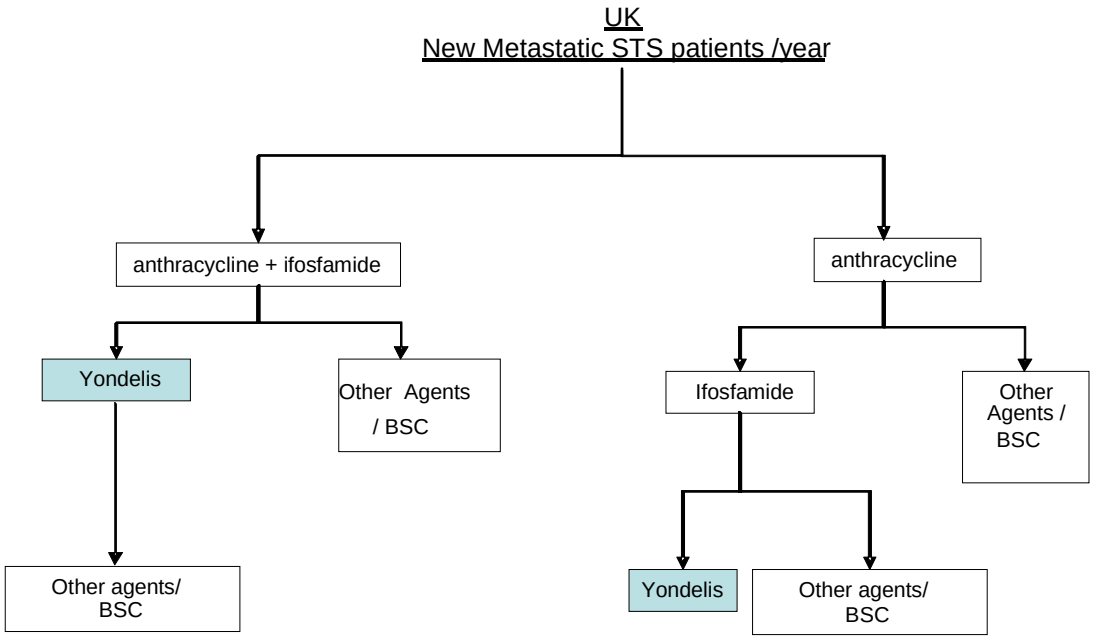
Apart from several specific histological subtypes, most STS are relatively insensitive to currently available cytotoxic agents.

The standard first-line treatment is an anthracycline (mainly doxorubicin) as a single agent or in combination with ifosfamide. Response rates of 10–25% are obtained with these agents in monotherapy. Their combination induces higher response rates but has not translated into a survival advantage in randomised studies.

Trabectedin has demonstrated clinical benefit in patients in whom STS has progressed despite standard anthracycline and ifosfamide therapy.

Trabectedin should therefore be used for the treatment of patients with advanced STS after failure of anthracyclines and ifosfamide or who are unsuited to receive these agents. For patients treated with anthracycline and ifosfamide combination therapy as first line, trabectedin may be considered as second line treatment, while those treated with an anthracycline and ifosfamide administered sequentially would be eligible to receive trabectedin as third-line treatment.

The figure below illustrates the positioning of trabectedin within the treatment pathway.



4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

There are no standard therapies approved for patients once their sarcomas progress in spite of anthracyclines and ifosfamide. Patients not receiving trabectedin would typically receive a variety of end-stage treatments upon failure with anthracyclines and ifosfamide. Such treatments include a number of options which are likely to vary from one patient to another. Typically, such treatments would possibly include (though are not restricted to) off-label chemotherapy, non-chemotherapy drugs, palliative care and even radiotherapy for a small number of patients.

Whilst other chemotherapies may be administered at this stage, none of these are approved therapies. Trabectedin, however, is approved for use in this patient group, with a safety and efficacy profile deemed suitable to the EMEA.

4.6 Provide details of any relevant guidelines or protocols.

- Guidelines published by NICE in 2006 (14) focus on how to run a service within the NHS for soft tissue and bone sarcoma patients, including their clinical and costs implication (15). However, no guidance was found on appropriate treatment to give to end-stage patients, and the care received by the targeted population of trabectedin.

- ESMO clinical recommendations (1) were formulated following a consensus event organized by ESMO in Lugano in October 2007. The consensus process involved experts from the community of the European sarcoma research groups and from some sarcoma centers of excellence outside Europe.

- Draft BSG Guidelines currently being developed for diagnosis, treatment and follow-up of STS position Trabectedin as a second-line option based on efficacy in leiomyosarcoma and liposarcoma (16).

5 Equity and equality

5.1 Identification of equity and equalities issues

Trabectedin is indicated for use in a very small and well-defined patient population with incurable disease. It was designated as orphan medicinal product in the treatment of STS both by EMEA (17) on 30 May 2001 and FDA in October 2004 (18).The status of trabectedin as being of potential significant benefit to those affected by this orphan condition was subsequently confirmed by the Committee for Orphan Medicinal Products (COMP) in a review of criteria for orphan drug designation (2). Despite available chemotherapy, the prognosis for these patients is very poor. Patients for whom standard first-line chemotherapy treatment has failed or who are unsuitable for treatment in the first instance are left with no alternative approved option. Trabectedin offers an option for patients who would otherwise most likely be offered unlicensed experimental chemotherapy regimens or palliative care.

5.2 How has the analysis addressed these issues?

Not applicable

6 Clinical evidence

6.1 Identification of studies

In relation to the decision problem, a systematic search of the literature was undertaken to identify any relevant studies investigating the clinical activity or safety of trabectedin in patients with advanced soft tissue sarcoma. Due to the expected low number of studies completed in this disease area, the search was not restricted by study design at this stage. The following databases were searched for relevant publications; Embase, Medline, Medline in process and the Cochrane library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, NHS Economic Evaluation Database). A search of the manufacturer's database was also carried out to identify all publications from relevant studies. Further information on the databases searched, inclusion and exclusion criteria, search strategies and the results of the searches can be found in Appendix 2 (section 10.3.1). In addition, a search of the current controlled trials meta-Register of controlled trials was run to identify any relevant trials that were currently being carried out. The databases searched using the meta-register were; ISRCTN Register , Action Medical Research , Leukaemia Research Fund , Medical Research Council (UK), National Health Service Research and Development Health Technology Assessment Programme (HTA), National Institutes of Health (NIH) - randomised trial records held on NIH ClinicalTrials.gov website, The Wellcome Trust and the UK Clinical Trials Gateway (see Appendix 2, section 10.3.5).

A list of abstracts presenting clinical efficacy and safety data from the pivotal phase II randomised trial (ET743-STS-201) was also identified from the manufacturers clinical study report. Details of the published abstracts can be found in Appendix 2 (section 10.3.5).

The results of the searches of Medline, Medline in process, Embase and the Cochrane Library were downloaded into reference management software (Reference Manger) and combined. Duplicate references were removed from the results and the titles and abstracts of the unique references were screened. Full paper manuscripts were obtained of any publications that were considered relevant. In cases where it was not possible to determine the relevance from the title or abstract alone, the full publication was also obtained. The relevance of each study was assessed according to the inclusion / exclusion criteria set out in section 6.2.2. Where multiple

publications from the same study were identified, the sources of the data were noted. In cases where the same data was presented in more than one paper data were extracted from the single most relevant publication to avoid the risk of duplicating data. The selection of full publications was checked by an independent reviewer and any differences in study selection determined. A final list of publications was produced after review of any differences by both researchers and agreement on the final list.

Where available, the following data was reviewed in the selected publications: population, intervention, comparator and outcomes (time to progression, progression free survival, overall survival and safety data).

6.2 Study selection

6.2.1 Complete list of RCTs

The systematic search identified that there was just one randomised study evaluating the efficacy or safety of trabectedin in patients with advanced soft tissue sarcoma; study ET743-STS-201 carried out by Pharma Mar. This study could not be carried out as a head to head comparison versus an alternative intervention or a placebo group for the following reasons;

1) There is no standard treatment for STS patients after failure of previous chemotherapy including both anthracyclines and ifosfamide;

2) Due to the poor prognosis of these patients, with a 6-month life expectancy and urgent need of palliation, it was not considered feasible to offer a placebo treatment in the context of a trabectedin trial, particularly because of previously published efficacy with this agent from three single-arm phase II trials (19-21).

Therefore, the STS-201 pivotal study compared the efficacy and safety profile of 1500 μg/m^2 trabectedin as a continuous 24 hr intravenous infusion given 3-weekly (q3wk 24-h) with a 3-hour infusion regimen given weekly (qwk 3-h).

The systematic search identified five published abstracts that present data from this single randomised trial STS-201:

1. J. A. Morgan, A. Le Cesne, S. Chawla, M. von Mehren, S. Schuetze, P. G. Casali, A. Nieto, Y. Elsayed, M. A. Izquierdo, G. D. Demetri, Yondelis Sarcoma Study Group Journal of Clinical Oncology, 2007

ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement).

2. Samuels BL, Rushing D, Chawla SP, Schuetze SM, Von Mehren M, Leohan ML, O'Donovan M, Wei X, Sternas LA and Demetri GD. randomised phase II study of trabectedin (ET-743) given by two different dosing schedules in patients (pts) with leiomyosarcomas (LMS) or liposarcomas (LPS) refractory to conventional doxorubicin and ifosfamide chemotherapy. [Abstract 9000]. Journal of Clinical Oncology 2004; 22(July 15 Supplement):14S.

3. Demetri GD, Schuetze S, Le Cesne A, Chawla S, Casali PG, Gomez J, Nieto A, Elsayed Y, Izquierdo MA and Blay JY. Impact of independent review on efficacy outcomes in a randomised multicenter trial of trabectedin given by two dosing regimens in patients (pts) with progressing leiomyosarcomas or liposarcomas (L-sarcomas). European Journal of Cancer 2007 Vol 5. No 4. Suppl (ECCO 14): Oral communication 7500, page 402.

4. Le Cesne A, von Mehren M, Chawla S, Blay JY, Shcuetze S, Nieto A, Gomez J, Santabarbara P, Izquierdo MA and Demetri GD on behalf of Yondelis Sarcoma Study Group. Assessing the clinical impact of trabectedin in patients with leiomyosarcomas or liposarcomas (L-sarcomas) progressing despite prior conventional chemotherapy: clinical benefit rate, growth modulation index and tumour variation as parameters of treatment efficacy in a randomised international trial of two trabectedin dosing regimens. European Journal of Cancer 2007 Vol 5. No 4. Suppl (ECCO 14): Poster 7511, page 405.

5. Chawla S, Casali PG, von Mehren A, Le Cesne A, Blay JY, Lebedinsky C, Alfaro V, Elsayed Y, Michiels B and Demetri GD on behalf of the Yondelis Sarcoma Study Group. Clinical tolerability of trabectedin administered by two different schedules (weekly for 3 of 4 weeks vs. q3 weeks) in patients with advanced/metastatic liposarcoma or leiomyosarcoma (L-sarcomas) progressing despite prior treatment with at least anthracycline and ifosfamide. European Journal of Cancer 2007 Vol 5. No 4. Suppl (ECCO 14): Poster 7517, page 407.

[redacted]

[redacted]

[redacted]

6.2.2 Inclusion and exclusion criteria

Exclusion criteria used were:

1. Publications should be in English language
2. Publications should report primary research
3. Publications should not report data already published
4. Publications should include trabectedin as an intervention
5. Publications should report on the treatment of soft tissue sarcoma patients
6. Publications should report clinical efficacy or safety data
7. Publications should be reporting on patients who have failed prior chemotherapy with anthracyclines or ifosfamide.

6.2.3 List of relevant RCTs

The single randomised phase II study identified (ET743-STS-201) was relevant to the decision problem. The five published abstracts presenting results from this study were assessed for relevance according to the inclusion/exclusion criteria in section 6.2.2. The following abstracts were considered as relevant:

1. J. A. Morgan, A. Le Cesne, S. Chawla, M. von Mehren, S. Schuetze, P. G. Casali, A. Nieto, Y. Elsayed, M. A. Izquierdo, G. D. Demetri, Yondelis Sarcoma Study Group Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement),

2. Demetri GD, Schuetze S, Le Cesne A, Chawla S, Casali PG, Gomez J, Nieto A, Elsayed Y, Izquierdo MA and Blay JY. Impact of independent review on efficacy outcomes in a randomised multicenter trial of trabectedin given by two dosing regimens in patients (pts) with progressing leiomyosarcomas or liposarcomas (L-sarcomas). European Journal of Cancer 2007 Vol 5. No 4. Suppl (ECCO 14): Oral communication 7500, page 402.

3. Le Cesne A, von Mehren M, Chawla S, Blay JY, Shcuetze S, Nieto A, Gomez J, Santabarbara P, Izquierdo MA and Demetri GD on behalf of Yondelis Sarcoma Study Group. Assessing the clinical impact of trabectedin in patients with leiomyosarcomas or liposarcomas (L-sarcomas) progressing despite prior conventional chemotherapy: clinical benefit rate, growth modulation index and tumour variation as parameters of treatment efficacy in a randomised international trial of two trabectedin dosing regimens. European Journal of Cancer 2007 Vol 5. No 4. Suppl (ECCO 14): Poster 7511, page 405.

4. Chawla S, Casali PG, von Mehren A, Le Cesne A, Blay JY, Lebedinsky C, Alfaro V, Elsayed Y, Michiels B and Demetri GD on behalf of the Yondelis Sarcoma Study Group. Clinical tolerability of trabectedin administered by two different schedules (weekly for 3 of 4 weeks vs. q3 weeks) in patients with advanced/metastatic liposarcoma or leiomyosarcoma (L-sarcomas) progressing despite prior treatment with at least anthracycline and ifosfamide. European Journal of Cancer 2007 Vol 5. No 4. Suppl (ECCO 14): Poster 7517, page 407.

Excluded publication:

Samuels BL, Rushing D, Chawla SP, Schuetze SM, Von Mehren M, Leohan ML, O'Donovan M, Wei X, Sternas LA and Demetri GD. randomised phase II study of trabectedin (ET-743) given by two different dosing schedules in patients (pts) with leiomyosarcomas (LMS) or liposarcomas (LPS) refractory to conventional doxorubicin and ifosfamide chemotherapy. [Abstract 9000]. Journal of Clinical Oncology 2004; 22(July 15 Supplement):14S.

The abstract by Samuels et al (2004) was not considered relevant as it presented data from an interim analysis that was included in a later analysis published in the abstract Morgan et al, (2007).

6.2.4 List of relevant non-randomised controlled trials

Due to a lack of standard treatment for patients with soft tissue sarcoma who have failed prior chemotherapy with anthracyclines and ifosfamide, there are no non-randomised controlled trials examining the efficacy or safety of trabectedin in this patient group.

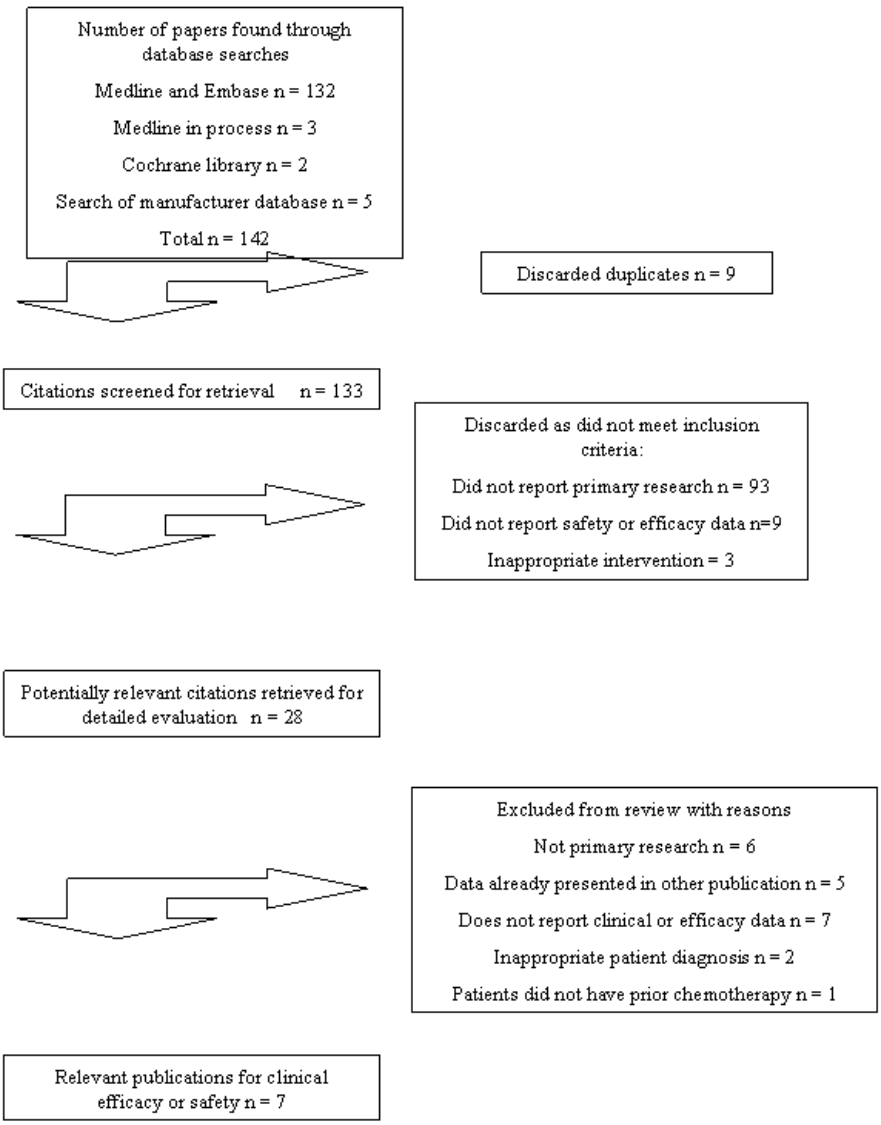
6.2.5 Ongoing studies

There are no known ongoing studies examining the clinical efficacy or safety of trabectedin in STS patients who have failed prior chemotherapy with anthracyclines and ifosfamide. A search of a clinical trial meta-Register showed the only relevant randomised trial to be ET743-STS-201 (see Appendix 3, section 10.3.5).

6.2.6 Flow diagram of search results and selection of relevant publications

The diagram below summarises the results from the searches of Embase.com, the Cochrane Library, and the results from requesting relevant information from the manufacturer, along with the reasons for exclusion of the studies (see *Figure 1)*

Figure 1 Summary flow diagram of the search results and selection of relevant publications



6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

Rationale

Soft tissue sarcomas (STS) are uncommon tumours, with an estimated prevalence of 2 cases per 10,000 population in the EU. Liposarcomas and leiomyosarcomas (L-sarcomas) constitute the most frequent histological STS subtypes, representing approximately 40-50% of all STS. Thus, the estimated prevalence of L-sarcomas is 1 case per 10,000 population in the EU.

For this rare target population, there is neither approved standard treatment nor a widely recognised therapeutic option; these patients have exhausted all established therapies. STS relapsed or refractory to anthracyclines and ifosfamide are aggressive cancers causing symptoms frequently related to bulky disease. These patients need active palliation, and have a short life expectancy (median survival in the range of 6 months). Thus, there is an unmet medical need of new therapeutic alternatives for this patient population.

The efficacy of trabectedin q3wk 24-h in patients with heavily pre-treated, advanced or metastatic STS was initially evaluated in three non-randomised phase II studies (19-21). These studies included patients whose disease had relapsed or was refractory following previous standard therapy consisting of an anthracycline with or without ifosfamide. A pooled analysis of these studies suggested a slightly higher efficacy for trabectedin in L-sarcomas relative to other histological types (22), although the numbers within each of the other STS types were too small to draw firm conclusions.

Interventions

Therefore, the single relevant RCT (ET743-STS-201) was conducted to evaluate in a randomised, controlled fashion, the efficacy and safety of trabectedin in a more homogeneous population of patients with L-sarcoma in whom anthracyclines and ifosfamide had failed. Patients were randomly assigned to receive either 1.5 mg/m^2 administered as a 24-hour IV infusion every 21 days (q3wk 24-h regimen) or 0.58 mg/m^2 administered as a 3-hour IV infusion on days 1, 8 and 15 of a 28-day cycle (qwk 3-h regimen).

Randomisation

Randomisation was by the permuted-block method and was stratified according to baseline ECOG Performance Status, 0 versus 1. Randomisation

codes for the treatment were generated by the Sponsor and assigned to eligible subjects through an Interactive Voice Response System (IVRS) prior to the treatment. All patients also received anti-emetic prophylaxis with dexamethasone, administered 30 minutes before each infusion (qwk 3-h regimen, 10 mg; q3wk 24-h regimen, 20 mg). Treatment continued as long as therapeutic benefit was derived, until disease progression, or for at least 2 courses of therapy beyond confirmed complete response. Subjects who experienced disease progression on either arm could be treated with the alternate treatment arm, at the discretion of the investigator.

Protocol amendment

The study was originally designed as an open-label, non-comparative randomised evaluation of the two trabectedin regimens previously described. The primary endpoint of the trial was clinical benefit, defined as the rate of complete plus partial responses plus disease stabilisation of at least 6 month duration. Given the exploratory nature of such design, the outcomes of the trial could be monitored on an ongoing basis without restriction. Preliminary descriptive data presented at the 2004 ASCO annual meeting lead to the perception that the q3wk 24-h regimen might be more efficacious than the qwk 3-h regimen, although the latter was also perceived as active. After a series of thorough discussions between study investigators and the Sponsor, a study protocol amendment was implemented in August 2004 of which the following points are of note:

1. Change of primary endpoint from “clinical benefit” to a time-to-event endpoint, namely time to progression (TTP). TTP was considered a more meaningful efficacy endpoint as time-related endpoints are increasingly recognised as the most appropriate means to evaluate clinical benefit in STS trials. After the imatinib experience in GIST, an increasing body of evidence indicated that RECIST or WHO defined response rates (RR) do not adequately reflect the magnitude of the therapeutic benefit in sarcoma patients and thus RR has been considered a suboptimal endpoint. TTP was chosen over PFS as the time-to-event endpoint that was closest to the initial endpoint of clinical benefit. Moreover, the new primary endpoint for this trial would allow the formal comparison of the efficacy of the two trabectedin regimens through the appropriate Kaplan-Meier and log-rank methodology.

2. Increase in sample size. This was implemented to provide sufficient statistical power for a formal comparison of TTP. Thus, sample size was increased to 260 patients.

3. The remaining features of the original design, including patient eligibility, treatment regimens and randomisation of treatment allocation were maintained. It was felt that, given the rarity of STS and the difficulty of enrolling these patients in randomised trials, the patients already recruited to study ET743-STS-201 should be maintained in the amended study population. Acknowledging the theoretical caveats of such a major protocol amendment, the Sponsor carried out several sensitivity analyses which were provided to EMEA with the MAA dossier. These analyses showed lack of noticeable bias between the pre-and post-amendment patient populations as well as efficacy outcomes. As a result, methodological concerns over the consequences of this protocol amendment were mitigated.

Study objectives

The study objectives of the amended protocol were:

Primary objective:

To compare TTP after treatment with trabectedin, administered on two different treatment schedules in patients with liposarcoma or leiomyosarcoma (L-sarcomas) who had been previously treated with an anthracycline and ifosfamide.

Secondary objectives:

To estimate the rate and duration of best overall objective response [(ORR. i.e., complete (CRs) and partial responses (PRs) of each schedule];

- To compare progression-free survival (PFS) and overall survival (OS) between the two schedules;
- To characterize the safety profile;
- To estimate the pharmacokinetics of trabectedin.

Blinded assessment of images used for primary endpoint (TTP)

The protocol amendment also included instituting an external, independent review panel whose members were blinded to treatment arm for the tumour assessments used in the TTP analyses. Data from the non-blinded investigators were used as supporting evidence.

The following table summarises the methodology of trial ET743-STS-201.

Table 1 Summary of trial methodology for ET743-STS-201

Indication	Advanced L-sarcomas refractory to previous treatment with anthracyclines and ifosfamide
Study design	Randomised, multi-centre, open-label study
Study sites	United States of America (n=181), Russia (n=28), Canada (n=24), France (n=17), Italy (n=8), Australia (n=4),Belgium (n=3), Spain (n=3) and Germany (n=2).
Recruitment & follow-up period	Efficacy: subjects followed for survival every 8 weeks after the end of treatment until death or the study termination, whichever is sooner. Adverse events: until 30 days from the date of last administration of study drug, or the end of the study.
Interventions	1.5 mg/m2 administered as a 24-hour IV infusion every 21 days (q3wk 24-h regimen) or 0.58 mg/m2 administered as a 3-hour IV infusion on days 1, 8 and 15 of a 28-day cycle (qwk 3-h regimen).
Patient numbers (randomised) (see section 6.3.3 Figure 2)	At the time of the final time to progression analysis 270 patients had been randomised, 260 patients had been treated, 251 patients (248 per independent review) were evaluable for response, and 8 patients were ongoing in the q3wk 24-h arm.

6.3.2 Participants

Patients were recruited for this study who had locally advanced or metastatic liposarcoma and leiomyosarcoma and whose disease had relapsed or become refractory after treatment with at least an anthracycline and ifosfamide, given either in combination or in sequence.

Subjects had to satisfy the following criteria to be enrolled in the study:

1. Signed informed consent.
2. Male or female subjects 18 years-of-age or older.
3. Unresectable advanced or metastatic histologically proven liposarcoma or leiomyosarcoma. Subjects with GIST (gastrointestinal stromal tumours) are not eligible.
4. Subjects must have pathology specimens available for centralised review.

5. Subjects must have relapsed or progressive disease prior to enrollment. Subjects must have been treated with an anthracycline and ifosfamide, administered either in combination or as sequential regimens.
6. Progressive, measurable disease as defined in the RECIST guidelines. If the only indicator lesion is in a previously irradiated area, the recurrence must be biopsy proven.
7. Recovery from toxic effects of prior therapies to National Cancer Institute-Common Toxicity Criteria (NCI CTC) Grade 1 or better.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Haematologic variables:
    - Haemoglobin ≥9 g/dL
    - Absolute neutrophil count (ANC) ≥1,500/μL
    - Platelet count ≥100,000/μL
10. Serum creatinine ≤ upper limit of normal (ULN)
11. Hepatic function variables:
    - Total bilirubin ≤ ULN
    - Total alkaline phosphatase ≤ ULN, or if > ULN, then alkaline phosphatase liver fraction or 5'-nucleotidase must be ≤ ULN.
    - AST (serum aspartate transaminase [SGOT]) and ALT (serum alanine transaminase [SGPT]) must be ≤2.5xULN
    - Albumin ≥2.5 g/dL

Potential subjects who met any of the following criteria were excluded from participating in the study:

1. Pregnant or breast–feeding women or male or female patients who were not using adequate contraception. Acceptable birth control measures included intrauterine devices, oral contraceptives, sub-dermal implant, and a condom with a contraceptive sponge or suppository.
2. Prior exposure to trabectedin.
3. More than two prior cytotoxic chemotherapy regimens. Adjuvant therapy completed more than 18 months before randomization was not considered a regimen.
4. Less than four weeks from last dose of systemic cytotoxic therapy, radiation therapy, or therapy with any investigational agent.
5. Grade 2 or worse peripheral neuropathy.

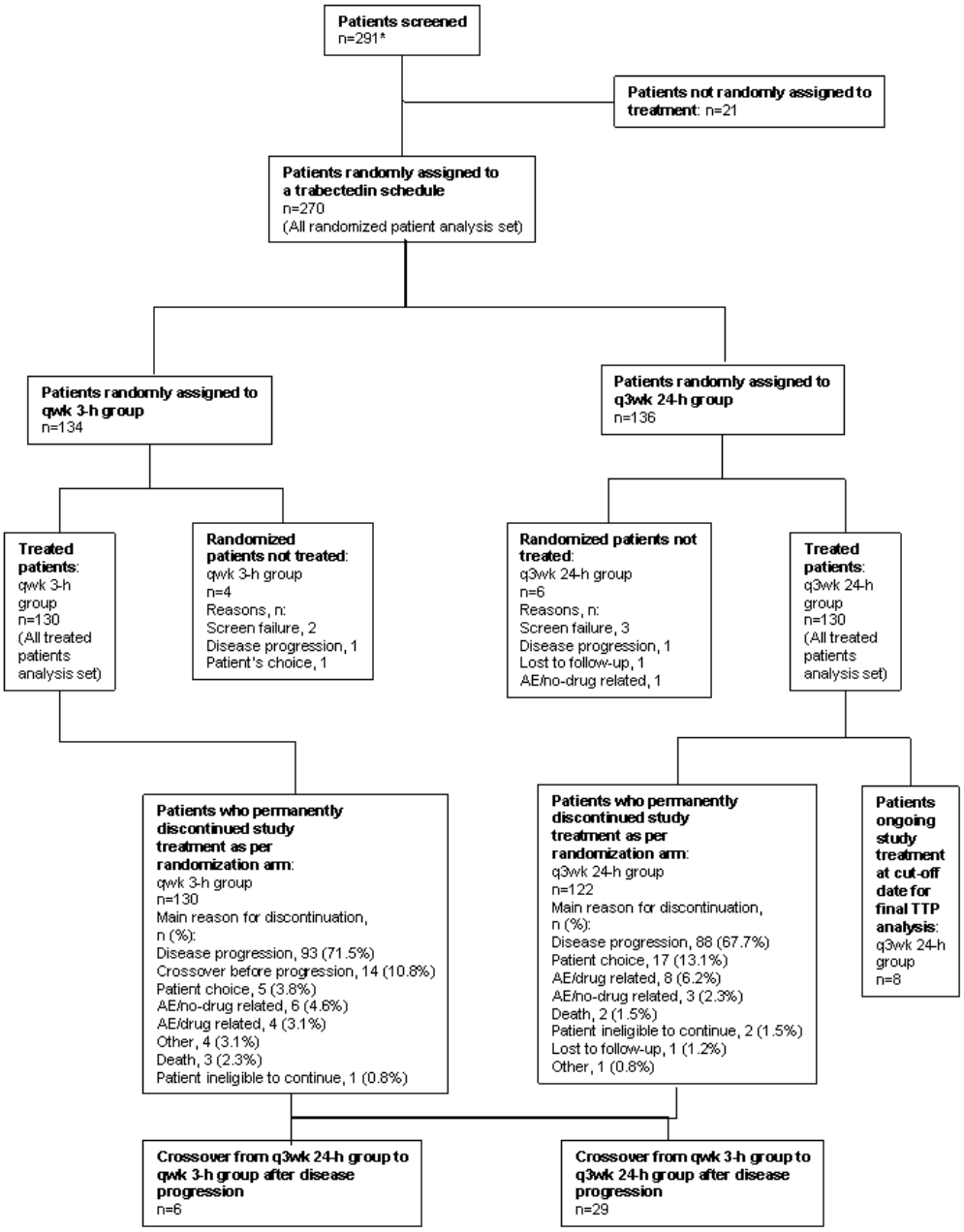
6. History of another neoplastic disease, except basal cell carcinoma or adequately treated cervical carcinoma in situ, unless the disease had been in remission for ≥5 years.
7. Known central nervous system metastasis.
8. Active viral hepatitis or chronic liver disease.
9. Unstable cardiac condition, including congestive heart failure or angina pectoris, myocardial infarction within one year before enrollment, uncontrolled arterial hypertension or arrhythmias.
10. Active infection.

Two-thirds of the patients were female and approximately 90% were white. The median age was 53 years and 13% of patients were 65 years old or older. Approximately two-thirds of the patients had leiomyosarcoma and the remaining one-third had liposarcoma. Likewise, two-thirds of the patients had aggressive (high-grade) tumours. Most patients had metastatic disease (93%). The median number of metastatic sites per patient was two in each study arm and 32% of patients had more than two metastatic sites. In addition, two-thirds of patients (66.9%) had bulky disease, defined by lesions ≥50 mm in diameter.

All patients, with one exception, had previously received both anthracyclines and ifosfamide – the available standard-of-care agents – and two-thirds of the patients had previously received additional chemotherapeutic agents, including gemcitabine and/or docetaxel in one-third of the cases. Approximately 50% had also received prior radiotherapy.

6.3.3 Patient numbers

Figure 2 Flow diagram for study ET743-STS-201



6.3.4 Outcomes

There is no existing approved chemotherapy for the targeted population of trabectedin. Trabectedin should therefore be incorporated into the treatment algorithm following the approved agents, with the aim of slowing disease progression and therefore potentially prolonging patient survival as well as reducing tumour size. Although ET743-STS-201 measured overall survival as a secondary outcome, the surrogate outcome TTP was the primary endpoint of the study. As previously discussed, in patients with advanced/metastatic STS, particularly in those whose sarcoma is progressing after standard chemotherapy, the evaluation of time-to-event endpoints such as TTP or PFS appears to be a more meaningful indicator of clinical benefit than tumour response rate, which is typically low even with standard chemotherapeutic agents (anthracyclines and ifosfamide) administered as initial therapy in STS.

Primary endpoint

The primary endpoint in the pivotal phase II randomised trial ET743-STS-201 was time to progression (TTP), defined as time between randomization and the first documentation of disease progression or death due to progressive disease. The final analysis of TTP data was prospectively planned on 31 May 2006, when 217 events of progression per independent review were estimated. Actually, a total of 216 and 206 TTP events were recorded according to the investigator's assessment and the independent review, respectively. Results for the intention-to-treat analysis of TTP data carried out by independent review are reported here along with the supportive data from the analysis of the investigator assessed datasets.

The median follow-up for progression was not significantly different in both study arms: 10.8 months (95% CI: 6.0-11.6) in the qwk 3-h arm and 14.7 months (95% CI: 10.9-22.5) in the q3wk 24-h arm (p=0.0549).

Secondary endpoints

Secondary endpoints included progression-free survival (PFS), overall survival (OS) and the rate and duration of best overall objective response (OOR) [complete responses (CRs) and partial responses (PRs)] of each schedule.

Progression free survival

Progression free survival was defined as the time between randomisation and disease progression. Death from any cause was considered a

progression event. Results for the intention-to-treat analysis of PFS data carried out on the independent review dataset are reported here along with the supportive data in the investigators dataset. The follow up for this endpoint was the same as for the TTP endpoint.

Overall survival

The final overall survival analysis was prospectively scheduled with at least 234 events. OS was calculated as time between randomisation and death. Patients who died, regardless of the cause of death were considered to have an event. Patients who were lost to follow-up before the end of the study or who were withdrawn from the study were censored at the time of last contact. Patients who were still being treated in the study were censored at the last available date where the patient was known to be alive. The final OS analysis was conducted with 235 death events. The median follow-up was 41.4 months (95% CI:35.5-48.9) in the qwk 3-h arm and 41.3 months (95% CI:37.0-54.6) in the q3wk 24-h arm.

Best overall objective response rate

Best overall objective response rate was defined as the sum of complete responses (CR) and partial responses (PR). Tumour assessment was carried out by independent review and the investigators using the Response Evaluation Criteria in Solid Tumours (RECIST) up to 30 days before randomization and every 8 weeks thereafter until disease progression. Data presented here are from the intention-to-treat analysis.

6.3.5 Statistical analysis and definition of study groups

The primary objective was to demonstrate a significant difference in TTP between the 2 treatment arms (q3wk 24-h versus qwk 3-h). By randomising a total of 260 subjects and observing 217 events (progression or death due to progression as recorded on the CRF), the study had more than 90% power to detect a 60% improvement in TTP at a two-sided 5% significance level. Assuming that 10% randomized subjects would not have confirmed diagnosis, a sample size of 130 subjects per arm would lead to a 95% confidence interval with the lower limit higher than 5% when the observed best overall objective response rate is 10% or higher. For overall survival (OS), by observing 234 deaths, the study would have more than 80% power to detect 45% improvement in OS at a two-sided 5% significance level. Estimates of TTP and other time-to-event endpoints (PFS, OS) were calculated by the Kaplan-Meier method for each schedule. The analysis of the differences between the two

treatment arms in TTP, PFS and OS were carried out using the log-rank test. Hazard ratios of TTP, PFS and OS were analysed using Cox regression method. Analysis was carried out by intention-to-treat in the independent review and study investigators datasets. Statistical analysis of the difference in objective response rate between the two arms of the study was carried out using Fisher's test.

Adverse events (AEs) were summarized by system organ class and overall. The Medical Dictionary for Regulatory Activities (MedDRA) was used to code AEs, and their severity was coded according to the NCI-CTC, Version 2.0.

The results of a pre-planned subgroup analysis indicated that regardless of study arm, the efficacy outcomes appeared more favourable in liposarcomas than in leiomyosarcomas. This is not an unexpected finding, since histological subtype is a well known prognostic factor in STS, with liposarcomas having a more favourable prognosis than leiomyosarcomas (23).

6.3.6 Critical appraisal of relevant RCTs

Publications for the single relevant RCT are restricted to abstracts only (24-27). Therefore the clinical study reports were used to carry out a critical appraisal of the methodology.

- *How was allocation concealed?*

This was an open label trial, and therefore the subjects and study investigators were aware of the treatment allocation. The final analysis of the primary endpoint TTP was conducted based on the assessments of an independent panel blinded to study arm allocation. The review panel were blinded to confidential identifiers, such as subject name, and also unblinding information, such as the institution and healthcare personnel involved in subject treatment, all summary statements which suggest the nature of the site assessment or interpretation of response outcome, all reference to study medication treatment group, etc. This information was removed from the clinical oncology dossier prior to the independent assessment of clinical data. The detailed charter of such allocation was included in the Yondelis MAA and is available upon request.

- *What randomisation technique was used?*

Randomisation was by the permuted-block method and was stratified according to baseline ECOG Performance Status, 0 versus 1. Randomisation

codes for the treatment were generated by the Sponsor and assigned to eligible subjects through the Interactive Voice Response System (IVRS) prior to the treatment.

- *Was a justification of the sample size provided?*

Yes

- *Was follow-up adequate?*

Yes, subjects were followed for disease progression with scans and clinical evaluations performed symmetrically every 8 weeks during therapy and at identical intervals after treatment discontinuation, as specified in the study protocol. Similarly, patients were followed for survival until death or study termination. The clinical cut-off for the primary efficacy analysis of TTP was prospectively defined and aimed at acquiring at least 217 TTP events per independent radiology assessment. In actuality, at the cut-off date, a total of 206 independently assessed TTP events were available (n=216 by investigator assessment). The final OS analysis was conducted with 235 death events (the protocol required at least 234 deaths to provide the pre-specified statistical power for this analysis).

- *Were the individuals undertaking the outcomes assessment aware of allocation?*

Outcomes assessment for the primary analysis was carried out by an independent review panel blinded to study arm allocation (primary analysis). A supportive analysis was carried out using the outcomes assessed by study investigators (un-blinded to study arm). Both analyses provided consistent results demonstrating statistically superior efficacy with the q3wk 24-h trabectedin regimen.

- *Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.*

The study design allowed for subjects to cross-over to the alternative treatment arm upon progression, at the request of the subject and discretion of the investigator. As there were more progression events with the qwk 3-h regimen, most of the patients who crossed over (29/35) did so to the q3wk 24-h schedule. A carryover effect is likely and has been acknowledged in the Clinical Study Report for the secondary endpoint overall survival. Conversely, the crossover could not have any significant impact on the results and

interpretability of the primary analysis TTP, where patients were considered to have an event at the time of objective documentation of disease progression or death due to progressive disease.

- *Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?*

This was a multi-national study, though no study centres were in the UK. Study centres were located in United States of America (n=181), Russia (n=28), Canada (n=24), France (n=17), Italy (n=8), Australia (n=4), Belgium (n=3), Spain (n=3) and Germany (n=2). As there is no standard therapy in existence for STS patients who have experienced disease progression after previous anthracycline and ifosfamide chemotherapy, it is unlikely that practice in the trial will differ significantly from UK practice – a view supported by discussion with several UK clinical experts.

- *How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, and setting.*

These patients compare well with the anticipated STS patient population for the UK; 75% of the study participants were from North America, 91.1% of participants in the trial were classed as white, therefore no location effects are anticipated. L-sarcomas constitute the most frequent histological STS subtypes, representing approximately 40-50% of all STS; therefore this group of patients represents a large proportion of all STS patients. Most patients (97%) had had previous surgery and approximately 50% had received radiotherapy. Virtually all patients (99%) had been previously treated with both anthracyclines and ifosfamide. Two thirds of the patients had received additional agents, including gemcitabine (32%), docetaxel (24%) and dacarbazine (20%). These treatments represent typical chemotherapeutic approaches to STS therapy.

- *For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?*

The dosage regimens used were:

1. 0.58 mg/m^2 as a 3-hour infusion on Days 1, 8, and 15 of each 28-day treatment cycle.

2. 1.5 mg/m^2 as a 24-hour infusion on Day 1 of each 21-day treatment cycle.

Regimen 2 is the recommended regimen from the SPC.

- *Were the study groups comparable?*

Yes.

- *Were the statistical analyses used appropriate?*

Yes

- *Was an intention-to-treat analysis undertaken?*

Yes

- *Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?*

It is acknowledged that the substantial crossover from the qwk 3-h to the q3wk 24-h arm may have introduced a confounding factor for the evaluation of the secondary endpoint OS. The overall effect of this was to reduce the differences between treatment arms in the intention-to-treat analysis. A sensitivity analysis provided to EMEA as part of the MAA dossier clearly documents such crossover effect. A much stronger trend toward a survival advantage with the q3wk 24-h regimen appears when patients are censored for the analysis at the time of crossover (see Appendix 4).

6.4 Results of the relevant comparative RCTs

Time to progression

The STS-201 trial met its primary endpoint, TTP per independent review, by showing significantly better outcomes for the 1.5 mg/m^2 24-hour IV infusion every 3 weeks schedule versus the 0.58 mg/m^2 3-h IV infusion for 3 out of 4 weeks schedule. The difference between the two treatment groups was statistically significant (p=0.0320), with a hazard ratio (HR) of 0.734, indicating a 27% reduction in the relative risk of progression for patients receiving the q3wk 24-h regimen compared with the qwk 3-h regimen. A median TTP of 2.3 months was observed in the qwk 3-h arm versus 3.7 months in the q3wk 24-h arm. TTP rates at 3 months were 53.4% (q3wk 24-h) versus 45.1% (qwk 3-h)

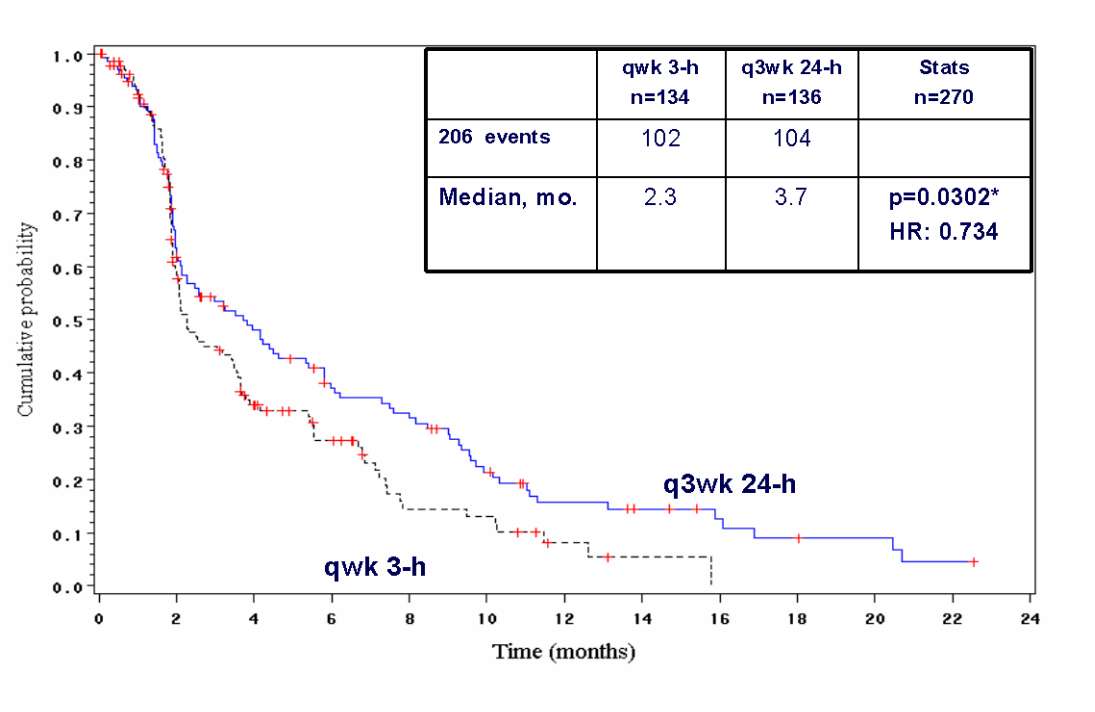
and the corresponding TTP rates at 6 months were 37.2% versus 27.3%. (See Table 2 and Figure 3.)

Table 2 TTP clinical analyses from an independent review and from investigators

Efficacy variables	**qwk3-h**	**q3wk24-h**	**LR* (p value)** **HR* (p value)**
TTP, months (independent review)			
Number of events, n (%)	102 (76.1%)	104 (76.5%)	
Median (95% CI)	2.3 (2.0 -3.5)	3.7 (2.1-5.4)	LR; 4.698 (p=0.0302) HR: 0.734 (p=0.0320)
No PD at 3 months. % (95% CI)	45.1% (36.3-53.9%)	53.4% (44.6-62.2%)	
No PD at 6 months, % (95% CI)	27.3% (19.0-35.6%)	37.2% (28.4-46.0%)	
TTP, months (investigator)			
Number of events	106 (79.1%)	110 (80.9%)	
Median (95% CI)	2.5 (2.1-3.5)	4.2 (2.6-6.5)	LR: 8.208 (p=0.0042)*** HR; 0.668 (p=0.0046)
No PD at 3 months, % (95% CI)	47.8% (39.1-56.6%)	56.6% (47.9-65.2%)	
No PD at 6 months, % (95% CI)	29.5% (21.3-37.8%)	44.4% (35.7-53.1%)	

LR, log ratio; HR, hazard ratio; TTP, time to progression; PD, progressive disease; CI, confidence interval.

Figure 3 TTP Final Results Primary Analysis TTP All Randomised (Independent Review)



Secondary endpoints

Progression free survival

PFS was significantly prolonged in patients randomised to receive the q3wk 24-h regimen (median 3.3 months vs. 2.3 months). PFS rates at three months were 51.5% in the q3wk 24-h regimen and 44.7% in the qwk 3-h regimen. The six-month PFS rates were 35.5% and 27.5%, respectively. The six-month PFS rates obtained with trabectedin are considerably greater than the six-month PFS of 14% reported by Van Glabbeke (23) for active regimes in pre-treated patients with STS in an analysis of PFS rates for active and inactive treatments in pre-treated patients from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) published data (see Table 3).

Table 3 PFS rates at 3- and 6- months in pre-treated STS patients

	EORTC STBSG (23)		ET-743-STS-201 (all randomized - independent review)(28)	
	Inactive regimen in pre-treated STS patients	Active regimen in pre-treated STS patients	q3wk 24-h	qwk 3-h
n	234	146	136	134
PFS-3 months	21 +/- 3%*	39+/- 4%*	51.5% (43.0-60.1%)**	44.7% (36.0-53.3)**
PFS-6 months	8 +/- 2%*	14 +/-3%*	35.5% (27.1-43.9%)**	27.5 % (19.4-35.5)**

*Mean ± standard error (EORTC STBSG data). **95% confidence interval. Active agents (EORTC STBSG): ifosfamide and dacarbazine after failure of an anthracycline-containing regimen. Inactive agents (EORTC STBSG): mitozolomide, nimustine, fotemustine, miltefosine, liposomal muramyl tripeptide phosphatidylethanolamide, temozolamide, etoposide, tomudex and gemcitabine in STS pretreated patients. EORTC-STBSG: Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer.

Overall survival

Median survival was 13.9 months (95% CI: 12.5-18.6) for the q3wk 24-h regimen and 11.8 months (95% CI: 9.9-14.9) for the qwk 3-h regimen (p=0.1985). One-year OS rates were 60.3% (52.0-68.5) for the q3wk 24-h regimen vs. 50.0% (41.5-58.4) for the qwk 3-h regimen (p=0.0770).

Acknowledging the limitations of all historical comparisons, these survival data compare favourably with survival data reported in the EORTC STBSG database in four phase II studies in adult advanced/metastatic pre-treated STS patients (i.e. similar clinical context as in trial ET743-STS-201). Survival data reported for patients failing after second-line ifosfamide (survival after progression on second-line ifosfamide, studies 62912 and 62953): median OS, 5.9 months; 1-year OS, 20% (29;30) and for patients

who received Dacarbazine (DTIC, study 62841): median OS, 6.6 months; 1-year OS, 18% or Etoposide (study 62932): median OS, 6.3 months; 1-year OS, 15% (31) after failure on standard chemotherapy (see

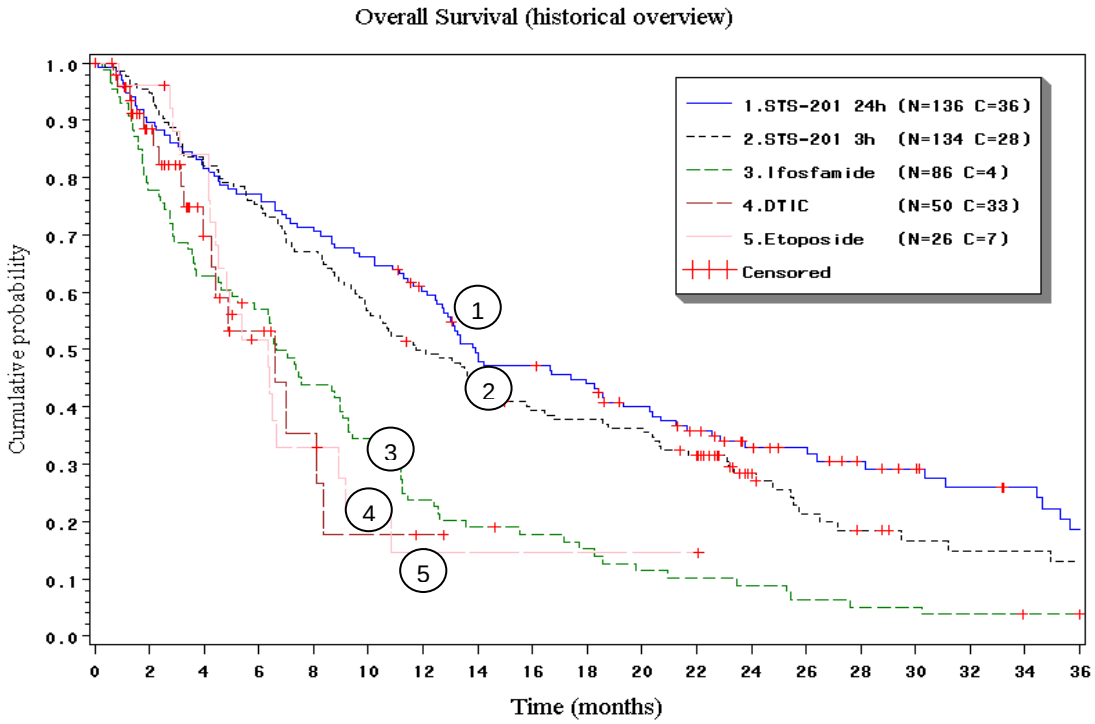
Table 4 and Figure 4).

Table 4 Overall survival in the pivotal randomised study ET743-STS-201 and in EORTC STBSG studies with ifosfamide (survival after progression to ifosfamide, studies 62912 and 62953), dacarbazine (DTIC, study 62841) and etoposide (study 62932)

	ET743-STS-201		**Historical controls**		
	Trabectedin qwk 3-h	Trabectedin q3wk 24-h	Ifosfamide	Dacarbazine	Etoposide
N	134	136	86	50	26
Events	119 (88.8%)	116 (85.3%)	82 (95.3%)	17 (34.0%)	19 (73.1%)
Censored	15 (11.2%)	20 (14.7%)	4 (4.7%)	33 (66.0%)	7 (26.9%)
Median (Months) (95% CI)	11.8 (9.9-14.9)	13.9 (12.5-18.6)	6.6 (5.0-9.0)	6.6 (4.3-8.4)	6.3 (4.4-8.9)

CI: confidence interval; OS, overall survival.

Figure 4.Overall survival in the pivotal randomised study ET743-STS-201 and in EORTC STBSG studies with ifosfamide (survival after progression to ifosfamide, studies 62912 and 62953), dacarbazine (DTIC, study 62841) and etoposide (study 62932)



In spite of the acknowledged limitations of historical comparisons, the median overall survival with the qwk 3-h regimen (the worst performing arm of the STS-201 trial) is clearly above the curves in the EORTC STBSG studies in pretreated STS. The substantial separation of the curves provides reassurance that the qwk 3-h arm has a favourable outcome relative to historical controls. The 11.8 month median survival achieved with trabectedin qwk 3-h regimen is remarkable in the context of an expected 6-month survival without effective therapy in pretreated patients with STS after failure of anthracycline-based chemotherapy.

Furthermore, the 11.8 months median survival obtained with trabectedin qwk 3-h compares favourably with data from first-line chemotherapy in STS, which show a median survival of approximately 12 months (range 7.3–13.3 months). The one-year OS of 60.3% observed with the q3wk 24-h trabectedin schedule improves on the one-year OS from first line chemotherapy (range 13–53%) counted from the initiation of anthracycline-based chemotherapy (Table 5).

Table 5 Overall survival from start of first-line anthracycline-based chemotherapy for advanced/metastatic STS in randomised clinical trials

Study	Treatment	Evaluable patients	Median survival months	Estimated 1-year survival %
Chang et al, 1976 (32)	DOX	17	10.1	-
	DOX/STREPT	14	10.6	-
Schoenfeld et al, 1982 (33)	DOX	66	8.5	40
	DOX/VCR/CYCLO	70	9.5	37
Omura et al, 1983 (34)	DOX	120	7.7	31
	DOX/DTIC	106	7.3	36
Muss et al, 1985 (35)	DOX	50	11.6	49
	DOX/CYCLO	54	10.9	49
Borden et al, 1987 (36)	DOX	94	8.0	32
	DOX loading -->weekly DOX/DTIC	88	8.4	36
		92	8.0	32
Borden et al, 1990 (37)	DOX	151	9.4	41
	DOX/VND	147	9.9	48
Antman et al, 1993 (8)	DOX/DTIC	170	13.3	51
	DOX/IFOS/DTIC	170	11.9	46
Edmonson et al, 1993 (38)	DOX	90	8.4	40
	DOX/IFOS	88	11.5	48
	DOX/MITC/CDDP	84	9.4	40
Santoro et al, 1995 (39)	DOX	240	12.0	50
	DOX/VCR/CYCLO/DTIC	134	11.8	50
	DOX/IFOS	231	12.7	53
Jelic et al, 1997 (9)	EPI	50	-	13
	EPI/CDDP	56	-	30
Le Cesne et al, 2000 (7)	DOX/IFOS	149	12.9	50
	DOX/IFOS/rhGM-CSF	145	12.7	50
Judson *et al,* 2001 (40)	DOX	43	8.2	30
	CAELYX	50	10.7	42
Lorigan *et al,* 2007 (41)	DOX	110	12	49
	IFOS 3*3	109	10.9	46
	IFOS 9	107	10.9	46

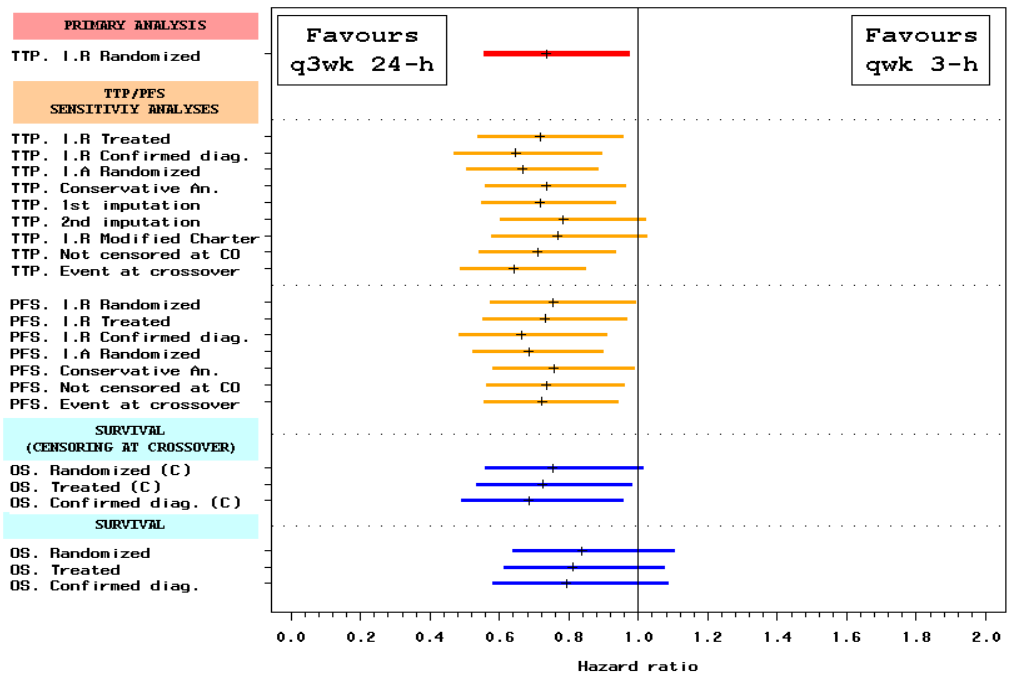
CDDP= cisplatin; CYCLO=cyclophosphamide; DOX= doxorubicin; DTIC= dacarbazine; EPI= epirubicin ; IFOS= ifosfamide; MITC= mitomycin; rhGM-CSF= recombinant human granulocyte-macrophage colony stimulating factor; STREPT= streptozotocin; VCR= vincristine; VND= vindesine.

In summary, these observations suggest that it is highly unlikely that the survival outcome obtained with the least performing trabectedin regimen (qwk 3-h) in the ET743-STS-201 study is inferior to what could be expected with a placebo, or with inactive agents in STS. Therefore, trabectedin qwk 3-h is an efficacious therapy against STS and can be considered as an appropriate active control arm for the pivotal trial.

The results of this study therefore demonstrate that trabectedin, administered at the recommended dose schedule (1.5 mg/m^2 q3wk 24-h produces significant clinical benefit in patients with STS when compared with the qwk 3-h regimen. This was therefore the recommended regimen by the EMEA for use in the treatment of patients with STS and is the regimen upon which the modelled economic evaluation is based.

As explained above, the q3wk 24-h arm performed consistently better in all clinical study endpoints. Figure 5 illustrates the consistency of the superior efficacy outcomes with the q3wk 24-h over the qwk 3-h regimen in TTP, PFS and OS across the various datasets evaluated according to the statistical analysis plan of the pivotal study STS-201.

Figure 5 Consistency of HRs for time to-event endpoints in various subsets



The consistency in better time-to event outcomes with trabectedin q3wk 24-h strongly supports a true and clinically meaningful treatment effect and superior benefit with the recommended schedule for the approved indication.

Best overall response rate

Per independent review, nine patients achieved a PR: two patients in the qwk 3-h group and seven patients in the q3wk 24-h group. Therefore, the ORR per independent review was 1.5% (95% CI: 0.2%-5.3%) in the qwk 3-h group and

5.1% (95% CI: 2.1%-10.3%) in the q3wk 24-h group, respectively (Fisher's p-value=0.1724) (Table 6). Additionally, 118 patients had SD as overall best response: 52 patients (38.8%) in the qwk 3-h group and 66 patients (48.5%) in the q3wk 24-h group. The PD rate was 51.5% in the qwk 3-h group and 38.2% in the q3wk 24-h group.

Per investigator's assessment, one patient achieved a CR and 17 patients had a PR. The CR was achieved in one patient of the qwk 3-h group, and PRs occurred in two patients of the qwk 3-h group and 15 patients of the q3wk 24-h group, respectively. Therefore, the ORR per investigator's assessment was 2.2% (95% CI: 0.5%- 6.4%) in the qwk 3-h group and 11.0% (95% CI: 6.3%-17.5%) in the q3wk 24-h group, respectively (Fisher's p-value=0.0058) (Table 6).

Table 6 Overall best response and objective response rate

		Data from independent review			Data from investigators report		
		qwk 3-h	**q3wk 24-h**	**total**	**qwk 3-h**	**q3wk 24-h**	**total**
n		134	136	270	134	136	270
Overall best response	CR	0	0	0	1 (0.7%)	0	1 (0.4%)
	PR	2 (1.5%)	7 (5.1%)	9 (3.3%)	2 (1.5%)	15 (11.0%)	17 (6.3%)
	SD	52 (38.8%)	66 (48.5%)	118 (43.7%)	59 (44.0%)	62 (45.6%)	121 (44.8%)
	PD	69 (51.5%)	52 (38.2%)	121 (44.8%)	65 (48.5%)	51 (37.5%)	116 (43.5%)*
	NE	11 (8.2%)	11 (8.1%)	22 (8.1%)	7 (5.2%)	8 (5.9%)	15 (5.6%)
Objective response (95% CI)		2 (1.5%) (0.2-5.3%)	7 (5.1%) (2.1-10.3%)	9 (3.3%) (1.5-6.2%)	3 (2.2%) (0.5-6.4%)	15(11.0%) (6.3-17.5%)	18 (6.7%) (4.0-10.3%)

6.5 Meta-analysis

Only a single relevant RCT was identified, therefore no meta-analysis is possible.

6.6 Indirect/mixed treatment comparisons

Not applicable - no indirect comparison was carried out as only a single relevant RCT was identified.

6.7 Safety

The randomised pivotal trial (ET-743-STS 201) which forms the basis for this submission investigated safety outcomes as a secondary endpoint. The safety profile of trabectedin presented here is based on data from the pivotal trial supplemented by data from supportive studies that included the administration of trabectedin at the recommended dose and schedule in pre-treated patients with STS.

These supportive studies are the three relevant single-arm phase II studies, all of which investigated safety as a secondary outcome (20;21;42). The results from all four studies consistently demonstrate that trabectedin is generally well tolerated with adverse events being non-cumulative, reversible and manageable. No cumulative toxicities have been observed in patients treated with multiple cycles.

The main treatment-related severe (grade 3/4) toxicities observed in all studies were transient, reversible and non-cumulative neutropenia and transaminase elevations without clinical consequences. Grade 3/4 nausea and vomiting were also observed in some patients.

The course of neutropenia followed a predictable pattern of rapid onset and reversibility, occurring on approximately Day 15 in the randomised study and lasting for a median of 7 days (24;27). Grade 3/4 neutropenia did not increase with additional number of cycles of treatment, thus indicating that the toxicity was not cumulative. In all studies, the incidence of febrile neutropenia was low; occurring in 2% of patients and in less than 1% of cycles (43).This compares favourably with doxorubicin which has been reported to induce febrile neutropenia in 16% of patients when administered at the standard dose of 75 mg/m2 q3wk (40) and ifosfamide, which has been reported to induce febrile neutropenia in 30-40% of patients when administered at a dose of 4 mg/m2/day for 3 consecutive days every 4 weeks (20;30). The incidence of haematological toxicities is presented in Table 7.

Table 7 Incidence (%) of severe (grade 3/4) haematological toxicities with trabectedin therapy at the recommended regimen in the 3 single-arm phase II studies and the randomised pivotal study

Study	**EORTC study** (20) n=801	**French study** (21), n=54	**US study** (19), n=36	**Randomised study**(24) ; (24;26;27) n=130
Neutropenia	50	61	34	47
Febrile neutropenia	7	7	6	1 patient (0.8%)
Thrombocytopenia	14	19	17	12
Anaemia	14	22	9	8

[1] data for the EORTC study are for patients included after the protocol amendment which excluded patient with raised alkaline phosphatase levels at baseline.

ALT and AST increases did not follow a cumulative pattern but showed a decreasing tendency over time. Transient grade 3/4 increases of AST and ALT were observed in 41% and 51% of the patients. The median time to reach the peak values was 5 days for both AST and ALT. Most of the values had decreased to grade 1 or resolved by day 14-15. Incidence of non haematological toxicities is presented in Table 8.

Table 8 Incidence (%) of severe (grade 3/4) non-haematological toxicities during therapy with the recommended regimen in the 3 single-arm phase II studies and the randomised study.

Study	**EORTC study** (20), n=80[1]	**French study** (21), n=54	**US study** (19), n=36	**Randomised study** (24;26;27)n=130
AST elevation	38	48	26	32
ALT elevation	46	57	20	48
Nausea	5	7	6	4
Vomiting	8	9	3	2
Asthenia/fatigue		15	0	6

[1] data for the EORTC study are for patients included after the protocol amendment which excluded patient with raised alkaline phosphatase levels at baseline.

Unlike other commonly used cytotoxic agents, no cardiotoxicity or neurotoxicity was observed, and alopecia (generally mild) occurred infrequently (44) (45;46). A safety profile comparison with other chemotherapy in this setting shows the following (see Table 9):

Table 9 Comparison of safety profile of trabectedin (from randomised study) with current standard therapies, doxorubicin and ifosfamide

Side effects	**Doxorubicin (75 mg/m^2)** (40;47)	**Ifosfamide (≥10g/m2)** (20;30) (48)	**Trabectedin qwk 3-h**	**Trabectedin q3wk 24-h** (24;27)
Toxic deaths	0-4%	0-4%	2.3%	3.1%
Grade ¾ neutropenia	77%	100%	13.3%	47.0%
Febrile neutropenia	19%	39%	0.8%	0.8%
Grade ¾ AST	NR	NR	3.1%	31.5%
Grade ¾ ALT	NR	NR	9.4%	47.7%
Cardiac toxicity	5-10%	-	-	-
Neurotoxicity	10%	30%	<1%	2%
Alopecia	100%	100%	-	<1%

Details of the safety profile of trabectedin are derived from both the Drug Safety Database (DSD), reporting serious adverse events (SAEs) from patients exposed to trabectedin and a second database, the ISD, containing safety data from case report forms. The latter includes SAEs as well as laboratory data from 1,164 patients and 5,060 treatment cycles (data cut-off 30 April 2007) from patients treated with trabectedin given either q3wk 24-h or qwk 3-h.

The ISD also reports on haematological laboratory abnormalities. Table 10 shows the most serious per patient safety haematological outcomes. The database provides safety biochemical laboratory abnormalities (Table 11).

Table 10 Trabectedin-related haematological adverse events

Event	q3wk 24-h	qwk 3-h
	N=569 (%)	N=337 (%)
Haemoglobin grade 3	55(10)	13(4)
Haemoglobin grade 4	17(3)	4(1)
Neutrophils grade 3	150(26)	27(8)
Neutrophils grade 4	136(24)	4(1)
Platelets Grade 3	65(11)	10(3)
Platelets Grade 4	12(2)	1(<1)

Table 11 Trabectedin-related biochemical adverse events

Event	24-hr q3wk	3-hr qwk
	N=569 (%)	N=337 (%)
Creatine kinase grade 3	7(3)	11(4)
Creatine kinase grade 4	4(2)	6(2)
Creatinine grade 3	5(1)	0(0)
Creatinine grade 4	3(1)	2(1)

Hepatobiliary laboratory abnormalities are presented in Table 12.

Table 12 Trabectedin-related hepatobiliary adverse events

Event	q3wk 24-h	qwk 3-h
	N=569 (%)	N=337 (%)
Alk Phos grade 3	16(3)	15(4)
Alk Phos grade 4	2(<1)	1(<1)
ALT grade 3	248(44)	39(12)
ALT grade 4	42(7)	0(0)
AST grade 3	214(38)	11(3)
AST grade 4	17(3)	0(0)
Bilirubin grade 3	4(1)	1(<1)
Bilirubin grade 4	0(0)	0(0)

6.8 Non-RCT evidence

6.8.1 Details of how the relevant non-RCTs have been identified and selected

The following non-RCTs were identified using the systematic search described previously (see section 6.1) and the specified inclusion and exclusion criteria (see section 6.22):

1. R. Garcia-Carbonero, J.G.Supko, J.Manola, M.V.Seiden, D.Harmon, D.P.Ryan, M.T.Quigley, P.Merriam, J.Canniff, G.Goss, U.Matulonis, R.G.Maki, T.Lopez, T.A.Puchalski, M.A.Sancho, J.Gomez, C.Guzman, J.Jimeno, and G.D.Demetri, Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy, J Clin Oncol 22 (2004) 1480-1490.

2. Yovine, M.Riofrio, J.Y.Blay, E.Brain, J.Alexandre, C.Kahatt, A.Taamma, J.Jimeno, C.Martin, Y.Salhi, E.Cvitkovic, and J.L.Misset, Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients, J Clin Oncol 22 (2004) 890-899.

3. Le Cesne, J.Y.Blay, I.Judson, A.Van Oosterom, J.Verweij, J.Radford, P.Lorigan, S.Rodenhuis, I.Ray-Coquard, S.Bonvalot, F.Collin, J.Jimeno, E.Di Paola, M.van Glabbeke, and O.S.Nielsen, Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial, J Clin Oncol 23 (2005) 576-584.

6.8.2 Summary of methodology of relevant non-RCTs

A summary of the methodology of these studies is presented in Table 13.

Table 13 Summary of methodology of relevant non-RCT studies with trabectedin at the recommended dose and schedule (1500 µg/m2 q3wk 24-h)

Study	Study design	Patient group(s	Outcomes
Garcia-Carbonero et al (2004)	Single arm multicentre (3 institutions in the USA), phase II study, 2-stage Simon design	Histologically confirmed recurrent or metastatic STS Disease progression despite prior chemotherapy with ≤2 prior regimens	Primary endpoint: response rate /RR). Secondary endpoionts: response duration, TTP, OS, safety and pharmacokinetics
Yovine et al (2004)	Single arm, multicentre (4 institutions in France), phase II study, 2-stage Gehan design	Advanced or metastatic, histologically proven STS. Two cohorts 1) prior therapy with one or two single agents or one combination 2) prior therapy with ≥ 3 single agents or ≥ 2 combinations	Primary endpoint RR Secondary endpoints: response duration, TTP, OS, safety
Le Cesne et al (2005)	Single arm, multicentre (8 European centres) phase II study, 2-stage Simon design on two separate cohorts	Histologically proven metastatic or unresectable loco-regional recurrent STS (non-GIST) with prior chemotherapy	Primary endpoint: RR Secondary endpints: response duration, TTP, OS

6.8.3 Critical appraisal of relevant non-RCTs

The relevant non-RCTs were critically appraised according to the check-list developed by (49) for the assessment of methodological quality for non-randomised studies. The results of this assessment are presented in Table 14.

Table 14 Critical appraisal of relevant non-RCT studies according to Downs and Black criteria

	Criteria	Garcia-Carbonero et al (2004)	Yovine et al (2004)	Le Cesne et al (2005)
Reporting	*Is the hypothesis/aim/objective of the study clearly described?*	Y	Y	Y
	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Y	Y	Y
	Are the characteristics of the patients included in the study clearly described ?	Y	Y	Y
	Are the interventions of interest clearly described?	Y	Y	Y
	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N	N	N
	Are the main findings of the study clearly described?	Y	Y	Y
	Does the study provide estimates of the random variability in the data for the main outcomes?	Y	Y	Y
	Have all important adverse events that may be a consequence of the intervention been reported?	Y	Y	Y
	Have the characteristics of patients lost to follow-up been described?	Y	N	Y
	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	N	N	N
External validity	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*	unable to determine	unable to determine	unable to determine
	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	unable to determine	unable to determine	unable to determine
	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	unable to determine	unable to determine	unable to determine
Internal validity - bias	*Was an attempt made to blind study subjects to the intervention they have received ?*	N	N	N
	Was an attempt made to blind those measuring the main outcomes of the intervention?	N	N	N
	If any of the results of the study were based on "data dredging", was this made clear?	Y	Y	Y
	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?	Y	Y	Y
	Were the statistical tests used to assess the main outcomes appropriate?	Y	Y	Y
	Was compliance with the intervention/s reliable?	Y	Y	Y
	Were the main outcome measures used accurate (valid and reliable)?	Y	Y	Y
	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	unable to determine	unable to determine	unable to determine
	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	unable to determine	unable to determine	unable to determine
	Were study subjects randomised to intervention groups?	N	N	N
	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N	N	N
	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N	N	N
	Were losses of patients to follow-up taken into account?	Y	Y	Y
	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%	NA	NA	NA
Overall score (out of 27)		11	13	14

NA not assessed

6.8.4 Results of the relevant non- RCTs

A summary of the results of the non-RCTs are presented in Table 15

Table 15 Summary of results from relevant non-RCTs

Study	Efficacy	Safety
Garcia-Carbonero et al (2004)	Median follow-up at the time of analysis for surviving patients was 25 months (range, 7 to 44 months). During follow up 31 patients progressed and 26 patients died. 6/35 assessable patients responded (overall response rate of 17.1% (95% CI: 6.6% to 33.6%)) Objective responses were identified in: myxoid/round-cell liposarcoma (3); leiomyosarcoma (1); fibrosarcoma (1); synovial cell sarcoma (1). Minor responses in leiomyosarcoma (1), an overall clinical benefit rate of 20%. Complete responses in myxoid/ round-cell liposarcoma (1). The estimated progression-free survival at 6 months was 24.4% (95% CI: 13% to 44%), and the estimated 1-year progression-free survival rate was 21% (95% CI: 11% to 41%; The overall survival rate at 1 year was 72% (95% CI: 59% to 88%).	Haematological toxicities: Grade 3 to 4 leukopenia (22%) and neutropenia (33%), transaminitis grade 3 (34%) and grade 4 (36%), study withdrawal caused by a persistent alkaline phosphatase elevation on day 35 for 2 patients. Hepatotoxicity, emesis and fatigue were the most frequently occurring nonhaematologic toxicities.
Yovine et al (2004)	Median follow-up was 26.0 months (range, 15.3 to 38.9 months).Fifty-two patients were assessable for response (WHO criteria). Two partial responses (3.7%; 95% CI: 0.5 to 12.8), four minor responses (7.4%), and nine with stable disease for > or equal to 6 months (17%).28 patients had progressive disease (51.9%) Median progression-free survival was 1.9 months (range, 0.69 to 17.90 months); 24% of patients were progression free at 6 months. Median survival was 12.8 months (range, 0.69 to 33.77 months), with 30% of patients alive at 2 years, all with PD at the cut-off date.	Anaemia and thrombocytopenia reached grade 3 to 4 in 22% and 18% of patients, respectively. Grade 3 to 4 neutropenia was more frequent (61% of patients). Four patients (7.4%) discontinued the study because of treatment-related adverse events, including two treatment related deaths.
Le Cesne et al (2005)	Estimated median follow-up (Kaplan-Meier estimate) was 34 months. 104 patients were included in an intent to treat analysis, of which: 6 were not assessable (5.8%); 8 showed a partial response (7.7%); 35 showed progression (33.7%); 45 showed no change (43.3%); 4 died form progressive disease (3.8%); 4 died from toxicity (3.8%); 2 dies from other causes (1.9%).Responses were observed in leiomyosarcoma of all origins (n 5), in synovial sarcoma, liposarcoma, and malignant fibrous histiocytoma. The median duration of response was 352 days (50 weeks). Fourteen patients exhibited a tumour reduction of more than 15% (range, 15% to 47%). Twenty-six percent of patients experienced disease stabilization lasting for more than 6 months. The median time to progression was 105 days (95% CI: 75 to 124). 3-, 6-, and 12-month progression free survival figures were 52%, 29%, and 17%, respectively. Median overall survival was 278 days (9.2 months; 95% CI: 238 to 368). A progression arrest of tumour growth (PR NC) was seen 24 (56%) of 43 leiomyosarcomas.	Toxicities were mainly hepatic and haematologic; Grade 3 to 4 neutropenia (52.5%) and thrombocytopenia (18.2%); grade 3 to 4 anaemia (16%). A reversible grade 3 to 4 transient elevation of transaminases was seen in 35.3% and 44.5% of patients for AST and ALT, respectively.

6.9 Interpretation of clinical evidence

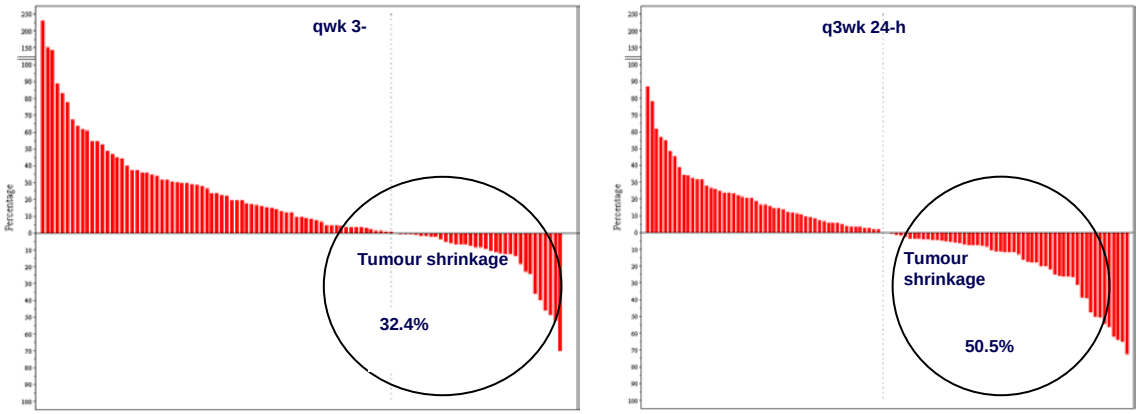
6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

From a clinical point of view, trabectedin offers patients with metastatic STS who have undergone disease progression after exhausting all approved options a further active chemotherapy treatment option. In doing so, disease progression can be delayed, thereby offering the opportunity of prolonging overall survival. TTP was the primary outcome of the pivotal study and results are described here. As presented in section 6.4, the median TTP was significantly prolonged in the q3wk 24-h treatment group compared to the qwk 3-h group.

There is no existing approved chemotherapy for the targeted population of trabectedin. Trabectedin should be incorporated into the treatment algorithm following failure of the approved standard-of-care agents (anthracyclines and ifosfamide) with the aim of slowing disease progression, and therefore potentially prolonging patient survival, as well as reducing tumour size.

In a population of 67% of patients with bulky tumours, trabectedin q3wk 24-h induced tumour shrinkage in a larger proportion of patients than qwk 3-h (p= 0.0008), as seen in Figure 6.

Figure 6 – Tumour size variation in target lesion.



The less active trabectedin schedule provided PFS rates at 3 and 6 months of 44.7% and 27.5%, respectively; considerably superior to the widely accepted EORTC criteria for anti-cancer activity in pretreated STS (PFS rates at 3 and 6 month for active agents are 39% and 14%, respectively).

As reported in Section 6.4, median survival for patients whose STS has progressed after prior treatment with anthracyclines and ifosfamide is 5.9 months (survival after progression on second line ifosfamide, studies 62912 (29) and 62953 (30) only). In the ET743-STS-201 study, the median OS with trabectedin q3wk 24-h was 13.9 months.

ET743-STS-201 showed a clear advantage of the 24-hour infusion every 3 weeks over the weekly regimen. The study demonstrated a statistically significant difference in TTP and PFS, and a favourable trend in prolonging OS. This, when considered in conjunction with the absence of other approved active chemotherapy agents for the patient population of interest, illustrates that this regimen provides a meaningful clinical benefit for a patient population without any available effective palliative therapies.

Common adverse events in patients treated with trabectedin included myelosuppression and elevations of hepatic transaminases, (see section 6.7). As detailed in Section 6.7, however, these toxicities are non-cumulative, reversible and generally well managed with the appropriate dose modifications following protocol and SPC recommendations. In contrast to that reported for trabectedin, doxorubicin and ifosfamide (the standard agents in STS) induce substantially more severe haematological toxicities. It is worth emphasising that many of the side effects commonly induced by cytotoxic chemotherapy which are unpleasant to patients, such as alopecia, or that in addition are potentially dose-limiting, debilitating, cumulative and/or life-threatening such as mucositis/stomatitis, diarrhoea, neurotoxicity, pulmonary toxicity, renal toxicity, skin/nail toxicity, hemorrhagic cystitis or cardiotoxicity, are not characteristic of trabectedin therapy.

Therefore, the safety profile of trabectedin compares favourably with that of standard agents in STS. In contrast with these standard agents, trabectedin may be administered to patients for as long as they sustain clinical benefit.

6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable

patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

The results from the pivotal trial presented here relate only to those patients with liposarcomas and leiomyosarcomas; while this group of tumours accounts for a large proportion of all soft tissue sarcomas (approximately 50%) the results of this trial are only applicable to those patients diagnosed with similar tumours. Evidence for the efficacy of trabectedin in other classes of soft tissue sarcomas comes from the non-randomised phase II single-arm trials showing similar levels of clinical benefit as in the randomised pivotal trial. Considering the lack of effective options for STS patients after failure of prior standard-of-care chemotherapy and that the safety of trabectedin is comparatively favourable in relation to that with other chemotherapeutic agents for this patient population, the existing level of evidence should not present a barrier to the use of trabectedin in the clinical management of STS patients as indicated.

One arm of the pivotal trial (50% of patients) contained the dose of trabectedin as recommended in the SPC, and all three of the supporting phase II single-arm trials utilised this dose (19-21). In terms of the safety data, the incidence of adverse events from the Integrated Safety Database are provided for two different dosing regimens, one of which is the q3wk 24-h as recommended in the SPC.

It is likely that patients in clinical trials providing the evidence for this document may have been under a more intensive follow-up than their counterparts in standard clinical practice. It is commonly assumed that more adverse events are reported in the clinical trial setting relative to the non-trial practice. However, it is worth noting that there is a large safety experience with trabectedin reflected in the pharmacovigilance database, which should more closely mimic standard clinical practice. This large safety dataset supports the favourable safety profile with this agent and it is likely to be a reliable indication of real-life events.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

A systematic search of the literature was undertaken to identify any relevant studies evaluating the cost-effectiveness of trabectedin in patients with advanced soft tissue sarcoma.

Keyword strategies were developed using key references retrieved through initial scoping searches. Search strategies did not include search terms or filters that would limit results to specific publication types or study design. No date restrictions were used.

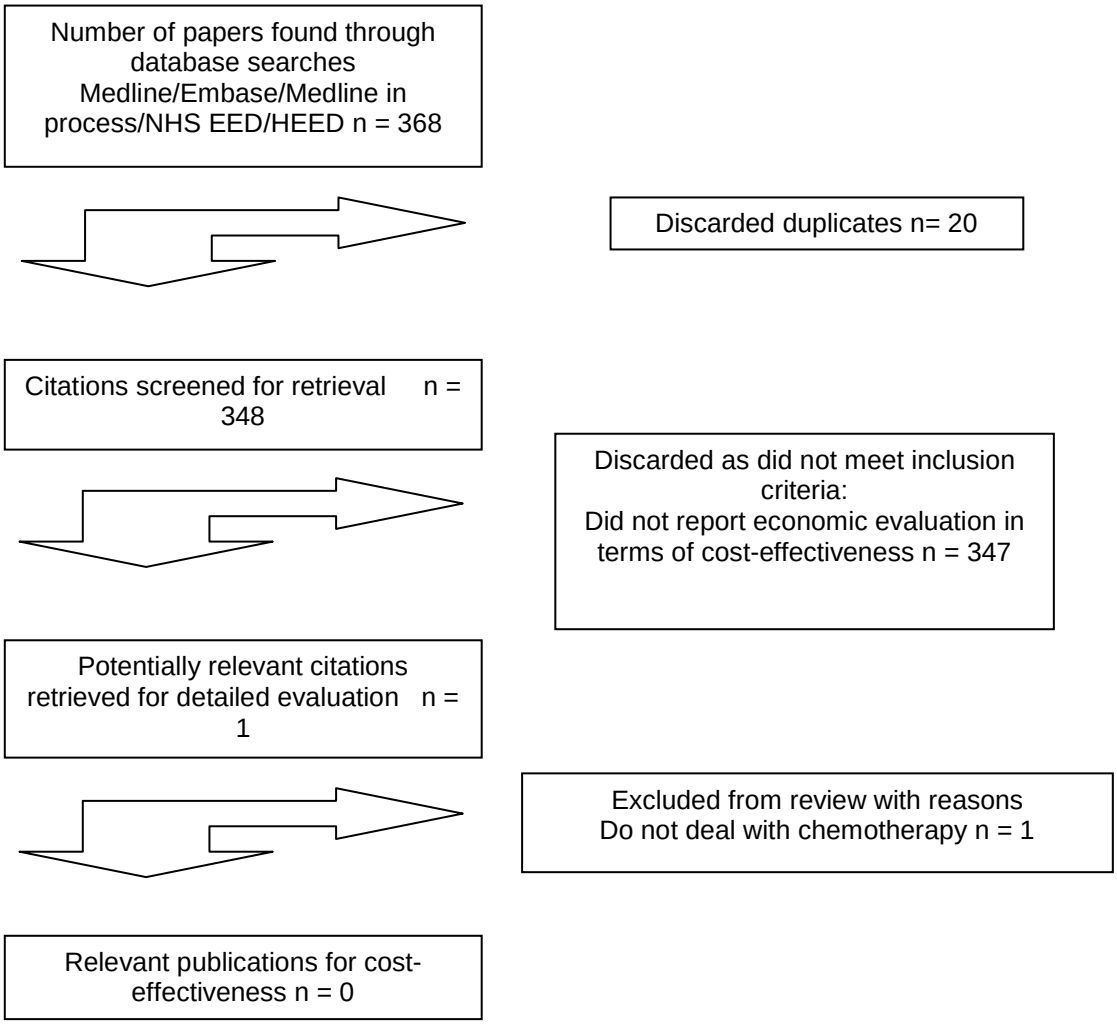
A search of Medline and Embase was conducted via the Embase.com portal.. Further searches were carried out in Medline In-process, HEED, NHS EED. A search of the manufacturer's database was also carried out to identify all publications from relevant studies. After duplicate references were removed, a total of 348 abstracts were identified and screened for relevance. All identified papers were excluded from further review as they did not meet the inclusion criteria. Further information on the databases searched, inclusion and exclusion criteria and the results of the searches can be found in Appendix 3.

Criteria for paper's inclusion comprised:

1. Publications should be in English language
2. Publication should report results of an economic evaluation in the form of cost-effectiveness
3. Publication should report on the treatment of soft tissue sarcoma patients
4. Publication should report on patients who have received prior chemotherapy with anthracyclines or ifosfamide.

The diagram below summarises the results from the literature searches along with the reasons for exclusion of the studies (see Figure 7).

Figure 7 Flow diagram of economic literature searches



7.1.2 Description of identified studies

No papers have been identified as relevant according to inclusion/exclusion criteria in section 7.11.

7.2 De novo economic evaluation(s)

7.2.1 Technology

7.2.1.1 *How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.*

The licensed patient group for trabectedin is adults with advanced soft tissue sarcoma who have failed an anthracycline and ifosfamide, or who are unsuited to receive these agents. The license is based on evidence including, but not limited to the STS-201 study.

Trabectedin's indicated dose for the treatment of patients with advanced STS is 1.5 mg/m2 administered over 24 hours every three weeks. It was observed in STS-201, however, that the actual dose administered to patients over the course of the trial was lower at 1.22 mg/m2. The difference is likely to be explained by dose reductions. It was assumed in the modelled economic evaluation that patients had an average body surface area of 1.7 m2. The per-patient dose used in the model, as presented below, was therefore 2.07 mg per administration.

Table 16 Per-patient dose of trabectedin

Row	Parameter	Value	Reference
A	Dose intensity (mg/m2) per administration	1.22	STS-201 (data on file)
B	Average body surface area (m2)	1.7	Assumption
C	Average dose per administration (mg)	2.07	Row C = row A × row B

Over the duration of the STS-201 study, patients in the treatment arm of interest (one 24 hour infusion every three weeks) received a mean of 7 cycles of treatment with trabectedin.

7.2.1.2 *Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following:*

- *the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)*

- *the robustness and plausibility of the endpoint on which the rule is based*
- *whether the 'response' criteria defined in the rule can be reasonably achieved*
- *the appropriateness and robustness of the time at which response is measured*
- *whether the rule can be incorporated into routine clinical practice*
- *whether the rule is likely to predict those patients for whom the technology is particularly cost effective*
- *issues with respect to withdrawal of treatment from non-responders and other equity considerations.*

Patients continue treatment as long as the patient has a benefit. In study STS-201 discontinuation was at clinician discretion. The amount of therapy received in the model is that observed in study STS-201.

7.2.2 Patients

7.2.2.1 *What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?*

The population included in the economic evaluation is based on the 24-hr q3wk regime from the STS-201 trial. STS-201 was a randomised study in 270 liposarcoma and leiomyosarcoma patients. Although the efficacy of trabectedin in the MAA dossier is based mainly on the results of the randomised trial STS-201, the results of the three initial phase II non-comparative studies in a total of n=183 soft tissue sarcoma patients (L (n=100) and non-L (n=83) sarcoma patients) are consistent and supportive, as recognised by EMEA evaluators. This is a rare patient population with no approved treatment options after failure of both anthracyclines and ifosfamide.

The main economic analysis considers patients with leiomyosarcomas and liposarcomas (L-sarcomas) enrolled in study STS-201.

A sensitivity analysis was conducted in a population including 183 sarcoma patients enrolled in 3 single arm trials that considered both L (n=100) and non-L (n=83) sarcoma patients. Details of the patients included in the three single arm trials can be found in Table 17.

Table 17 Histology types in initial Phase II studies

Histology	L-sarcoma (N=100)	Non L-sarcoma (N=83)	All patients (N=183)
Leiomyosarcoma	75 (75%)	-	75 (41%)
Liposarcoma	25 (25%)	-	25 (14%)
Angiosarcoma/ Hemangiopericytoma	-	3 (4%)	3 (2%)
Carcinosarcoma	-	1 (1%)	1 (<1%)
Endometrial stromal sarcoma	-	2 (2%)	2 (1%)
Fibrosarcoma	-	8 (10%)	8 (4%)
Malignant Fibrous Histiocytoma	-	9 (11%)	9 (5%)
Miscellaneous	-	8 (10%)	8 (4%)
Neurogenic sarcoma-schwanoma	-	5 (6%)	5 (3%)
Other	-	2 (2%)	2 (1%)
Rhabdomyosarcoma	-	4 (5%)	4 (2%
Sarcoma unclassified	-	16 (19%)	16 (9%)
Synovial sarcoma	-	25 (30%)	25 (14%)

7.2.2.2 *Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?*

No sub-group analysis was conducted.

7.2.2.3 *Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.*

No other sub-group analyses were conducted.

The scope of this appraisal included separate consideration of patients with rhabdomyosarcoma. This analysis was not conducted. Rhabdomyosarcoma is generally a malignancy of childhood would therefore be in any case outside the licensed indication for trabectedin. Adult onset rhabdomyosarcoma is extremely rare. These patients were not identified separately from other STS in the trabectedin clinical programme and we are aware of no additional data to support an analysis of this patient group.

7.2.2.4 *At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?*

Patients enter the model when eligible for treatment following the two standard chemotherapy regimens and exit on death.

7.2.3 Comparator technology

Since there are currently no convincing data to support treatment with other chemotherapies for these patients, the analysis is drawn against a population that has no trabectedin available to them. This population would receive best supportive care (BSC) immediately following failure with anthracyclines and ifosfamide. BSC comprises a number of treatments, which may include (though are not restricted to) non-chemotherapy drugs, palliative care and even radiotherapy for a small number of patients. Discussions held with expert clinicians in the UK support this approach. Consequently, the analysis drawn between trabectedin and BSC is relevant to the UK setting. BSC is the comparator recommended by the institute for this appraisal in the scope.

In a secondary analysis a proportion of patients were assumed to receive off-label chemotherapy as part of the sensitivity analysis.

The European Organisation for Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) database was accessed to estimate the appropriate probabilities for the BSC arm. The EORTC Soft Tissue and Bone Sarcoma Group has been investigating different chemotherapeutic regimens for the treatment of advanced and metastatic STS for more than 20 years. The data from all these clinical trials have been managed at the EORTC Data Centre, resulting in the largest and most comprehensive database available worldwide. This database includes prospectively collected data on more than 2,500 patients recruited into these clinical trials. An agreement between PharmaMar and the EORTC was established to have access and to exploit data from the non-industry sponsored studies included in the EORTC database. This approach is identical to that used to demonstrate the benefits

of trabectadin to the EMEA in the market authorisation application for trabectedin. Four studies were selected to contribute to this data. Details of the included studies are presented in Table 18

Table 18 Details of studies used to inform the probabilities in the BSC arm of the modelled economic evaluation

Study	Treatment administered	Protocol dose	Number of patients treated with STS	Previous treatment
van Oosterom et al (2002) (29)	Ifosfamide	5 g/m2 as a 24-hour continuous infusion every 3 weeks; or 3 g/m2 as a 4-hour continuous infusion on three subsequent days every 3 weeks	36 patients 41 patients	No more than one line of chemotherapy
Nielsen et al (2000) (30)	Ifosfamide	12 g/m2 as a 3-day continuous infusion every four weeks	28 patients	Standard dose ifosfamide (5 – 10 g/m2) or anthracyclines. Patients with more than one line of combination chemotherapy or two single-agent regimens were excluded
Buesa et al (1991) (50)	Darcarbazine	1200mg/m^2 every 3 weeks	50	Previous chemotherapy with doxorubin/4-epidoxorubicin or ifosfamdie/cyclophosphamide
Keizer et al (1997 (31))	Etoposide	50mg/m^2 orally for 21 consecutive days every 4 weeks	26	One two-drug schedule (usually ifosfamide and doxorubicin) or two single-drug schedules

These studies were selected for inclusion in the model because as they reported findings for patients most similar to those in the trabectedin clinical programme. We note that these studies were those selected as relevant in application to the EMEA for marketing authorization. The baseline patient characteristics of included studies are detailed in Table 19.

Table 19 Baseline demographics of study populations

	STS-201	Ifosfamide (29;30)	Etoposide (31)	Dacarbazine (50)
Patients no.	136	105	27	50
Sex				
Male (%)	44	53 (51%)	12 (44%)	23 (46%)
Female (%)	92	52 (49%)	15 (56%)	21 (42%)
Age				
Median (range)	53 (20-83)	49 (19-74)	53 (20-71)	51 (18-73)
Histology				
Fibrohistiosarcoma	0	11 (10%)	4 (15%)	6 (12%)
Liposarcoma	30 (22%)	11 (10%)	2 (7%)	3 (2%)
Leiomyosarcoma	72 (53%)	39 (37%)	8 (30%)	12 (24%)
Synovial	0	11 (10%)	2 (7%)	7 (14%)
Rhabdomyosarcoma	0		4 (15%)	
Miscellaneous	15 (11%)	10 (10%)		9 (18%)
Other	8 (6%)	23 (22%)	7 (26%)	13 (26%)
Performance status (WHO)				
0	70 (51%)	34 (32%)	10 (37%)	15 (30%)
1	66 (49%)	67 (64%)	17 (63%)	22 (44%)
>1	0	4 (4%)	0	7 (14%)

The use of the EORTC STBSG dataset, as with any historical comparison, has inherent limitations. While these limitations are acknowledged, it is pertinent to note that the reviewed studies with ifosfamide, etoposide and dacarbazine were conducted with very similar eligibility criteria and that the methodology for evaluating the efficacy endpoints was the same. The most important difference between the EORTC data and the STS-201 trial is that the efficacy data in the trabectedin pivotal trial was independently reviewed. In the best supportive care arm of the trial the data described above was used to estimate overall survival following disease progression.

A secondary analysis was conducted in which 33% of patients in the comparator arm received active therapy with either etoposide or dacarbazine. Time to progression and overall survival data from the EORTC data described above was also used to patients receiving off-label chemotherapy to stabilise for a period until disease progression.

7.2.4 Study perspective

The perspective for resource utilisation was from the UK NHS. This enables the additional cost associated with trabectedin itself to be considered concurrently with any cost offsets that may be available to other healthcare sectors.

Indirect, or societal costs, are not considered in the analysis and the analysis is therefore potentially conservative.

PSS costs were not included as no relevant data were identified.

7.2.5 Time horizon

The model runs for a total of 60 monthly cycles (5 years). At the cessation of this, the overwhelming majority of patients are deceased. An increase in the duration of the model would not be expected to markedly change the results.

7.2.6 Framework

a) Model-based evaluations

7.2.6.1 *Please provide the following.*

- *A description of the model type.*

The model employs a Markov chain structure with two arms and was constructed using Microsoft® ExcelTM. The first arm captures the costs and health outcomes associated with trabectedin, the other capturing analogous costs and outcomes that are associated with best supportive care. The modelled economic evaluation presents the incremental cost per life year and incremental cost per QALY gained that arises from treatment with trabectedin.

- *A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.*

The model includes four mutually exclusive health states:

- Disease stabilised with trabectedin
- Progressive disease treated with best supportive care following failure of trabectedin
- Progressive disease treated with best supportive care
- Death

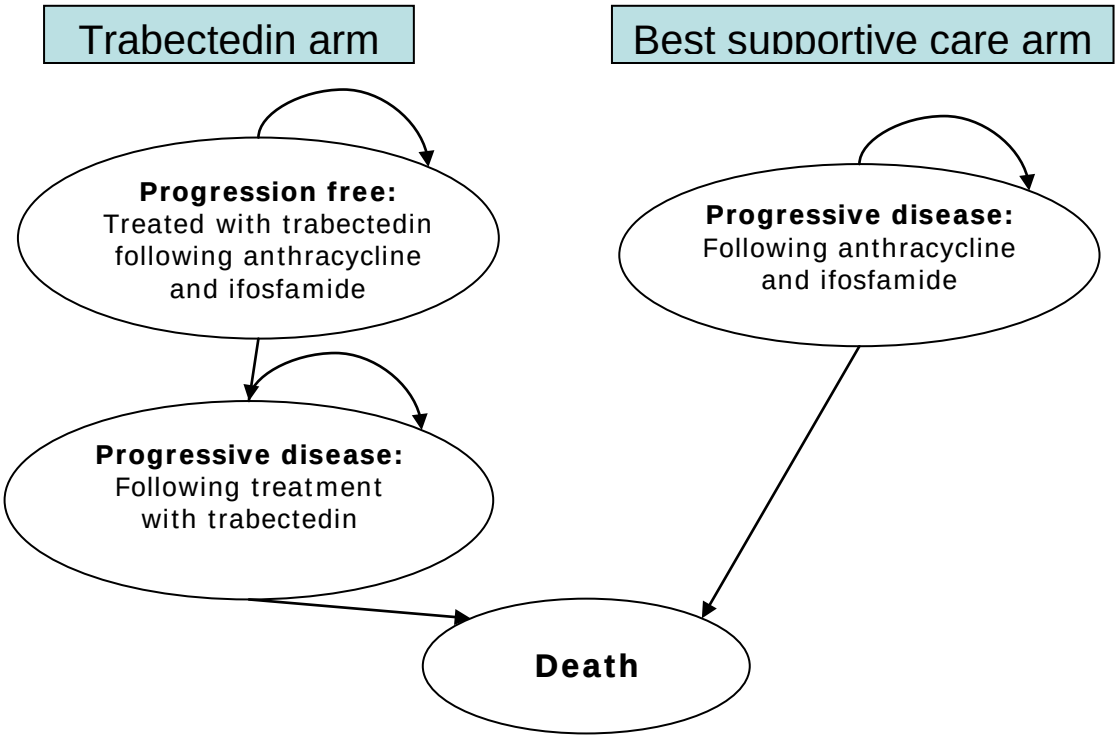
In the primary analysis no active therapies are assumed to be administered in the Best Supportive Care arm. All patients are assumed to start in the progressed health state. An alternative analysis is presented where 33% of patients receive chemotherapy.

Patients in the trabectedin arm start in the stable state. Patients continue treatment with trabectedin until they no longer experience benefit. The model does not include a health state for stable disease after cessation of trabectedin therapy.

Note that while the treatment cycle of trabectedin is a three-week period, the model uses monthly cycles. All costs and outcomes used in the model are therefore applied in monthly units.

A schematic of the model is presented below.

Figure 8: A schematic of the structure of the model



- *A list of all variables that includes their value, range (distribution) and source.*

The clinical inputs used in the trabectedin arm of the model are sourced from the STS-201 study, while the clinical inputs used to populate the best supportive care comparator (with and without chemotherapy) are sourced from the EORTC STBSG database. In the Best Supportive Care comparison EORTC data are used to estimate the duration between progression and mortality for patients who have previously received standard treatment (i.e. ifosfamide and anthracyclines). In the chemotherapy comparison the EORTC data are used to estimate time to progression and overall survival.

The probabilities of being in each health state at each cycle of the model are detailed below.

Trabectedin

Time To Progression, trabectedin arm

To estimate the deterministic probability of remaining progression free, the patient data from the STS-201 study were used to estimate a Weibull distribution. This allows the model to utilise time dependent probability of remaining progression free. The Weibull parameters were estimated in Stata 9.2 using patient level data from the STS-201 study. The variance-covariance matrix was generated in Stata for the probabilistic sensitivity analysis. The Weibull parameters are detailed in Table 20.

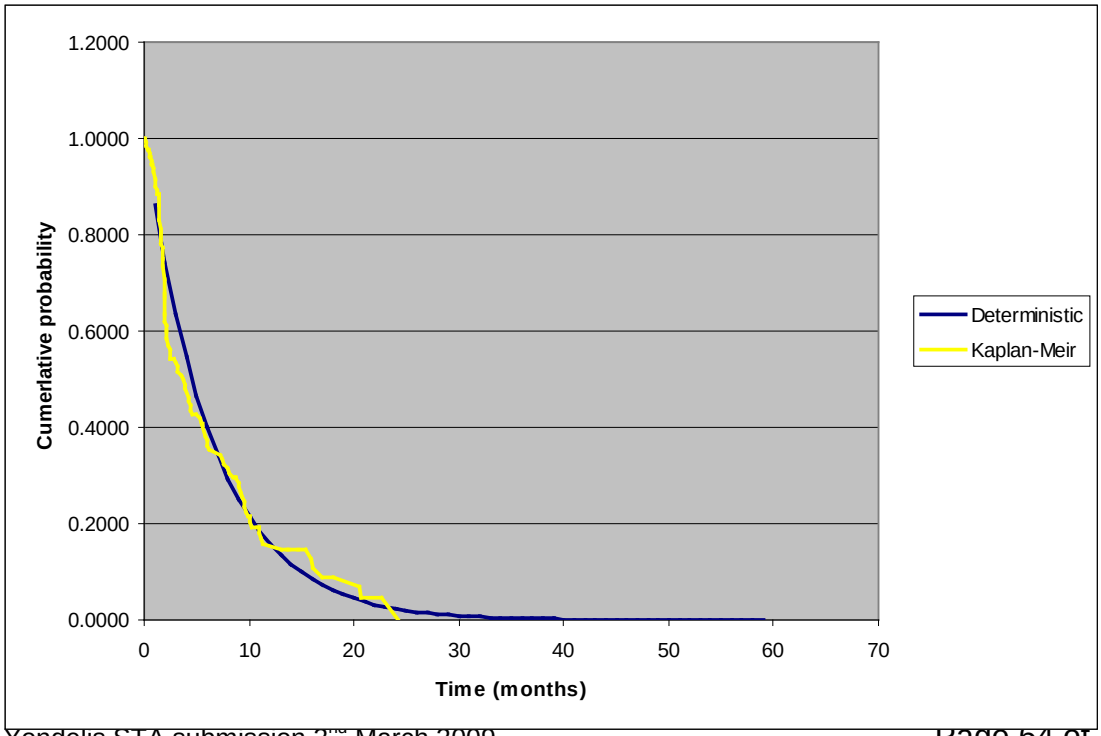
Table 20 Weibull parameters for the probability of remaining progression free

	Parameter
Lambda	0.1485
Gamma	1.0152

Source: STS-201 study

The Weibull estimates were compared with the Kaplan-Meir curves to observe the accuracy of the fitted values. The results can be found in Figure 9.

Figure 9 Comparison of the Weibull estimates with the Kaplan-Meir Curve: Progression free; trabectedin arm



Probability of mortality on trabectedin

The probability of mortality is estimated using the Weibull distribution from STS-201 patient level data. This allows the model to utilise time dependent probability of mortality. The Weibull parameters were estimated in Stata 9.2. The variance-covariance matrix was generated in Stata 9.2 for the probabilistic sensitivity analysis. The Weibull parameters are detailed in Table 21.

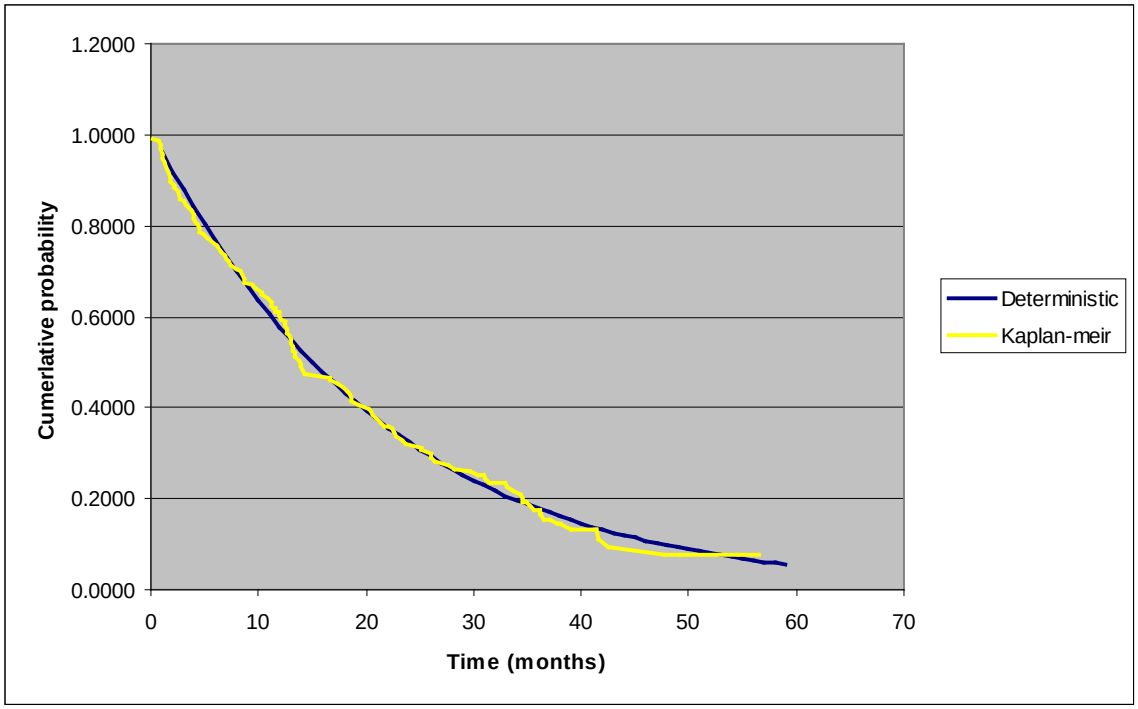
Table 21 Weibull parameters for overall survival, trabectedin arm

	Parameter
Lambda	0.0408
Gamma	1.0451

Source: STS-201 study

The Weibull estimates were compared with the Kaplan-Meir curves to observe the accuracy of the fitted values. The results can be found in Figure 10.

Figure 10 Comparison of the Weibull estimates with the Kaplan-Meir curve: Overall survival, Trabectedin arm



Probability of being in progressive disease while treated with trabectedin

This is the complement of the total probability of remaining progression free and the probability of mortality for each cycle.

Best Supportive Care

Transition from progressive disease treated with BSC to death

This is the sole transition probability applicable to the BSC arm of the model.

The EORTC data were used in the same manner as the STS-201 study data to estimate the probability of transition from progression to death. The individual patient TTP was subtracted from OS to calculated survival post progression. The probability of remaining in progressive disease was estimated from this patient level data using the Weibull distribution in Stata 9.2. The variance-covariance matrix was generated in Stata 9.2 for the probabilistic sensitivity analysis. The Weibull parameters are detailed in Table 22.

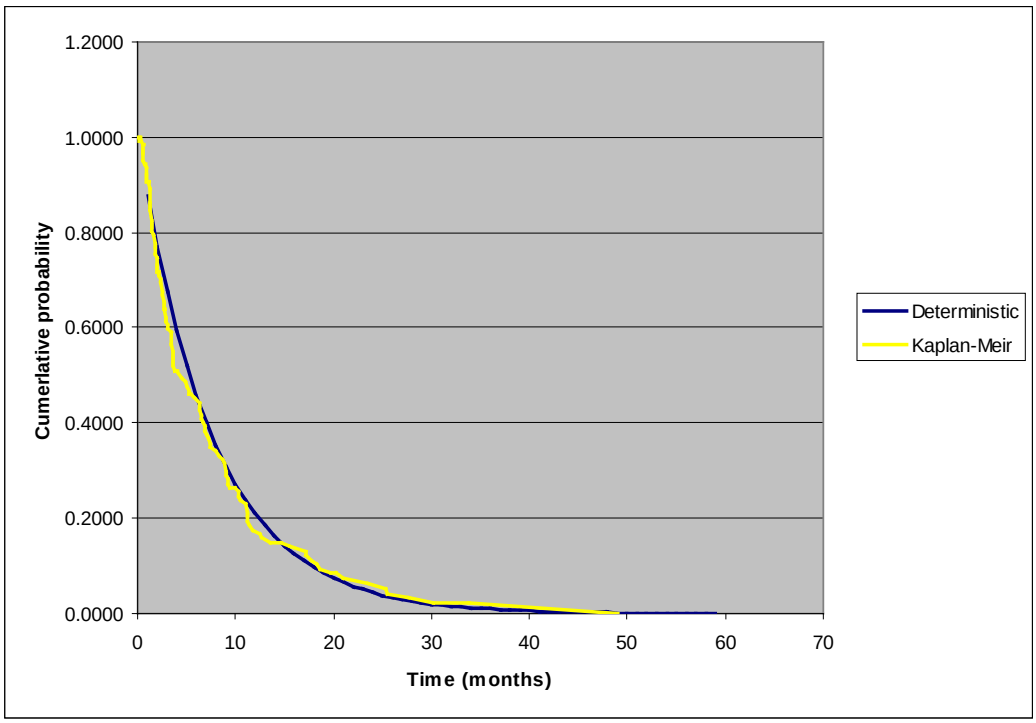
Table 22 Weibull parameters for the probability of remaining in progression, BSC group

	Parameter
Lambda	0.1307
Gamma	0.9979

Source: EORTC data

The Weibull estimates were compared with the Kaplan-Meir curves to observe the accuracy of the fitted values. The results can be found in Figure 11.

Figure 11 Comparison of the Weibull estimates with the Kaplan-Meir curve: Post progression survival, BSC arm



Other Chemotherapies

Probability of remaining progression free on other chemotherapies

In the secondary analysis the comparator included 33% of patients receiving chemotherapy. A separate arm of the model was constructed to estimate the transition of the chemotherapy patients. Data from the four EORTC studies was used to estimate the time to progression and overall survival for these patients. Consequently, the pathway described in the simplified schematic of the model in Figure 8 is the same for the chemotherapy arm as is detailed for trabectedin arm.

To estimate the deterministic probability of remaining progression free, the time to progression patient data from the EORTC studies were used to estimate a Weibull distribution. This allows the model to utilise time dependent probability of remaining progression free. The Weibull parameters were estimated in Stata 9.2 using patient level data from the EORTC studies. The Weibull parameters are detailed in Table 23.

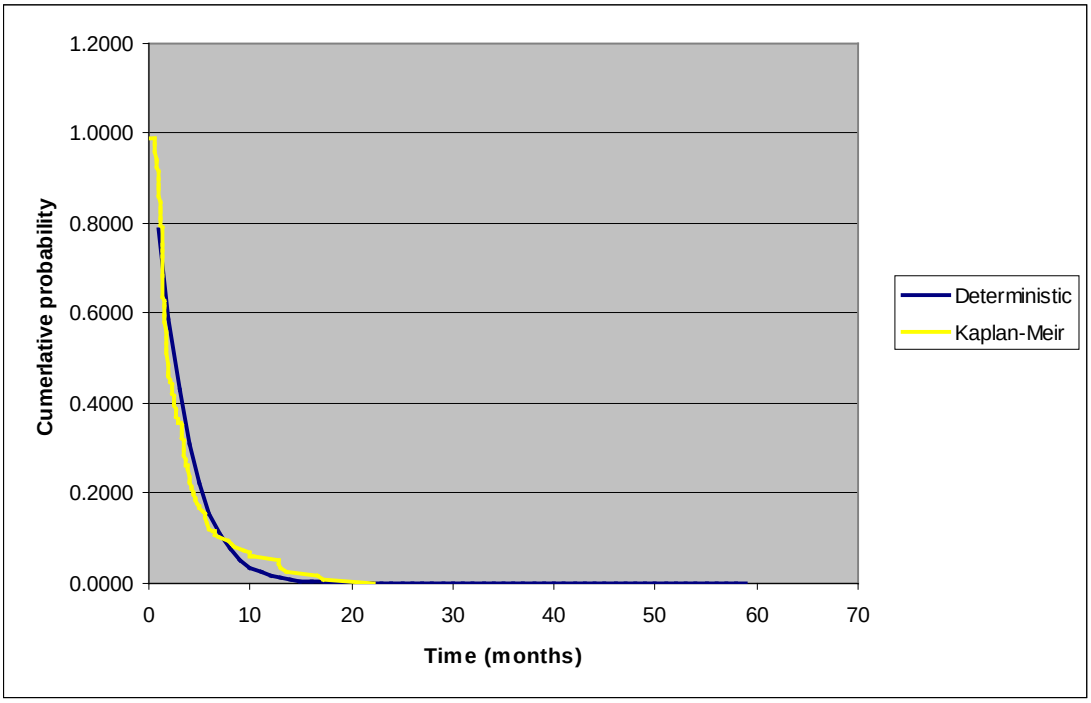
Table 23 Weibull parameters for the probability of remaining progression free: Secondary analysis, chemotherapy arm

	Parameter
Lambda	0.2702
Gamma	1.0045

Source: EORTC data

The Weibull estimates were compared with the Kaplan-Meir curves to observe the accuracy of the fitted values. The results can be found in Figure 12.

Figure 12 Comparison of the Weibull estimates with the Kaplan-Weir curve: Progression free, chemotherapy arm



Probability of mortality on other chemotherapies

The probability of mortality is estimated using the Weibull distribution from EORTC patient level data. This allows the model to utilise time dependent probability of mortality. The Weibull parameters were estimated in Stata 9.2. The Weibull parameters are detailed in Table 24.

Table 24 Weibull parameters for the probability of survival, chemotherapy arm

	Parameter
Lambda	0.0620
Gamma	1.1068

Source: EORTC study

The Weibull estimates were compared with the Kaplan-Meir curves to observe the accuracy of the fitted values. The results can be found in Figure 13.

Figure 13 Comparison of the Weibull estimates with the Kaplan-Meir curve: Overall survival, chemotherapy arm

Probability of being in progression while treated with other chemotherapies

This is the complement of the total probability of remaining progression free and the probability of mortality for each cycle.

- *A separate list of all assumptions and a justification for each assumption.*

The model assumes that in Best Supportive Care patients do not start the model progression free. The patient population have failed chemotherapy and have progressive disease. No treatments are licensed for this indication. This assumption is tested in the secondary analysis where 33% of patients receive other chemotherapy treatment.

7.2.6.2 *Why was this particular type of model used?*

State transitions models are widely used to describe treatments for advanced and metastatic cancer as they capture key time dependent clinical endpoints of overall survival and time progression free.

7.2.6.3 *What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.*

The chosen health states are commonly used in advanced and metastatic oncology models to capture the differential costs and quality of life. The health

state distribution between progression free, progressive disease and death suitably incorporates time to progression primary endpoint, and overall survival secondary endpoint of the STS-201 clinical trial. These endpoints are also consistently reported in other clinical trials. The model assesses differences in overall survival between all treatment regimens.

7.2.6.4 *What were the sources of information used to develop and inform the structure of the model?*

A search of cost-effectiveness studies in soft-tissue sarcoma identified no cost-effectiveness evaluations for chemotherapy.

The chosen structure adequately reflects the pathways of patients with advanced and metastatic soft-tissue sarcoma and has been adopted in many other metastatic cancer models.

7.2.6.5 *Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?*

It may have been possible to stratify progression free patients into complete and partial responders to trabectedin. This would be justified if there was sufficient evidence to suggest differential quality of life and costs between these health states. No reliable data was available to support this distinction. Its inclusion would therefore introduce additional uncertainty into the model.

7.2.6.6 *For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?*

A monthly cycle length was adopted in the model. This cycle length was considered appropriate period to distinguish the rates of disease progression and mortality between trabectedin and the comparator. While the treatment cycle of trabectedin is a three-week period, the model uses monthly cycles. All costs and outcomes used in the model are however applied in monthly units.

7.2.6.7 *Was a half-cycle correction used in the model? If not, why not?*

The model half-cycle corrects all health outcomes data and the ongoing costs of treatment. Chemotherapy drug costs are not half-cycle corrected as the model assigns all drug costs in the first cycle.

7.2.6.8 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?*

A number of patient observations were censored for TTP and overall survival in both the STS-201 and EORTC data. The Weibull estimation was used to account for the censoring of data and to extrapolate beyond patient follow-up.

b) Non-model-based economic evaluations

7.2.6.9 *Was the evaluation based on patient-level economic data from a clinical trial or trials?*

Not applicable.

7.2.6.10 *Provide details of the clinical trial, including the rationale for its selection.*

Not applicable.

7.2.6.11 *Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?*

Not applicable.

7.2.6.12 *Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?*

Not applicable.

7.2.6.13 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?*

Not applicable.

7.2.7 Clinical evidence

7.2.7.1 *How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.*

Risks of progression in all arms of the model were estimated independently based on evidence from STS-201 for trabectedin, and EORTC for BSC and other chemotherapies.

7.2.7.2 *How were the relative risks of disease progression estimated?*

As the economic evaluation is based upon the Weibull estimates from the respective trials, no relative risk reduction was calculated.

7.2.7.3 *Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?*

QALYs were estimated via the health states.

7.2.7.4 *Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?*

The health and cost effects of adverse events associated with trabectedin were addressed in the model.

A total of seven hospitalisations occurred for drug-related adverse events in 130 patients (7/130 = 5%) in the treatment arm of interest of STS-201. Vomiting and nausea were observed as the most common drug-related adverse events. It was assumed that the cost of inpatient treatment of vomiting was an appropriate proxy for the cost of treating adverse events. A health utility decrement associated with nausea and vomiting was sourced from the utility estimates to account for the health effects. The utility

decrement was applied to the proportion of patients experiencing the adverse event for the whole of the first cycle of treatment.

Table 25 Proportion of patients hospitalised for an adverse event

	Proportion of patients	Alpha	Beta	Distribution
Rate of hospitalisation for serious adverse event	0.05	7	123	BETA

7.2.7.5 *Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?*

Expert advice was sought in confirming clinical pathways, comparator, suitability of the EORTC database, and the use of proxy cancer utilities. However, the experts were not required to estimate any clinical parameters. Experts were identified by PharmaMar through links with cancer centres with STS oncology specialists.

7.2.7.6 *What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?*

No assumptions regarding clinical evidence have been made.

7.2.8 Measurement and valuation of health effects

7.2.8.1 *If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?*

Not applicable.

7.2.8.2 *Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.*

Life years gained and QALYs were the health effects measured. Utility values were assigned to the progression free and progressed health states of the model. A utility decrement was applied to the trabectedin arm of the model to account for the health effect of nausea associated with the treatment. The

utility decrement was applied to 5% of patients receiving trabectedin. The proportion of patients experiencing an adverse event was estimated from the number of patients hospitalised for nausea and vomiting.

7.2.8.3 *How were health effects measured and valued? Consideration should be given to all of the following:*

- *State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.*
- *Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.*
- *Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.*
- *How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?*
- *Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.*
- *Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.*

No measures of quality of life were collected as part of the clinical trials. A systematic search of the literature did not identify any studies reporting utilities in soft-tissue sarcoma patients. Consequently, utility estimates from a comparable patient population were sought.

Clinical expert input recommended that in the absence of STS specific data, lung cancer could act as an appropriate proxy disease, based on comparable prognosis and disease stage. Previous MTA and STAs were searched to identify appropriate measures of quality of life in advanced and metastatic lung cancer patients in patients who had failed previous chemotherapy.

Two health state evaluation studies were found in manufacturer submissions to NICE for this patient population. They are summarised below:

Table 26: Details of lung cancer utility estimates

NICE reference	Treatment indication	Utility measure used	Source
TA 162	Stage II/IV NSCLC patients having failed at least one prior chemotherapy	EQ-5D VAS	Unpublished source
TA 124	Second line advanced non-small cell lung cancer	Standard gamble	Nafees et al (2008) (51)

The EQ-5D VAS was not used in the base case of the model. Standard gamble was used in the TA124 submission and the study has been reported in a published article. This data is considered more robust and include measures of precision. The utility decrements are estimated from a mixed model analysis with random effects. The model results are detailed in Table 27. The EQ-5D VAS is not a preference based measure of health.

Table 27 Model estimates for utility decrements

Health Effect	Parameter estimate	Standard error	Source
Stable (intercept)	0.6532	0.0222	Nafees et al (2008) (51)
Progressive	-0.1798	0.0217	Nafees et al (2008) (51)
Nausea	-0.0480	0.0162	Nafees et al (2008) (51)

Demographic details of the population sampled to in Nafees et al (2008) (51) are detailed in Table 28. The demographic profile of the participants was reasonably similar to the UK population.

Table 28 Demographic characteristics

Demographic	Sample (N=100)
Age mean (SD)	40.51 (14.91)
Gender (% Female)	38%
White	74%
Black	14%
Asian	9%
Other	3%

The EQ-5D VAS score was used to measure utility in TA 162. It is not possible to apply these scores directly in the model because the VAS is not a preference based measure of health related quality of life.

7.2.8.4 *Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).*

No other generic or condition-specific preference based measures were used in the clinical trials.

7.2.8.5 *Were any health effects excluded from the analysis? If so, why were they excluded?*

No distinction was made between complete and partial response to trabectedin. All patients in the progression free health state were assumed to have an equal quality of life. No reliable data was available to support this distinction. Its inclusion would therefore introduce additional uncertainty into the model.

7.2.9 Resource identification, measurement and valuation

7.2.9.1 *What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)*

Resources incorporated into the modelled economic evaluation were drug costs and non-drug costs including procedures associated with the treatment of STS and the treatment of adverse events. These are outlined below.

Drug costs

The main drug cost included in the modelled economic evaluation was the cost of trabectedin itself. The per-unit costs of trabectedin are presented below.

Table 29 Unit costs of trabectedin

Vial size	Unit cost	Source
1 mg	£1,366.00	BNF56 (52)
0.25 mg	£363.00	BNF56 (52)

Trabectedin's indicated dose for the treatment of patients with metastatic STS is 1.5 mg/m2. It was observed in STS-201, however, that the actual mean dose administered to patients over the course of the trial was 1.22 mg/m2. The difference is not unexpected for a chemotherapy agent and can be adequately explained by dose reductions. It was assumed in the modelled economic evaluation that patients had an average body surface area of 1.7 m2. The per-patient dose used in the model, as presented below, was therefore 2.07 mg per administration.

Table 30 Per-patient dose of trabectedin

Row	Parameter	Value	Reference
A	Dose intensity (mg/m^2) per administration	1.22	STS-201 (data on file)
B	Average body surface area (m^2)	1.7	Assumption
C	Average dose per administration (mg)	2.07	Row C = row A × row B

Given the trabectedin vial sizes, it was assumed that patients received two 1mg vials and one 0.25mg vial per administration. This assumption includes a substantial degree of drug wastage. With this assumption in place, the average drug cost per patient is £3,095 per administration.

Over the duration of the STS-201 study, patients in the treatment arm of interest (one 24 hour infusion every three weeks) received a mean of 7 cycles of treatment with trabectedin. At the dose intensity presented in Table 30, this equates to an average total drug cost of £15,179 per patient, or £15,203 once

the cost of a dexamethasone injection received prior to trabectedin is included. Note that the dexamethasone cost was sourced from the BNF.

Table 31 Per-patient drug cost used in the modelled economic evaluation

Row	Parameter	Value	Reference
A	Average dose per patient (mg)	2.07	Table 13
B	Number of 1 mg vials required per dose	2	Assumption
C	Number of 0.25 mg vials required per dose	1	Assumption
D	Average trabectedin cost per dose	£3,095.00	Calculated
E	Dexamethasone injection prior to chemotherapy	£4.96	BNF56 ; 20mg dose = 2 × 2mL (4mg/mL) + 1 × 1mL (4mg/mL) (52)
F	Average number of drug administrations per patient	7	STS-201 (data on file)
G	Average drug cost per patient	£21,669	Row G = (row D + row E) × row F

The average, per-patient drug cost presented in Table 31 is applied to patients in the trabectedin arm of the economic model. This cost is applied in the first cycle of the model. This approach means that the variability of the cost of trabectedin between patients is not accounted for in the base case model. This may slightly overstate drug costs as costs for the minority of patients who continue to receive therapy in year 2 are not discounted.

In the secondary analysis the model also accounts for the cost of treatment with other chemotherapy agents for some patients. As outlined above, current clinical practice is such that the patient population used in the economic model is traditionally treated with an anthracycline and ifosfamide. Once these treatments have been exhausted, however, as evidenced by the patient undergoing disease progression, there are no further approved chemotherapy agents available. Despite this, patients may seek further chemotherapy. Discussions with clinicians indicated that the type of chemotherapy administered at this stage varies from patient to patient and is most often selected by doctors on the basis of what a patient is likely to tolerate and the histology of disease.

On the basis of interviews conducted with expert clinicians in England and Wales further chemotherapy treatment was assumed for 33% of patients – namely etoposide and dacarbazine. The assumed regimen details for etoposide were 120 mg/m2 for 3 days per 21 day cycle. Six cycles

administered per patient. Administered dose assumes wastage: 1 x 200mg vial, 1 x 100mg vial per patient. The assumed regimen details for dacarbazine were 1.2g/m2 for 1 day per 21 day cycle. Six cycles administered per patient. Administered dose assumes wastage: 2 × 1g vial, 1× 100mg vial per patient. Furthermore, patients receiving these two treatments were included in the EORTC data. The average cost per patient was weighted according to the estimated distribution of treatment types. This method captures the uncertainty regarding the type of chemotherapy administered. Table 32 presents the cost of drugs used in such treatment. The BNF was used to source the unit costs of these drugs.

Table 32 Cost of alternative chemotherapy agents (drug costs only)

Chemotherapy type	Proportion of patients who receive further chemotherapy [a]	Cost per therapy cycle [b]	Weighted cost per therapy cycle	Cost per patient for total treatment	Source
Etoposide	67%	£123.45	£82.30	£740.70	BNF (52)
Dacarbazine	33%	£68.65	£22.88	£411.90	BNF (52)
Total average cost of those patients receiving further chemotherapy				£1,701.88	

[a] *Based on clinician interviews*
[b] *Assumed body surface area of 1.7 m^2. Unit costs from BNF 56.*

Note that the cost presented in Table 32 is relevant to those who do receive further chemotherapy. Discussions held with expert clinicians in both England and Wales, however, indicate that not all patients will seek further chemotherapy. In the secondary analysis it was estimated that 33% would do so.

Drug administration costs

Trabectedin is administered as a continuous 24-hour infusion. The NHS Reference cost for chemotherapy is used in the economic evaluation. The costs were taken from the 2006-07 NHS reference costs (53) and inflated up to 2008 costs using the published PSSRU inflation indices (54).

Administration costs were accrued to all patients in the trabectedin arm of the economic model. It was assumed that all patients are treated on an inpatient basis. Note that this assumption is conservative. Trabectedin can be administered using ambulatory pumps, potentially reducing the cost associated with patients receiving trabectedin. Specifically, this would eliminate the need for an inpatient stay. It is expected that a proportion of

specialists would use this method of administration. Since the proportion of such use, however, is uncertain, a conservative approach is presented here.

The total, per patient cost of infusion is presented in Table 33. As with the drug costs, this is applied in the first cycle of the model as it is an average across all patients.

Table 33 Per-patient drug administration cost

Row	Parameter	Value	Reference
A	Unit cost of inpatient chemotherapy administration	£319.61	NHS Reference Costs 2006-2007, item SB12Z (53)
B	Average number of administrations per patient	6.99	Average number of treatment cycles in STS-201 (data on file)
C	Average cost of trabectedin administration	£2,234	Row C = row A × row B

The cost of administering those chemotherapy agents that are used once patients have exhausted the standard approved agents for STS is presented in Table 34.

Table 34 Cost of administration of alternative chemotherapy agents

Chemotherapy type	*Proportion of all patients* [a]	*Days of admin per cycle*	*Unit cost of admin* [b]	*Admin cost per cycle*	*Cycles of chemo-therapy*	*Total admin cost per patient*	*Weighted admin cost per patient*
Etoposide	*22%*	*3*	*£319.61*	*£958.83*	*6*	*£5,752.98*	*£1,265.66*
Dacarbazine	*11%*	*1*	*£319.61*	*£319.61*	*6*	*£1,917.66*	*£210.94*
Total average cost of further chemotherapy							*£1,476.60*

[a] *Based on the proportions presented in Table 16, but accounting for the proportion of patients seeking further chemotherapy (estimated to be 33%)*
[b] *NHS Reference Costs 2006-2007, item SB12Z (53)*

Adverse events

The model accounts for the cost impact of serious drug-related adverse events that led to hospitalisation. This approach ensures that the incremental impact of serious adverse events is adequately captured.

A total of seven hospitalisations occurred for drug-related adverse events in the treatment arm of interest of STS-201. Since vomiting and nausea were observed as the most common drug-related adverse events, it was assumed for costing purposes that the cost of inpatient treatment of vomiting was an appropriate proxy for the cost of treating adverse events. The impact of this assumption is tested in a sensitivity analysis.

Table 35 Cost of treating adverse events

Parameter	Value	Reference
Rate of hospitalisation for serious drug-related adverse events	0.05	Calculated from STS-201
Cost of treating adverse events	£624.06	NHS Reference Costs, item PA29Z (53)
Average cost of treating serious drug-related adverse events	£33.61	Calculated

The cost of treating serious adverse events was not applied to the Best Supportive Care arm of the model.

Ongoing costs associated with Progressed Disease

In addition to the chemotherapy costs outlined above, patients who have exhausted the traditional chemotherapy treatment options typically consume a variety of resources associated with end-stage treatments.

A cost of illness study by Judson et al, 2007 (55) reports those costs associated with such resource use. The study involved a retrospective analysis of data from 47 patients in four centres throughout the UK. Entry criteria included:

- Diagnosed with metastatic STS

- Aged 18 years or older
- A minimum of three months survival following diagnosis
- Complete follow-up records from date of diagnosis to death

These study estimated costs in 2006 prices from the NHS perspective and have been inflated to 2008 prices using the Price inflation indices published in the PSSRU (54). Those costs that were not chemotherapy related was used in the economic model to proxy the ongoing costs associated with EST. These are reported in Table 36.

Table 36 Ongoing costs associated with progressed disease

Cost category	Total cost	Average cost per patient
Diagnostic tests	£17,273.06	£367.51
Inpatient stay (administration, adverse events, terminal care)	£79,686.53	£1695.46
Total		£2,062.97

Data on file which was collected for the Judson et al, 2007 (55) study reported that the mean survival from diagnosis of metastatic disease until death was 1 year. Accounting for this data, the total average cost per one month cycle was £171.91. This cost is incorporated into the economic model to approximate the ongoing costs associated of disease management. It is, therefore, applied in each cycle of the economic model to all patients who have exhausted an anthracycline, ifosfamide and trabectedin.

7.2.9.2 *How were the resources measured?*

Resources were measured using data from the STS-201 clinical trial, consultation with clinical experts and a cost of illness study by Judson (2007) (55).

7.2.9.3 *Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?*

Only the dose intensity and number of cycles of treatment were estimated from the STS-201 trials.

7.2.9.4 *Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).*

Once patients treated with trabectedin have progressed the model assumes that they receive best supportive care. As such they incur the costs of progressed disease, but no additional treatment costs.

7.2.9.5 *What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.*

The cost of chemotherapy administration and hospitalisation due to nausea were sourced from the 2006/7 NHS Reference cost list (53). The cost of care in progressed patients was estimated from a published cost of illness study. Our literature review identified no other economic studies of soft tissue sarcoma.

7.2.9.6 *What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.*

Table 37 Unit cost of drugs

	Dose	*Unit cost*	*Source*
Trabectedin	*1mg*	*£1,366*	*BNF56 (52)*
Trabectedin	*0.25mg*	*£363*	*BNF56 (52)*
Etoposide	*5mL*	*£12.15*	*BNF56 (52)*
Etoposide	*10mL*	*£29.00*	*BNF56 (52)*
Dacarbazine	*100mg*	*£5.05*	*BNF56 (52)*
Dacarbazine	*1g*	*£31.80*	*BNF56 (52)*

7.2.9.7 *Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.*

None anticipated

7.2.9.8 *Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?*

Resource utilisation and costs were aligned with the model structure. They reflect the resource use of the patient population in this economic model.

7.2.9.9 *Were resource values indexed to the current price year?*

All prices were inflated to the most recently published inflation indices from the PSSRU (54).

7.2.9.10 *Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.*

No additional assumptions about resource use have been made.

7.2.10 Time preferences

Costs, life years and QALYs were discounted at 3.5%, as per the NICE reference case.

7.2.11 Sensitivity analysis

7.2.11.1 *Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.*

Uncertainty around the structural assumptions of the model has been accounted for with a number of scenarios. These are detailed below in Table 38.

Table 38 Details of structural sensitivity analysis

Description of analysis	Source
The comparator arm to include 33% of patients receiving chemotherapy on entry into the model. Patients on chemotherapy enter the model in progression free survival.	TTP and OS from the EORTC trials
The comparator arm to include 100% of patients receiving chemotherapy on entry into the model. Patients on chemotherapy enter the model in progression free survival.	TTP and OS from the EORTC trials
The trabectedin arm to be based on data from three Phase II non-comparative studies with a broader STS patient group	ET-B-005-98; ET-B-008-98; ET-B-017-98
No discount rate	
Differential discount rate for costs and outcomes (outcomes 1.5%; costs 6%)	

7.2.11.2 *Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?*

Univariate sensitivity analysis was conducted to test the sensitivity of the analysis to the individual variables. The details of the univariate sensitivity analysis are detailed in Table 39.

Table 39 Details of sensitivity analysis

	Description of analysis	Base case value	Sensitivity analysis value
1	Overall survival on trabectedin equal to the EORTC data	OS Lambda = 0.04; Gamma = 1.05	OS Lambda = 0.04 Gamma = 1.28
2	Trabectedin's indicated dose for the treatment of metatstatic STS	1.22mg/m^2	1.5mg/m^2
3	Number of trabectedin treatment cycles set to the median	6.99	5
4	Number of trabectedin treatment cycles estimated with a 17 cycle limit	6.99	6.4
5	Number of trabectedin treatment cycles set to the lower confidence limit	6.99	5.79
6	Number of trabectedin treatment cycles set to the upper confidence limit	6.99	8.19
7	Trabectedin administration assumed to occur on an outpatient basis (HRG SB12Z)	£319.61	£181.29
8	Chemotherapy administration cost to lower quartile	£319	£192
9	Chemotherapy administration cost to upper quartile	£319	£552
10	AE hospitalisation cost decreased to lower quartile	£624.23	£419
11	AE hospitalisation cost increased to upper quartile	£624.23	£847

12	Utility data set to 2.5th CI	PFS = 0.653; PFS-nausea = 0.605; P = 0.407	PFS = 0.61; PFS-nausea = 0.53; P = 0.39
13	Utility data set to 97.5th CI	PFS = 0.653 PFS-nausea = 0.605; P = 0.407	PFS = 0.70; PFS-nausea = 0.68; P = 0.56
14	Trabectedin time to progression at 2.5th CI (loglambda)	-1.9074	-1.5443
15	Trabectedin time to progression at 97.5th CI (loglambda)	-1.9074	-2.2705
16	Trabectedin overall survival at 2.5th CI (loglambda)	-3.1998	-2.65691
17	Trabectedin overall survival at 97.5th CI (loglambda)	-3.1998	-3.742727
18	BSC survival after progression at 2.5th CI (loglambda)	-2.0346	-1.6764
19	BSC survival after progression at 97.5th CI (loglambda)	-2.0346	-2.392793

7.2.11.3 *Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.*

Probabilistic sensitivity analysis was undertaken. A list the variables included, their distributions and sources are shown in Table 40. Drug prices and unit costs from NHS reference costs were not included in the PSA. Although there is regional variability in the NHS reference costs they are not uncertain variables. Transition probabilities in the model were varied using a bivariate normal distribution estimated using the variance-covariance matrices generated in the Weibull estimates. This suitably accounts for correlation between these parameters.

Table 40 Details of the variables included in the probabilistic sensitivity analysis

Variable – transition probabilities	**Variance-covariance matrix**		**Distribution**	**Source**
Trabectedin - TTP	0.034		BIVARIATE NORMAL	STS-201
	-0.012	0.006		
Trabectedin - OS	0.077		BIVARIATE NORMAL	STS-201
	-0.020	0.006		
EORTC – OS-TTP	0.033		BIVARIATE NORMAL	EORTC
	-0.011	0.005		
Variable – Costs	**Standard deviation**		**Distribution**	**Source**
Number of cycles of treatment	0.61		NORMAL	STS-201
Dose intensity	0.07		NORMAL	STS-201
AE hospitalisation rate	0.200		BETA	STS-201
Progressed inpatient stay costs	±25%		GAMMA	Assumption
Progressed diagnostic cost	±25%		GAMMA	Assumption
Variable – Utility	**Standard error**		**Distribution**	**Source**
Stable (Progression free)	0.022		NORMAL	Nafees et al. (2008) (51)
Progression free – nausea	0.016		NORMAL	Nafees et al. (2008) (51)
Progressed	0.022		NORMAL	Nafees et al. (2008) (51)

7.2.12 Statistical analysis

7.2.12.1 *How were rates or probabilities based on intervals transformed into (transition) probabilities?*

Not applicable

7.2.12.2 *Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.*

Evidence from the EORTC and STS-201 data suggests that risk of progression and mortality vary over time. This has been accounted for in the model by estimating Weibull distributions to generate time dependent transition probabilities.

7.2.13 Validity

Third party validation of the model was conducted at the Quality Control stage. An experienced programmer was asked to check the following aspects of the model:

- Accuracy of input data. This was checked by comparing the model inputs in Excel against the data sources referenced
- Top down tests. This involves systematic variation of the model input parameters to establish whether changes in inputs result in predictable changes in the model outputs. These tests are designed to identify failures in model logic or material computation errors.
- Computation checks of key sensitivities. The following aspects of the spreadsheet were identified as key areas for detailed checking of formulae: translation of drug prices into state costs; derivation of transition rates from clinical inputs; derivation of state distributions from transition rates. Formulae performing these transformations were checked.
- Report. The accuracy of the reporting of data inputs and outputs in the model was checked by reviewing the report against the model.

The validation identified no major issues with the computational accuracy of the model. A number of small inaccuracies were identified and rectified.

The model structure was validated with expert clinical advisors and reflects that used in many published economic evaluations in advanced and metastatic oncology.

Charts validating the close relationship between modelled and measured overall survival and time to progression are shown in 7.2.6.1.

7.3 Results

7.3.1 Base-case analysis

7.3.1.1 *What were the results of the base-case analysis?*

The following results are taken from the deterministic element of the economic model. In this analysis trabectedin is compared with BSC, assumed equal to patients failing treatment in the EORTC database.

Table 41 Results of the base case analysis

	Trabectedin	Best Supportive Care	Difference
Total costs	£26,140	£1,311	£24,829
Total life years	1.61	0.64	0.97
Total QALYs	0.86	0.30	0.56
Cost per life year			**£25,539**
Cost per QALY			**£44,567**

7.3.2 Subgroup analysis

7.3.2.1 *What were the results of the subgroup analysis/analyses if conducted?*

No sub-group analysis was conducted on the data from the STS-201 trial. However, an alternative analysis was conducted as part of the sensitivity analysis to investigate the cost-effectiveness of trabectedin in a broader population of soft-tissue sarcoma patients.

7.3.3 Sensitivity analyses

7.3.3.1 *What were the main findings of the sensitivity analyses?*

Sensitivity analysis - Comparator

The secondary analysis to include 33% patients receiving chemotherapy, which utilised time to progression data from the EORTC trials are detailed below.

Table 42 Results of the analysis comparing trabectedin against 33% active comparator / 67% BSC in L-sarcoma patients

	Trabectedin	Best Supportive Care	Difference
Total costs	£26,140	£1,570	£24,569
Total life years	1.61	0.72	0.89
Total QALYs	0.86	0.36	0.50
Cost per life year			**£27,592**
Cost per QALY			**£48,953**

Including a proportion of patients with a response to chemotherapy does not substantially increase the ICER results.

Additional analysis was conducted to compare trabectedin with chemotherapy only. The results are detailed below:

Table 43 Results of the analysis comparing trabectedin against 100% active comparator in L-sarcoma patients

	Trabectedin	Comparator	Difference
Total costs	£26,140	£2,098	£24,042
Total life years	1.61	0.88	0.72
Total QALYs	0.86	0.47	0.39
Cost per life year			**£33,183**
Cost per QALY			**£61,681**

The results suggest that comparing trabectedin with a more efficacious comparator increases the ICER results.

Sensitivity Analysis – Trabectedin patient population

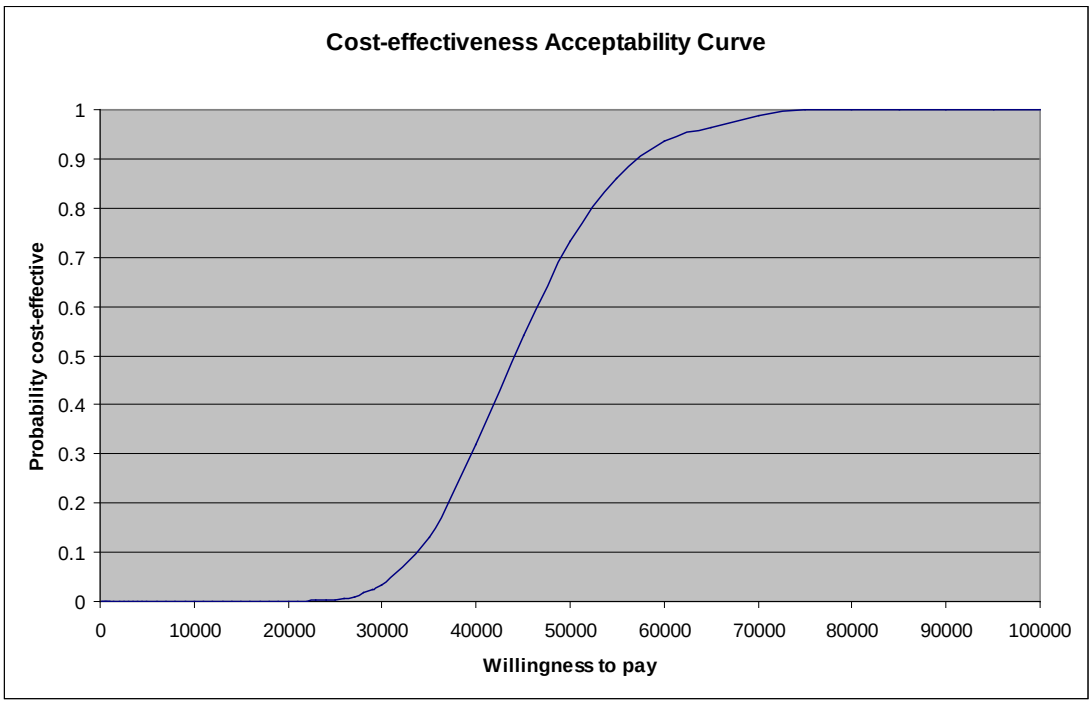
Additional analysis was conducted using pooled data from three Phase II non-comparative studies to describe the effectiveness of trabectedin. These studies included L-sarcoma and non-L-sarcoma patients.

Table 44 Results of the pooled trabectedin analysis: L-sarcoma and non-L-sarcoma patients

	Trabectedin	Best Supportive Care	Difference
Total costs	£25,916	£1,311	£24,605
Total life years	1.33	0.64	0.69
Total QALYs	0.70	0.30	0.40
Cost per life year			**£35,441**
Cost per QALY			**£62,275**

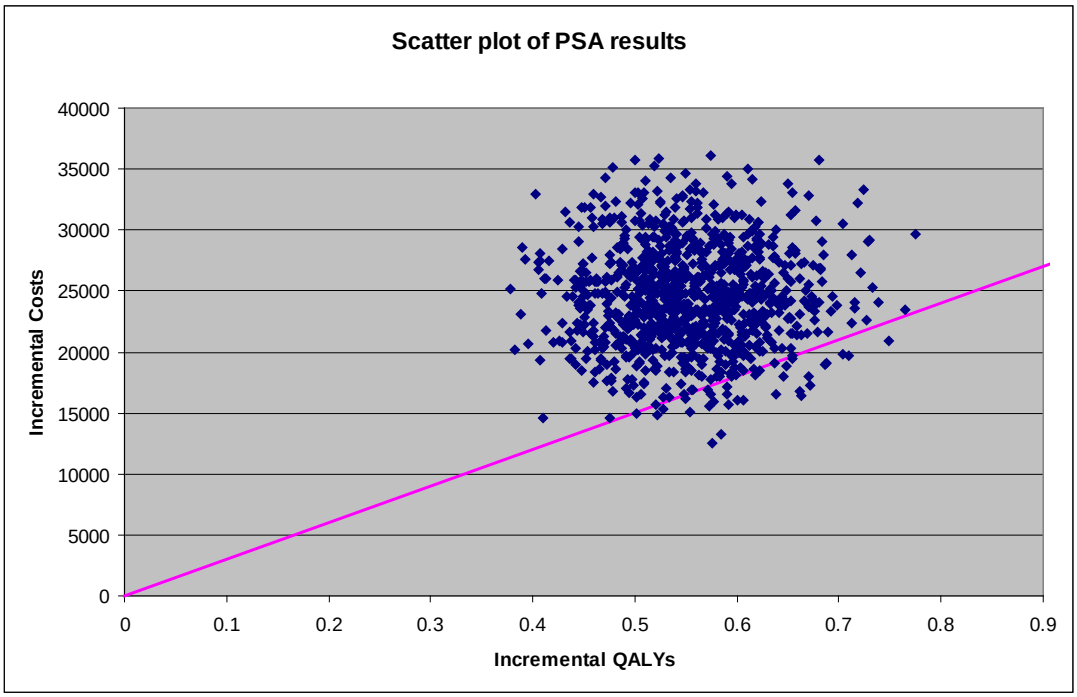
Probabilistic Sensitivity Analysis

Figure 14 Cost-effectiveness acceptability curve: base case comparison



The CEAC above shows that at a willingness to pay threshold above £40,000 per QALY trabectedin has a 32% probability of being cost-effective. Although trabectedin has a low probability of being cost-effective at the £30,000 threshold there is relatively low uncertainty in the results of the PSA. There is very little variation in the results of the sensitivity analysis as illustrated in the scatter-plot in Figure 15. The pink line represents the £30,000 cost-effectiveness threshold.

Figure 15 Scatter plot of PSA results



The scatter plot illustrates that all ICERs generated in the PSA fall within the North-East quadrant of the cost-effectiveness plane. The results of the net benefit analysis are detailed in

Table 45.

Table 45 Net benefit analysis

	Willingness to pay = £20,000		***Willingness to pay = £30,000***		***Willingness to pay = £40,000***	
	Expected net benefit	***Probability CE***	***Expected net benefit***	***Probability CE***	***Expected net benefit***	***Probability CE***
Trabectedin	*-£8,760.56*	*0.000*	*-£240*	*0.032*	*£8,280*	*0.318*
Best Supportive Care	*£4,680.88*	*1.000*	*£7,675*	*0.968*	*£10,669*	*0.682*

Discount rate sensitivity analysis

Table 46 Results of the discount rate sensitivity analysis

	Inc. costs	Inc. QALYs	ICER
Discount rate is zero	£24,923	0.581	£42,906
Discount rate is 6%	£24,769	0.542	£45,720
Discount rate is 6% for costs and 1.5% for outcomes	£24,769	0.570	£43,428

Univariate sensitivity analysis

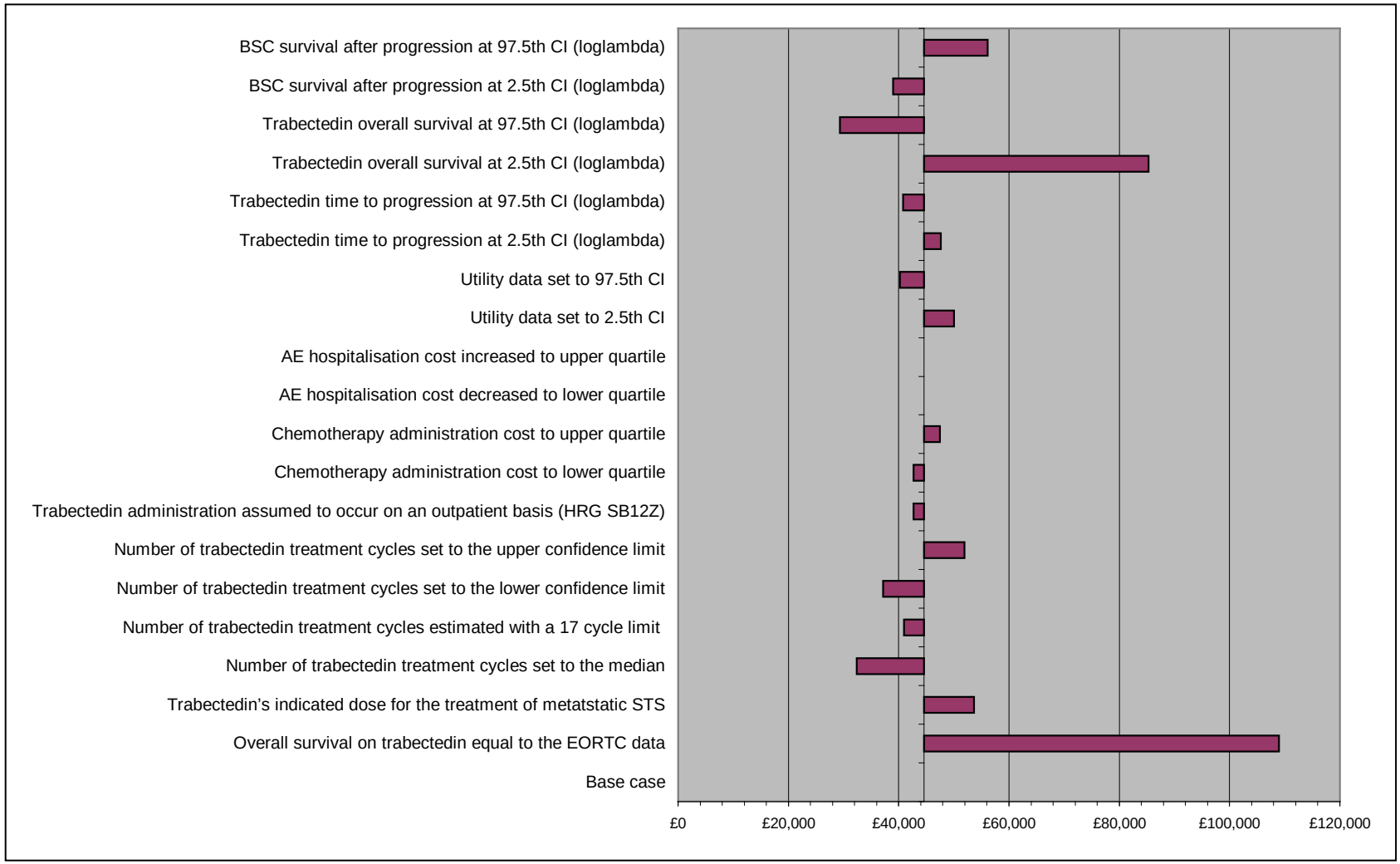
The results of the univariate sensitivity analysis described in section 7.2.11.2 are detailed below.

Table 47 Results of the univariate sensitivity analysis

	Inc. costs	Inc. QALYs	ICER
Overall survival on trabectedin equal to the EORTC data	£23,335	0.214	£108,971
Trabectedin's indicated dose for the treatment of metatstatic STS	£29,904	0.557	£53,676
Number of trabectedin treatment cycles set to the median	£18,024	0.557	£32,352
Number of trabectedin treatment cycles estimated with a 17 cycle limit	£22,812	0.557	£40,945
Number of trabectedin treatment cycles set to the lower confidence limit	£20,726	0.557	£37,201

Number of trabectedin treatment cycles set to the upper confidence limit	£28,933	0.557	£51,932
Trabectedin administration assumed to occur on an outpatient basis (HRG SB12Z)	£23,783	0.557	£42,690
Chemotherapy administration cost to lower quartile	£23,783	0.557	£42,690
Chemotherapy administration cost to upper quartile	£26,454	0.557	£47,483
AE hospitalisation cost decreased to lower quartile	£24,818	0.557	£44,547
AE hospitalisation cost increased to upper quartile	£24,841	0.557	£44,588
Utility data set to 2.5th CI	£24,829	0.496	£50,029
Utility data set to 97.5th CI	£24,829	0.618	£40,180
Trabectedin time to progression at 2.5th CI (loglambda)	£25,159	0.528	£47,618
Trabectedin time to progression at 97.5th CI (loglambda)	£24,364	0.598	£40,767
Trabectedin overall survival at 2.5th CI (loglambda)	£23,607	0.277	£85,338
Trabectedin overall survival at 97.5th CI (loglambda)	£26,311	0.897	£29,328
BSC survival after progression at 2.5th CI (loglambda)	£25,218	0.646	£39,016
BSC survival after progression at 97.5th CI (loglambda)	£24,286	0.433	£56,142

Figure 16 Results of one-way sensitivity analysis: Cost per QALY



7.3.3.2 *What are the key drivers of the cost effectiveness results?*

The key drivers of the cost-effectiveness model are:

- Overall survival on trabectedin
- Overall survival in BSC
- Utility
- Number of cycles of treatment on trabectedin

7.3.4 Interpretation of economic evidence

7.3.4.1 *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

There is insufficient published economic literature in soft-tissue sarcoma to make a comparison.

7.3.4.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology?*

The base case analysis shows that trabectedin is effective in patients with L-sarcoma and that the incremental life years gained was 0.97 in the base case. This is a substantial amount in a population of patients with short life expectancy. Additional analysis of the pooled Phase II studies, which include a wider population of patients, estimates the cost-effectiveness of trabectedin in an additional group of patients who potentially could use the technology. The results of this analysis do not substantially increase the results.

7.3.4.3 *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

Strengths

- Survival data based on relatively complete follow-up for trabectedin
- Well-established model structure for advanced oncology
- Several alternative scenarios for the comparator are presented

Weaknesses

- No direct comparison available for trabectedin vs. best supportive care
- no study data available to estimate health-related quality of life
- Proxy utility estimates from lung cancer used in the model
- Assumed ranges for costs included in the probabilistic sensitivity analysis

7.3.4.4 *What further analyses could be undertaken to enhance the robustness/completeness of the results?*

- A study reporting direct comparison between trabectedin and best supportive care
- Evidence of preference based quality of life in advanced soft tissue sarcoma

8 Assessment of factors relevant to the NHS and other parties

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

The results of the one year budget impact model are detailed below:

Table 48 Results of the one-year budget impact model

	Scenario 1: without trabectedin	Scenario 2: with trabectedin	Difference
No. patients treated with trabectedin	0	78	
No. patients treated with other chemotherapy	1050	972	
Cost per treated STS patient	£3,327	£14,113	£10,856
Total annual cost	£2,532,028	£4,220,042	£1,688,014

Over 5 years the net annual impact of introducing trabectedin for the treatment of advanced and metastatic soft-tissue sarcoma is detailed below.

Table 49 Results of the five year budget impact model

	Year 1	Year 2	Year 3	Year 4	Year 5
No. patient treated with trabectedin	78	137	157	198	199
Net budget impact	£1,688,014	£2,971,749	£3,416,662	£4,296,453	£4,322,232

8.2 What number of patients were assumed to be eligible? How was this figure derived?

The BIM calculates the eligible patient population from the total population via the incidence rates and the proportion of patients with metastases that are specified. The new guidelines of April 2008 establish the incidence of STS (all histologies) to be around 0.4/10,000 (1). In 2007 the population of the UK was 60,975,000. This estimates an annual incidence of 2,439. Trabectedin is assumed to be available at two points in the treatment pathway. Firstly, in patients previously treated with combination therapy (anthracycline and ifosfamide) trabectedin is a treatment option as second line therapy. Secondly, patients treated with a single agent (either anthracycline or ifosfamide) as first line therapy would not be eligible for trabectedin until they had been sequentially treated with both agents (i.e., trabectedin as third line therapy). An important feature of the BIM at this stage is the estimates of the proportion of patients going on to receive each line of therapy. These estimates were derived through consultation with UK specialists. The number of patients receiving second or third line therapy in the first year of the model is estimated to be 1050.

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

Anthracyclines and ifosfamide are the only agents considered active in this area. Patients with advanced STS may also receive second and third line chemotherapy.

8.4 What assumption(s) were made about market share (where relevant)?

In the first year the model assumes that Yondelis captures 20% of the market share for second line chemotherapy in patients who received ifosfamide and anthracycline as first-line and 20% of the market share in third line patients. For the 5-year analysis the market share assumptions are detailed in Table 50.

Table 50 Market share estimates

Year 1	Year 2	Year 3	Year 4	Year 5
20%	35%	40%	50%	50%

8.5 What unit costs were assumed? How were these calculated?

The cost of trabectedin was calculated using the mean dose observed in the STS-201 clinical trial.

Table 51 Dose assumptions for trabectedin

Row	Parameter	Value	Reference
A	Dose intensity (mg/m^2) per administration	1.22	STS-201 (data on file)
B	Average body surface area (m^2)	1.7	Assumption
C	Average dose per administration (mg)	2.07	Row C = row A × row B

The unit costs are detailed in Table 52.

Table 52 Unit costs for trabectedin

Vial size	Unit cost	Source
1 mg	£1,366.00	BNF (52)
0.25 mg	£363.00	BNF (52)

The costs of second and third line chemotherapy were estimated from a published cost of illness study (49) and inflated to 2008 costs. The costs used in the model are detailed in Table 53.

Table 53 Other chemotherapy costs

	Cost per patient	Source
Second-line chemotherapy	£2556.52	Judson et al (2008) (55)

Third-line chemotherapy	£2001.13	Judson et al (2008) (55)

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

No other costs were considered in the budget impact analysis. These costs are not anticipated to differ between the treatment options.

8.7 Were there any estimates of resource savings? If so, what were they?

No estimates of resource savings were made.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No opportunities for resource savings have been excluded.

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10 Appendices

10.1 Appendix 1

Abbreviated Summary of Product Characteristics - (full SPC provided with reference pack).

1. Yondelis® (trabectedin) -Abbreviated Prescribing Information. Please refer to full Summary of Product Characteristics when prescribing. 2. Presentation: Yondelis® is presented as a powder for concentrate for solution for infusion. Vial containing trabectedin 0.25 mg powder for concentrate for solution for infusion. Vial containing trabectedin 1 mg powder for concentrate for solution for infusion. When reconstituted 1 ml of solution contains 0.05 mg of trabectedin. 3. Uses: Advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or where anthracyclines and ifosfamide are not indicated. 4. Dosage and administration: Yondelis® must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to qualified oncologists or other healthcare professionals specialised in the administration of cytotoxic agents. Yondelis® 1.5 mg/m2 body surface area is administered as an intravenous infusion over 24 hours, once per three-week cycle. All patients must receive 20 mg of dexamethasone intravenously 30 minutes prior to Yondelis®. Administration of Yondelis® through a central venous line is strongly recommended. The following criteria must be satisfied prior to each infusion of Yondelis®: absolute neutrophil count >1,500/mm3, platelet count >100,000/mm3, haemoglobin >9 g/dl, bilirubin <ULN, alkaline phosphatase <2.5 x ULN, alanine aminotransferase and aspartate aminotransferase <2.5 x ULN, albumin >25 g/l, creatinine clearance >30 ml/min, creatine phosphokinase <2.5 x ULN. Haematological, hepatic and muscle variables should be monitored regularly during treatment. For detailed treatment protocols and rules for dose adjustment and delaying treatment in the presence of abnormal laboratory test results please consult the SPC. 5. Elderly: No dose adjustment specified. 6. Children: Yondelis® is not indicated for paediatric use. 7. Hepatic impairment: Special caution is advised and dose adjustments may be necessary in patients with impaired hepatic function, since systemic exposure is probably increased and the risk of hepatotoxicity might be increased. Patients with elevated bilirubin must not be treated with Yondelis®. 8. Renal impairment:

No dose adjustment specified in patients with mild or moderate renal impairment. Contraindicated if creatinine clearance <30 ml/min 9. Contraindications: hypersensitivity to trabectedin, concurrent serious or uncontrolled infection, breast-feeding, combination with yellow fever vaccine. 10. Precautions: Caution in presence of hepatic impairment. Patients with clinically relevant liver diseases, such as active chronic hepatitis, must be closely monitored and the dose adjusted if needed. Caution with hepatotoxic drugs and abnormal transaminases, avoid alcohol. Caution in severe renal impairment. Caution in grade 3 or grade 4 neutropenia and thrombocytopenia (active supportive therapy should be started immediately). Anti-emetic prophylaxis with dexamethasone must be administered to all patients. Yondelis® must not be used in patients with CPK >2.5 ULN. Avoid concomitant treatment with drugs associated with rhabdomyolysis. Avoid CYP3A4 inhibitors. Use of central venous access. Combination of trabectedin with phenytoin or live attenuated vaccines is not recommended. Men who are fertile and women of childbearing potential must use effective contraception during and after treatment. 11. Interactions: The following drugs may interact with trabectedin (consult SPC for details): ketoconazole, fluconazole, ritonavir, clarithromycin, rifampicin, phenorbarbital, Saint John's Wort, alcohol, cyclosporine and verapamil. 12. Use in pregnancy and lactation: Trabectedin should not be used during pregnancy unless clearly necessary. Breast-feeding is contraindicated during treatment and 3 months thereafter. 13. Ability to drive: Fatigue and/or asthenia have been reported with trabectedin and may affect ability to drive or operate machines. 14. Side effects: Most patients (90%) experience adverse reactions to trabectedin: 40% of patients will have grade 3 or grade 4 reactions. Fatal adverse reactions have occurred in about 2% of patients. Common and very common adverse reactions are: nausea, vomiting, constipation, diarrhoea, anorexia, stomatitis, abdominal pain, dyspepsia, dehydration, decreased appetite, hypokalaemia leukopenia, neutropenia, thrombocytopenia, anaemia, infection, febrile neutropenia, creatine phosphokinase increased, creatinine increased, albumin decreased, liver function test abnormalities, hyperbilirubinemia, Alanine aminotransferase increased, Aspartate aminotransferase increased, blood alkaline phosphatase increased, Gamma-

glutamyltransferase increased, weight decreased, headache, peripheral sensory neuropathy, dysgeusia, dizziness, paraesthesia, dyspnoea, cough, alopecia, myalgia, arthralgia, back pain, hypotension, flushing, pyrexia, oedema, injection site reaction, fatigue, asthenia, insomnia. 15. Basic NHS price: Yondelis® 0.25 mg £363 /vial, Yondelis® 1 mg £1,366 /vial. 16. Legal category: POM. 17. Product Licence numbers: EU/1/07/417/001, EU/1/07/417/002 18. Product Licence holder: Pharma Mar, S.A. Avda. de los Reyes 1, Polígono Industrial La Mina 28770 Colmenar Viejo (Madrid), Spain. 19. Further information may be obtained from the UK distributor: IDIS Ltd, IDIS House, Churchfield Road, Weybridge, KT13 8DB. 01932 824 100. 20. Date of preparation: November 2007 Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to IDIS Ltd on 01932 824 100.

10.2 Appendix 2: search strategy for section 6

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were used for the identification of evidence for clinical efficacy in soft tissue sarcoma patients:

1. *Service provider: Embase.com (www.embase.com)*

   Databases searched:

   - *Medline*
   - *Embase*

2. *Service provider: Cochrane Library (http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME)*

   Databases searched:

   - *Cochrane Database of Systematic Reviews*
   - *Database of Abstracts of Reviews of Effects*
   - *Cochrane Central Register of Controlled Trials*
   - *Cochrane Methodology Register*
   - *Health Technology Assessment Database*
   - *NHS Economic Evaluation Database*

3. *Request of relevant publications form the manufacturer: the manufacturer was contacted to provide a list of relevant publications relating to the decision problem being addressed.*

10.2.2 The date on which the search was conducted.

Search run on Embase.com: 20/1/2009

Search run on Cochrane Library: 27/1/20

10.2.3 The date span of the search.

Search run on Embase.com: no restrictions

Search run on Cochrane Library: 1800 to 2009

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The results from the search run on Embase.com and the Cochrane Library were downloaded into reference management software (Reference Manager v11) and duplicates removed. The titles and abstracts of the remaining references were then screened. To be included in the assessment of the full paper, the following list of exclusion criteria were used:

The publication should report:

1. *primary research*
2. *the use of trabectedin as an intervention*
3. *the treatment of patients with soft tissue sarcoma*
4. *clinical or efficacy data*

In cases where it was not possible to determine the content of the paper from the title or abstract, the whole paper was obtained and examined.

10.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

Search of registered trials.

To identify all registered trials that had been carried out on trabectedin, a search of the current controlled trials meta-register of controlled trials (http://www.controlled-trials.com/mrct/) was carried out.

The date when the search was run: 19/01/2009

The years covered by the search: no restrictions

Databases searched:

- *ISRCTN Register*
- *Action Medical Research*
- *Leukaemia Research Fund*
- *Medical Research Council (UK)*
- *National Health Service Research and Development Health Technology Assessment Programme (HTA)*
- *National Institutes of Health (NIH) - randomised trial records held on NIH ClinicalTrials.gov website,*
- *The Wellcome Trust*
- *UK Clinical Trials Gateway*

Search strategy used for the current controlled trials meta-register of controlled trials:

#	Term	Hits
1	***Yondelis OR trabectedin***	***4***

10.2.6 The inclusion and exclusion criteria.

The results of this search were assessed according to the following inclusion/exclusion criteria:

- *Trial should be either completed or currently running with interim analysis available*
- *Intervention should be trabectedin*
- *Patients population should be those diagnosed with soft tissue sarcoma*

The reasons for exclusion are as follows:

Study title and link to current-controlled trials Meta-register	***Reason for exclusion***
A Study Comparing the Combination of Doxil and Yondelis, to Doxil Alone for Subjects With Ovarian Cancer	*wrong diagnosis (ovarian cancer)*
A Study of the Safety and Effectiveness of Trabectedin Versus Doxorubicin-Based Chemotherapy in Patients With Translocation-Related Sarcomas (TRS)	*trial not yet recruiting*
A Study of Effectiveness of Trabectedin for the Treatment of Patient With Specific Subtypes of Metastatic Breast Cancer	*wrong diagnosis (breast cancer)*

Included trials:

Study title and link to current-controlled trials Meta-register:
A Study of ET743 in Subjects With Advanced Liposarcoma or Leiomyosarcoma

The single registered study that was identified was study ET743-STS-201 which was the only randomised phase II study carried out on trabectedin.

10.2.7 The data abstraction strategy.

List of abstracts identified from a request to the manufacturer for publications relevant to the decision problem.

J. A. Morgan, A. Le Cesne, S. Chawla, M. von Mehren, S. Schuetze, P. G. Casali, A. Nieto, Y. Elsayed, M. A. Izquierdo, G. D. Demetri, Yondelis Sarcoma Study Group Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 10060
Samuels BL, Rushing D, Chawla SP, Schuetze SM, Von Mehren M, Leohan ML, O'Donovan M, Wei X, Sternas LA and Demetri GD. randomised phase II study of trabectedin (ET-743) given by two different dosing schedules in patients (pts) with leiomyosarcomas (LMS) or liposarcomas (LPS) refractory to conventional doxorubicin and ifosfamide chemotherapy. [Abstract 9000]. Journal of Clinical Oncology 2004; 22(July 15 Supplement):14S.
Demetri GD, Schuetze S, Le Cesne A, Chawla S, Casali PG, Gomez J, Nieto A, Elsayed Y, Izquierdo MA and Blay JY. Impact of independent review on efficacy outcomes in a randomised multicenter trial of trabectedin given by two dosing regimens in patients (pts) with progressing leiomyosarcomas or liposarcomas (L-sarcomas). European Journal of Cancer 2007 Vol 5. No 4. Suppl (ECCO 14): Oral communication 7500, page 402.
Le Cesne A, von Mehren M, Cahwla S, Blay JY, Shcuetze S, Nieto A, Gomez J, Santabarbara P, Izquierdo MA and Demetri GD on behalf of Yondelis Sarcoma Study Group. Assessing the clinical impact of trabectedin in patients with leiomyosarcomas or liposarcomas (L-sarcomas) progressing despite prior conventional chemotherapy: clinical benefit rate, growth modulation index and tumour variation as parameters of treatment efficacy in a randomised international trial of two trabectedin dosing regimens. European Journal of Cancer 2007 Vol 5. No 4. Suppl (ECCO 14): Poster 7511, page 405.
Chawla S, Casali PG, von Mehren A, Le Cesne A, Blay JY, Lebedinsky C, Alfaro V, Elsayed Y, Michiels B and Demetri GD on behalf of the Yondelis Sarcoma Study Group. Clinical tolerability of trabectedin administered by two different schedules (weekly for 3 of 4 weeks vs. q3 weeks) in patients with advanced/metastatic liposarcoma or leiomyosarcoma (L-sarcomas) progressing despite prior treatment with at least anthracycline and ifosfamide. European Journal of Cancer 2007 Vol 5. No 4. Suppl (ECCO 14): Poster 7517, page 407.

10.3 Appendix 3: search strategy for section 7

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- Health Economic Evaluation Database
- NHS Economic Evaluation Database (NHS EED).

The following databases and service provider were searched:

- *Medline (Embase)*
- *Embase (Embase)*
- *Medline In-Process (PubMed)*
- *Health Economic Evaluation Database (Wiley Interscience)*
- *NHS Economic Evaluation Database (NHS EED) (Cochrane Library)*

10.3.2 The date on which the search was conducted.

Medline/Embase – 01/02/2009

Medline In-Process/HEED/NHS EED – 18/02/2009

10.3.3 The date span of the search.

Medline/Embase/HEED/NHS EED – 1890-2009

Medline In-Process – last 30 days

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

<u>Medline and Embase</u>

#	Term	Hits	Comments
1	Yondelis/exp OR Yondelis:ti,ab,de	358	
2	trabectedin/exp OR trabectedin:ti,ab,de	360	
3	ecteinascidin 743'/exp OR 'ecteinascidin 743':ti,ab,de	556	
4	et 743'/exp OR 'et 743':ti,ab,de	439	
5	et743:ti,ab,de	187	
6	OR: #1-5	582	
7	soft tissue sarcoma'/exp OR 'soft tissue sarcoma':ti,ab,de	7,603	
8	sts OR sts:ti,ab,de	6,161	
9	soft part sarcoma'/exp OR 'soft part sarcoma':ti,ab,de	6,663	
10	OR:#7-#9	13,566	
11	#10 OR #6	14,010	
12	pharmacoeconomics/exp OR pharmacoeconomic*:ti,ab,de	122,227	
13	#11 and #12	55	
14	health economics'/exp OR 'health economics':ti,ab,de	431,671	
15	"economic aspect"/exp OR "economic aspect":ti,ab,de	789,368	
16	"economic evaluation"/exp OR "economic evaluation":ti,ab,de	142,999	
17	"cost utility analysis"/exp OR "cost utility":ti,ab,de	3,255	
18	economic*:ti,ab,de and (evaluat* or analy*):ti,ab,de	103,870	
19	resource*:ti,ab,de and utili*:ti,ab,de	18,150	
20	cost*:ti,ab,de and (effect* or utili* or benefit*):ti,ab,de	225,548	
21	cost*:ti,ab,de and (minim* or stud* or effic*):ti,ab,de	205,897	
22	economic*:ti,ab,de and model*:ti,ab,de	30,637	
23	OR: #14- #22	915,273	
24	#23 AND #11	324	
25	#13 OR #24	325	saved as economic search 3
	# 26 #13 OR #24 AND [english]/lim	**312**	saved as economic search 3 limit

NHS EED

#	Term	Hits	Comments
1	(soft tissue sarcoma) or (sts) or (soft part sarcoma) in Economic Evaluations	10	saved as NHS EED 1

HEED

#	Term	Hits	Comments
1	(soft tissue sarcoma) or (sts) or (soft part sarcoma) in Economic Evaluations	13	saved as HEED

MEDLINE (in process)

#	Term	Hits	Comments
1	"soft"[All Fields] AND "tissue"[All Fields] AND "sarcoma"[All Fields]	9019	
2	"soft tissue sarcoma"[All Fields]	3264	

3	*soft[All Fields] AND part[All Fields] AND ("sarcoma"[MeSH Terms] OR "sarcoma"[All Fields])*	*916*	
4	*OR:1-3*	*9403*	
5	*#4 Limits: added to PubMed in the last 30 days*	*33*	***saved as economic in process***

10.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

A search of the manufacturer's database was also carried out to identify all publications from relevant studies.

10.4 Appendix 4 – additional analysis to assess the impact of crossover

The Statistical Analysis Plan (SAP) prospectively stated that patients who crossed over to the alternate treatment arm before progression would be censored at the time of crossover for the final time to progression (TTP) analysis. The rationale behind was that the alternate trabectedin schedule was considered as a next-line chemotherapy. The status of progression was obtained from the Independent Review. Thus, the TTP results presented in the Interim and Final TTP analyses were based on this approach, which was felt to be the most conservative.

1. Time to Progression (TTP)

To provide further clarification on cross-over of Day 180 LOI on Clinical Aspects, two additional sensitivity analyses following the other two options considered: TTP with event assigned at crossover and TTP followed until progression or censoring in the alternate arm for patients with crossover. Three different TTP analyses, including the primary final TTP analysis as per SAP and these two additional sensitivity analyses performed, are summarised in Table 54.

Table 54. Time to progression (TTP): results of primary TTP analysis (already shown in the Updated Clinical Study Report) and two additional sensitivity analyses according to Question 3 of Day 180 LOI on Clinical Aspects.

		Trabectedin qwk 3-h (n=134)	**Trabectedin q3wk 24-h** (n=136)	**Total** (n=270)	**Parameter**	**p-value**
TTP-Primary analysis (Censored at crossover before progression)	**Events** **Median (95% CI)**	102 (76.1%) 2.3 (2.0-3.5)	104 (76.5%) 3.7 (2.1-5.4)	206 (76.3%) 2.7 (2.1-3.6)	Log-rank: 4.698 HR: 0.734 95%CI (0.554-0.974)	LR:0.0302 HR: 0.0320
TTP-Sensitivity analysis (Events assigned at crossover)	**Events** **Median (95% CI)**	115 (85.8%) 2.1 (1.9-3.4)	105 (77.2%) 3.7 (2.1-5.4)	220 (81.5%) 2.6 (2.1-3.6)	Log-rank: 10.25 HR: 0.643 95% CI (0.489-0.846)	LR:0.0014 HR:0.0016
TTP-Sensitivity analysis (Patients with crossover followed until progression or censoring in the alternate arm)	**Events** **Median (95% CI)**	111 (82.8%) 2.3 (2.0-3.4)	105 (77.2%) 3.7 (2.1-5.4)	216 (80.0%) 2.6 (2.1-3.6)	Log-rank: 6.178 HR: 0.710 95%CI (0.540-0.933)	LR:0.0129 HR :0.0140

Median in months. All analyses conducted in "All randomised" populations (analysed in the arm where they had been randomised).
HR: q3wk 24-h compared to qwk 3-h group. HR and p-value as determined by Cox regression.
CI, confidence interval; HR, hazard ratio; LR, unstratified log-rank; TTP, time to progression.

1.1. Sensitivity Analysis Counting as TTP Event at the Time of Crossover to the Alternate Arm

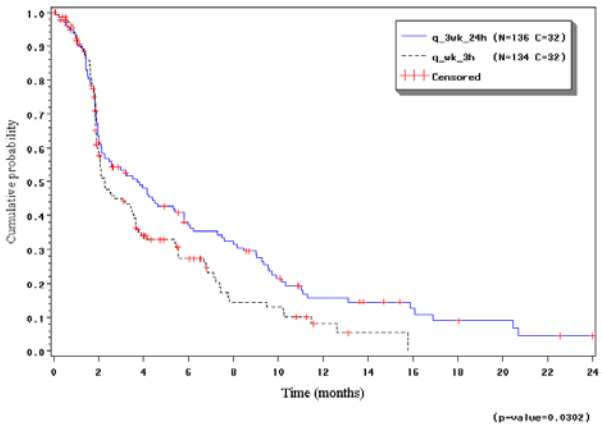
Fourteen additional events were achieved in this sensitivity analysis when time of crossover was counted as TTP event. The hazard ratio showed a 35.7% reduction in the relative risk of progression for patients treated in the q3wk 24-h group (HR=0.643; p=0.0016).

1.2. Sensitivity Analysis Following until Progression or Censoring on Alternate Arm and Analysed in the arm where they had been randomised (according to the Principles of ITT).

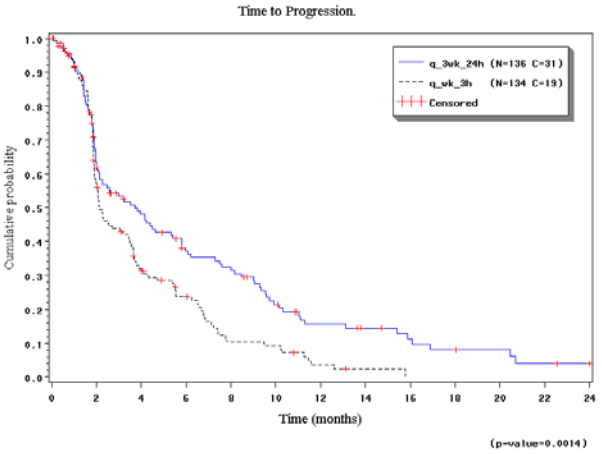
Ten additional events are achieved in this sensitivity analysis when censoring at crossover was not done and patients were analysed in the arm where they had been randomised. The hazard ratio showed a 29.0% reduction in the relative risk of progression for patients treated in the q3wk 24-h group (HR=0.710; p=0.0140).
Kaplan-Meier plots for all three TTP analysis, primary (per SAP) analysis and the two sensitivity analysis, are shown in Figure 7.

Figure 17. Kaplan-Meier plot of TTP – all randomised patients. Log-rank p-values are shown in the footnote of each figure.

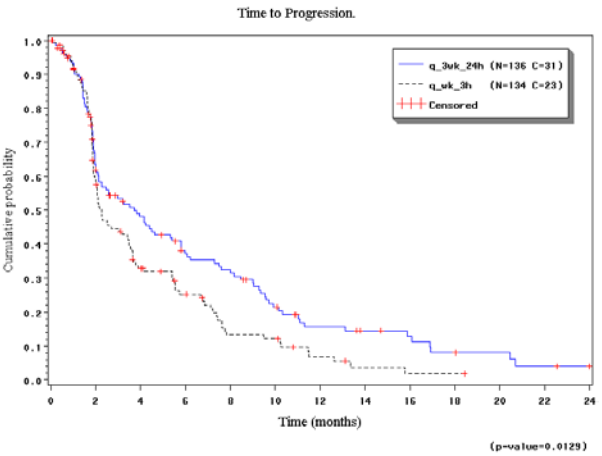
A: Primary TTP analysis as per SAP (presented in the Updated Clinical Study Report and in the Responses to the Consolidated Day 120 LoQ on Clinical Aspects).



B: First sensitivity analysis (events assigned at crossover).



C: Second sensitivity analysis (patients with crossover followed until progression or censoring in the alternate arm).



2. Progression-free Survival (PFS)

The same approach has been followed for calculation of progression-free survival (PFS). The results obtained are summarised in Table 33.

Table 55. Progression-free survival (PFS): results of final PFS analysis (as shown in the Updated Clinical Study Report) and two additional sensitivity analyses according to Question 3 of Day 180 LOI on Clinical Aspects.

		Trabectedin qwk 3-h (n=134)	**Trabectedin q3wk 24-h** (n=136)	**Total** (n=270)	**Parameter**	**p-value**
PFS-Primary analysis (Censored at crossover before progression)	**Events**	107 (79.9%)	111 (81.6%)	218 (80.7%)	Log-rank: 4.144 HR: 0.755 95%CI (0.574-0.992)	LR:0.0418 HR:0.0438
	Median (95% CI)	2.3 (2.0-3.4)	3.3 (2.1-4.6)	2.6 (2.1-3.6)		
PFS-Sensitivity analysis (Events assigned at crossover)	**Events**	117 (87.3%)	112 (82.4%)	229 (84.8%)	Log-rank: 5.887 HR: 0.723 95%CI (0.555-0.942)	LR:0.0153 HR:0.0163
	Median (95% CI)	2.2 (2.0-3.4)	3.3 (2.1-4.6)	2.5 (2.1-3.5)		
PFS-Sensitivity analysis (Patients with crossover followed until progression or censoring in the alternate arm)	**Events**	116 (86.6%)	112 (82.4%)	228 (84.4%)	Log-rank: 5.288 HR: 0.735 95%CI (0.564-0.958)	LR:0.0215 HR:0.0228
	Median (95% CI)	2.2 (2.0-3.4)	3.3 (2.1-4.6)	2.5 (2.1-3.5)		

Median in months. All analyses conducted in "All randomised" populations (analysed in the arm where they had been randomised).
HR: q3wk 24-h compared to qwk 3-h group. HR and p-value as determined by Cox regression.
CI, confidence interval; HR, hazard ratio; LR, unstratified log-rank; PFS, progression-free survival.

3. Conclusion

- Significantly better TTP and PFS have been obtained with the q3wk 24-h schedule, with decreases in the risk of progression of 35.7% and 29.0% in both additional sensitivity analyses. These data confirm that the primary TTP analysis per SAP, censoring patient at crossover, was the most conservative approach.
- The finding of lower p-values in the sensitivity analyses may be related to the higher number of TTP events.
- Overall, these results further support the robustness of the TTP results shown in the Updated Clinical Study Report and provide additional reassurance that the meaningful clinical benefit obtained with the q3wk 24-h trabectedin schedule is not spurious, but reflects a true trabectedin treatment effect.

4. Survival analysis

An updated survival analysis (including a specific, additional analysis censoring patients at the time of crossover) has been done with data from the randomised pivotal study ET743-STS-201. In addition, sensitivity analyses have been repeated with the updated survival data to better ascertain the impact of the crossover. Finally, the updated survival data, in particular that obtained with the (least efficacious) qwk 3-h schedule, is presented into the appropriate historical context.

The overall survival is a secondary endpoint in study ET743-STS-201. Therefore, the success of the trial should be primarily evaluated based on the results of the primary endpoint, TTP per independent review. The potential for this trial to detect significant differences in overall survival between the two trabectedin treatment arms was seriously hampered by the crossover. As over one third of patients crossed over to the alternate arm, it appears unrealistic to expect that the differences in TTP will translate into similar statistical differences in survival. Nonetheless, the Applicant acknowledges the importance of survival as a robust secondary endpoint in support of the final TTP analyses recently provided in the Updated Clinical Study Report.

At the cut-off date (25 May 2007), a total of 206 deaths had been reported in all randomised patients (last death recorded on 19 April 2007): 106 deaths in the qwk 3-h arm and 100 deaths in the q3wk 24-h arm. The median follow-up was 30.0 months (95% CI, 25.0-36.6 months) in the q3wk 24-h arm and 27.9 months (95% CI, 23.6-37.3 months) in the qwk 3-h arm (p=0.7838).

4.1. Updated Overall Survival: Intent-to-Treat Analyses (without Censoring Patients at the Time of Crossover)

Table 56 shows the updated results of overall survival (OS) for both treatment arms, qwk 3-h and q3wk 24-h, from the pivotal randomised study ET743-STS-201.

All randomised. In all 270 randomised patients, the hazard ratio showed a 16.2% reduction in the relative risk of death for patients treated in the q3wk 24-h group (HR=0.838; p=0.2052) and 2.1 months improvement in median survival (11.8 and 13.9 in the qwk 3-h and q3wk 24-h schedules, respectively). As anticipated, this result is very similar to that previously described in the Updated Clinical Study Report (HR=0.823; p=0.1985).

All treated. From the 270 randomised patients, 10 patients were never treated with trabectedin: 4 in the qwk 3-h arm and 6 in the q3wk 24-h arm. As was also done in the Updated Clinical Study Report, OS was calculated for trabectedin-treated patients. The hazard ratio showed an 18.9% reduction in the relative risk of death for patients treated in the q3wk 24-h group (HR=0.811; p=0.1413) and 2.1 months improvement in median survival (11.9 and 14.0 in the qwk 3-h and q3wk 24-h schedules, respectively).

Confirmed L-sarcoma. A total of 213 patients had confirmed diagnosis of L-sarcoma (liposarcoma or leiomyosarcoma) by central pathology review: 111 and 102 patients in the qwk 3-h and q3wk 24-h schedules, respectively. The hazard ratio showed a 20.6% reduction in the relative risk of death for patients treated in the q3wk 24-h group (HR=0.794; p=0.1452) and 4.8 months improvement in median survival (12.6 and 17.4 in the qwk 3-h and q3wk 24-h schedules, respectively).

Table 56. Updated overall survival (OS) (without censoring) in pivotal randomised study ET743-STS-201 (cut-off, 25 May 2007).

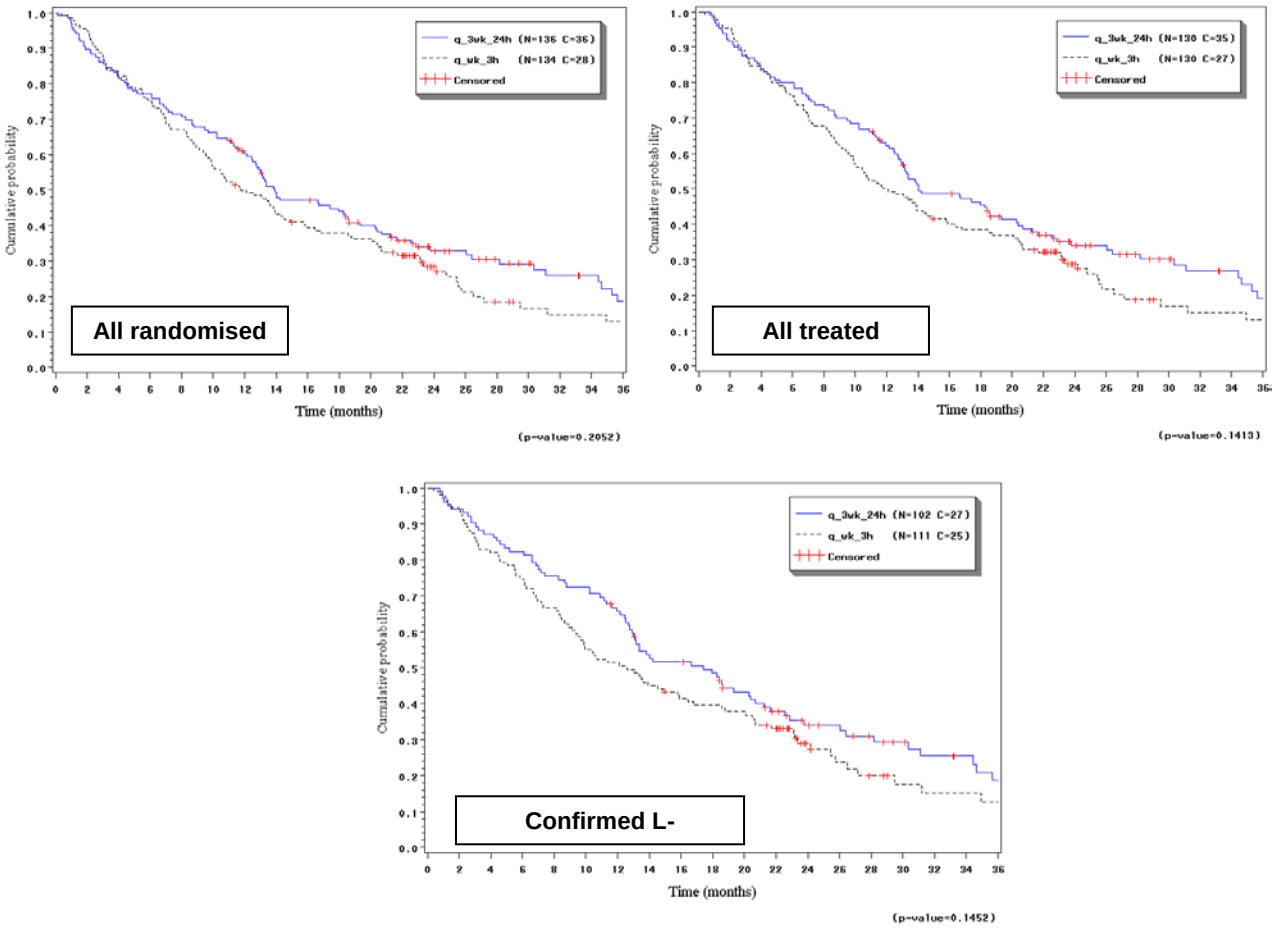
		Trabectedin qwk 3-h	Trabectedin q3wk 24-h	Total	Parameter	p-value
OS (All randomised patients)	*n*	134	136	270		
	Events	106 (79.1%)	100 (73.5%)	206 (76.3%)	Log-rank: 1.605 HR: 0.838 95%CI (0.637-1.102)	LR:0.2052 HR: 0.2051
	Median (95% CI)	11.8 (9.9-14.9)	13.9 (12.5-18.6)	13.3 (11.6-15.8)		
OS (All treated patients)	**n**	130	130	260		
	Events	103 (79.2%)	95 (73.1%)	198 (76.2%)	Log-rank: 2.164 HR: 0.811 95%CI (0.613-1.073)	LR:0.1413 HR: 0.1423
	Median (95% CI)	11.9 (9.9-15.8)	14.0 (12.7-19.3)	13.4 (12.1-16.6)		
OS (All randomised patients, confirmed L-sarcoma)	**n**	111	102	213		
	Events	86 (77.5%)	75 (73.5%)	161 (75.6%)	Log-rank: 2.122 HR: 0.794 95%CI (0.582-1.084)	LR:0.1452 HR: 0.1461
	Median (95% CI)	12.6 (9.5-16.5)	17.4 (13.0-20.7)	13.8 (12.5-18.4)		

Median in months. Median follow-up: 30 months [95% CI: (25.0-36.6)] in the q3wk 24-h group and 27.9 months [95% CI: (23.6-37.3)] in the qwk 3-h group. HR: q3wk 24-h compared to qwk 3-h group. HR and p-value as determined by Cox regression.

CI, confidence interval; HR, hazard ratio; L-sarcoma, liposarcoma or leiomyosarcoma; LR, unstratified log-rank; OS, overall survival.

Kaplan-Meier plots for these three survival analyses without censoring are shown in Figure 18.

Figure 18. Kaplan-Meier plots of overall survival (OS) without censoring for all randomised patients, all treated patients and patients with confirmed L-sarcoma.



4.2 Updated Overall Survival: Sensitivity Analyses to Assess the Impact of the Crossover

Forty-three patients (32.1%) crossed over from the qwk 3-h to the q3wk 24-h arm, most of them (29 patients) after progression of the disease. Only six patients (4.4%) crossed over from the q3wk 24-h to the qwk 3-h arm, all of them after disease progression. Thus, it appears plausible that the substantial crossover from the qwk 3-h to the q3wk 24-h treatment arm may have contributed to obscure the differences in overall survival between the two treatment arms.

At cut-off date for this updated analysis, 64 of the 270 patients (23.7%) were still alive: 28 patients in the original qwk 3-h arm and 36 patients in the original q3wk 24-h arm. Of interest, of the 28 patients still alive in the qwk 3-h arm, 19 patients (67.9%) had crossed over to the q3wk 24-h arm. Thus, nine patients (32.1%) remain alive in the qwk 3-h and have not crossed over.

4.2.1. Updated Overall Survival Censoring Patients at the Time of Crossover

In order to address the potential impact of crossover in the updated survival data, additional OS analyses have been done by censoring patients at the time of crossover to the alternative trabectedin regime.

All randomised. This sensitivity analysis showed a 24.6% reduction in the relative risk of death with trabectedin q3wk 24-h (HR=0.754; p=0.0611). The reduction in the risk of death was higher compared to the non-censored analysis, despite having a lower number of death events (179 instead of 206). In addition, there was a 3.1 months improvement in median survival with the q3wk 24-h schedule.

All treated. The hazard ratio showed a 27.6% reduction in the relative risk of death for patients treated in the q3wk 24-h group (HR=0.724; p=0.0359) and 3.2 months improvement in median survival.

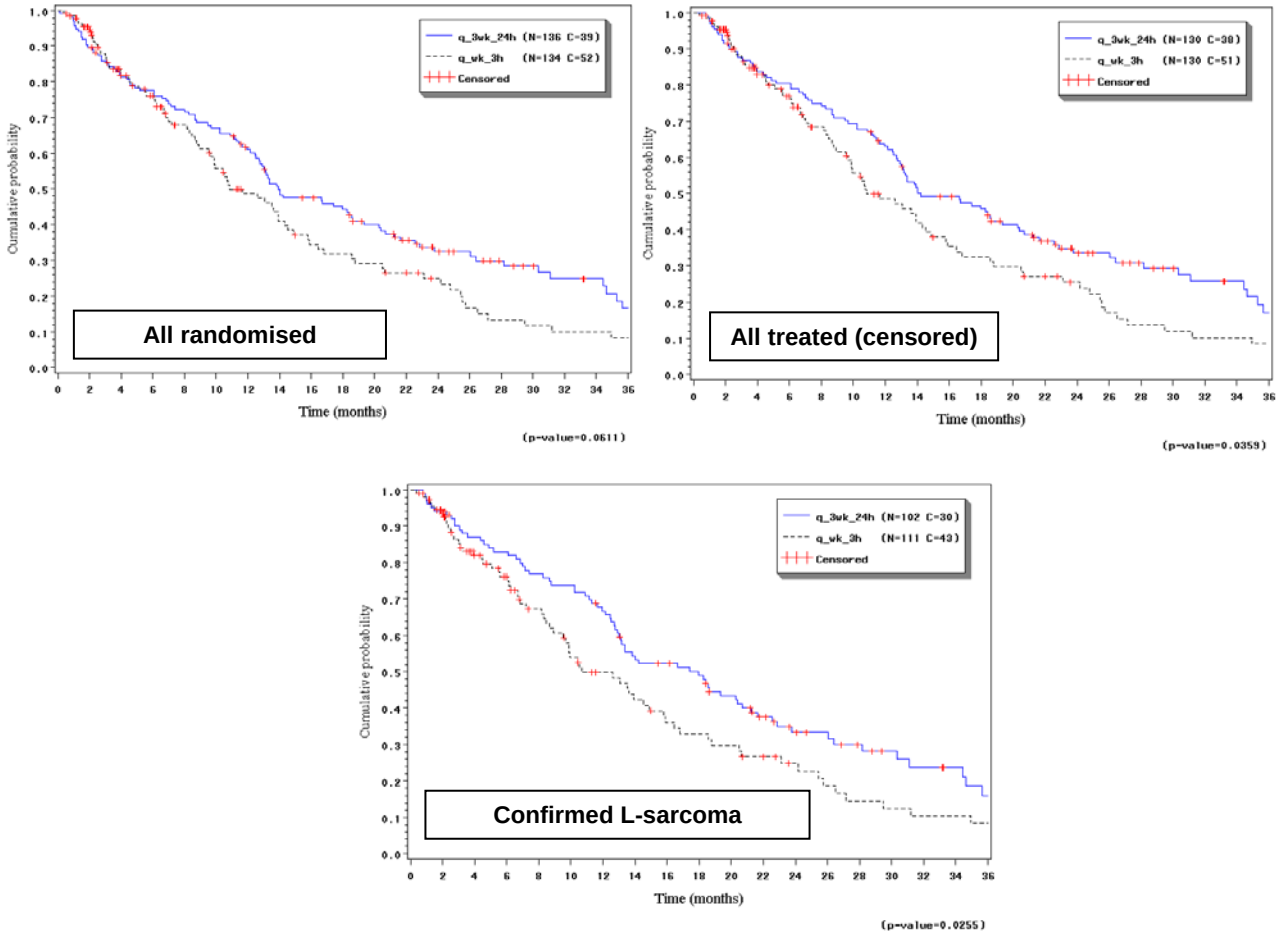
Confirmed L-sarcoma. The hazard ratio showed a 31.5% reduction in the relative risk of death for patients treated in the q3wk 24-h group (HR=0.685; p=0.0255) and 7.2 months improvement in median survival.

Table 57. Updated overall survival (OS) (sensitive analysis, with censoring at time of crossover) in pivotal randomised study ET743-STS-201 (cut-off, 25 May 2007).

		Trabectedin qwk 3-h	Trabectedin q3wk 24-h	Total	Parameter	p-value
OS (All randomised patients, censored)	*N*	134	136	270		
	Events	82 (61.2%)	97 (71.3%)	179 (66.3%)	Log-rank: 3.506 HR: 0.754 95%CI (0.560-1.014)	LR:0.0611 HR: 0.0622
	Median (95% CI)	10.8 (9.7-14.3)	13.9 (12.7-18.6)	13.3 (12.0-14.9)		
OS (All treated patients, censored)	*n*	130	130	260		
	Events	79 (60.8%)	92 (70.8%)	171 (65.8%)	Log-rank: 4.404 HR: 0.724 95%CI (0.534-0.980)	LR:0.0359 HR: **0.0368**
	Median (95% CI)	10.8 (9.7-14.5)	14.0 (12.9-20.3)	13.6 (12.5-16.5)		
OS (All randomised patients, confirmed L-sarcoma, censored)	*n*	111	102	213		
	Events	68 (61.3%)	72 (70.6%)	140 (65.7%)	Log-rank: 4.992 HR: 0.685 95%CI (0.490-0.957)	LR:0.0255 HR: **0.0264**
	Median (95% CI)	10.7 (9.5-15.8)	17.9 (13.0-20.7)	13.8 (12.6-17.4)		

Median in months. Median follow-up: 30 months [95% CI: (25.0-36.6)] in the q3wk 24-h group and 27.9 months [95% CI: (23.6-37.3)] in the qwk 3-h group. HR: q3wk 24-h compared to qwk 3-h group. HR and p-value as determined by Cox regression. In **bold**, statistically significant results. CI, confidence interval; HR, hazard ratio; L-sarcoma, liposarcoma or leiomyosarcoma; LR, unstratified log-rank; OS, overall survival.

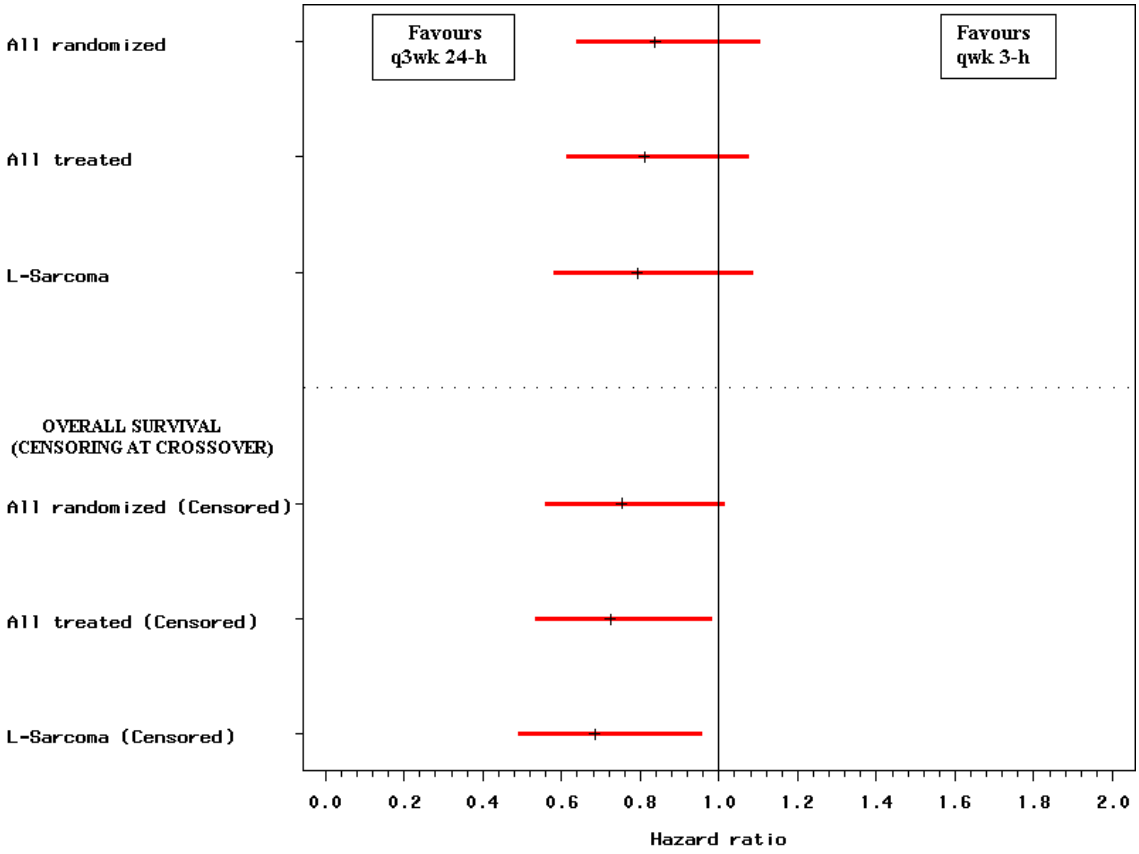
Figure 19. Kaplan-Meier plots of overall survival (OS) with censoring for all randomised patients, all treated patients and patients with confirmed L-sarcoma.



As shown in Figure 18, when patients were not censored at the time of crossover, the survival curve of the q3wk 24-h schedule is still consistently above that of the qwk 3-h schedule throughout the observation period. However, the curves tend to converge at approximately 22-24 months, precisely when an accumulation of censoring exists. Of interest, when patients are censored at the time of crossover (Figure 9), the trend of the curves to converge at 22-24 months disappears and they remain consistently separated. This observation suggests that the impact of the crossover is greatest around that particular time interval.

A visual display of the hazard ratios and 95% confidence intervals for OS is provided as a forest plot in Figure 20, illustrating the consistent pattern of treatment benefit favouring the q3wk 24-h trabectedin regime. Censoring of patients at time of crossover to the alternative regime increased the difference in overall survival between treatment arms, which was statistically significant in favour of the q3wk 24-h regime in two of the three sensitivity analyses.

Figure 20. Hazard ratios and 95% confidence intervals for the different analyses of overall survival (primary and sensitivity) with trabectedin q3wk 24-h vs. qwk 3-h in the pivotal randomised study ET743-STS-201 (cut-off, 25 May 2007).



The central vertical line denotes a HR of 1. Each black mark denotes an individual HR and the horizontal red lines their 95% CI. HR <1 indicates lower relative risk of death in the q3wk 24-h trabectedin arm relative to the qwk 3-h arm. Results reach statistical significance (at a 5% significance level) if the red line does not cross the vertical line. L-sarcoma, liposarcoma or leiomyosarcoma.

4.2.2. Updated Overall Survival Rate at 12 Months

The survival rate at 12 months appears a characteristic and appropriate time point to further explore a potential impact of the crossover on survival. The reasons are: 1) at this relatively early time, any potential impact of crossover on survival will be certainly less pronounced than at later time points; 2) there were sufficient number of events to perform a meaningful comparison between treatment arms, and 3) the data were very mature since there was a very low censoring at 12 months [4 patients (1.5%): one patient in the qwk 3-h arm and three patients in the q3wk 24-h arm]. Table 58 summarises the 12-month survival rates in the different populations analysed.

Table 58. Updated survival rates at 12 months from the pivotal randomised study ET743-STS-201 (cut-off, 25 May 2007).

		Trabectedin qwk 3-h	Trabectedin q3wk 24-h	Total	p-value
Without censoring					
OS (All randomised patients)	*n*	134	136	270	
	OS at 12 months (95% CI)	50.0% (41-5-58.4)	60.2% (52.0-68.5)	55.1 (49.2-61.1)	0.0892
OS (All treated patients)	**n**	130	130	260	
	OS at 12 months (95% CI)	50.0% (41.4-58.6)	62.2% (53.9-70.6)	56.1% (50.1-62.2)	**0.0452**
OS (All randomised patients, confirmed L-sarcoma)	**n**	111	102	213	
	OS at 12 months (95% CI)	51.4% (42.1-60.6)	65.7% (56.4-74.9)	58.2% (51.6-64.8)	**0.0323**
Sensitivity analyses: with censoring at time of cross-over					
OS (All randomised patients, censored)	*n*	134	136	270	
	OS at 12 months (95% CI)	48.7% (38.7-58.7)	61.0% (52.7-69.2)	56.0% 49.6-62.4)	0.0646
OS (All treated patients, censored)	*n*	130	130	260	
	OS at 12 months (95% CI)	48.5% (38.3-58.7)	63.0% (54.6-71.4)	57.0% (50.5-63.5)	**0.0309**
OS (All randomised patients, confirmed L-sarcoma, censored)	*n*	111	102	213	
	OS at 12 months (95% CI)	49.9% (38.9-60.8)	66.7% (57.5-76.0)	59.1% (52.0-66.3)	**0.0209**

Median follow-up for the primary analysis: 30 months [95% CI: (25.0-36.6)] in the q3wk 24-h group and 27.9 months [95% CI: (23.6-37.3)] in the qwk 3-h group. In **bold**, statistically significant results. L-sarcoma, liposarcoma or leiomyosarcoma; OS, overall survival.

The survival at 12 months was in the range of 48.5-51.4% in the qwk 3-h arm and in the range of 60.2-66.7% in the q3wk 24-h arm. A strong trend towards improvement in one-year survival with trabectedin q3wk 24-h was found in the "all randomised" population and a statistically significant improvement was found in the "all treated" and "confirmed L-sarcoma" populations. Of note, this significant improvement in one-year survival was obtained even in the analyses without censoring patients at crossover. Hence, all these data support that the q3wk 24-h trabectedin regime had a better survival outcome compared to the qwk 3-h regime at the 12-month fixed time point when a minimum impact of crossover is likely to be expected. In this updated analysis, no such significant difference was observed at 24 months. However, at this later time point, there was a higher rate of censoring (in particular, between 20 and 24 months) and a likely more profound impact of crossover on survival.

The advantage in favour of the q3wk 24-h schedule was achieved despite the high one-year survival rate obtained with the qwk 3-h schedule. As detailed in Section 5, a review of the available literature on published clinical trials with new investigational agents evaluated in pretreated STS patients (including 43 phase II studies on 24 single agents) shows for the vast majority of reports 12-

month survival rates substantially lower than the 50% achieved in the current trial with the less active agent (trabectedin qwk 3-h), except for temozolomide (50%; Trent *et al.*; Cancer 2003; 98:2693-2699).

4.2.3. Summary of the Updated Overall Survival Analyses to Assess the Impact of the Crossover.

The updated data of the secondary endpoint overall survival confirm a strong trend toward better survival with trabectedin q3wk 24-h. Such a strong trend despite the substantial crossover (i.e., 32.1% of patients from the qwk 3-h crossed over to the q3wk 24-h arm) is *per se* noteworthy. The sensitivity analyses (censoring at crossover) to assess the impact of the crossover further strengthen this trend in the “all randomised” patients and confirm a statistically significant longer survival with trabectedin q3wk 24-h in the “all treated” and “confirmed L-sarcoma” patients. Additionally, the one-year survival rates, less likely to be affected by crossover, consistently favour the q3wk 24-h schedule. Taken together, these data reinforce the concept that, in the absence of crossover, a significantly longer survival would have likely been obtained with the q3wk 24-h schedule.