Pharma Mar
Colmenar Viejo, Madrid. Spain

INTERIM STUDY REPORT

ET743-STS-201

A RANDOMIZED, MULTICENTER, OPEN-LABEL STUDY OF YONDELIS (ET-743 ECTEINASCIDIN) ADMINISTERED BY 2 DIFFERENT SCHEDULES (WEEKLY FOR 3 OF 4 WEEKS VS. Q3 WEEKS) IN SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC LIPOSARCOMA OR LEIOMYOSARCOMA FOLLOWING TREATMENT WITH AN ANTHRACYCLINE AND IFOSFAMIDE

Compound Number:	ET-743
Name of Test Drug:	Trabectedin (YONDELIS)
Protocol Number:	ET743-STS-201
EudraCT:	2004-002106-29
Study Start Date:	12 May 2003 (First randomization date)
Cut-off Date for Interim Data Analysis:	31 May 2005
Principal Investigator Name and Affiliation:	George Demetri, M.D. Dana-Faber Cancer Institute, Center for Sarcoma and Bone Oncology/Adult Oncology 44 Binney Street, Shields-Warren Building, Room 530, Boston, MA 02115 (USA)
Responsible Medical Officer (for interim report production):	Miguel Angel Izquierdo, M.D. Ph.D. Director Clinical Research and Development. Pharma Mar S.A. Colmenar Viejo, Madrid, Spain
Earlier Approved Reports:	None
Version:	Final version
Approval Date:	26 June 2006

2. SYNOPSIS

Name of Sponsor/Company: Johnson & Johnson, Pharmaceutical Research and Development (J&JPRD) **Sponsor in Belgium, France, Germany, Italy and Spain:** Pharma Mar S.A. **Name of finished product:** YONDELIS **Name of active ingredient(s):** Trabectedin	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(*For National Authority Use only*)**
Protocol number	ET743-STS-201.	
EudraCT	2004-002106-29.	
Title of the study	A Randomized, Multicenter, Open-label Study of YONDELIS (ET-743 Ecteinascidin) Administered by 2 Different Schedules (Weekly for 3 of 4 weeks vs. q3 Weeks) in Subjects With Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma Following Treatment With an Anthracycline and Ifosfamide.	
Coordinating Investigator	George Demetri, M.D.	
Center (coordinating investigator)	Dana-Faber Cancer Institute, Center for Sarcoma and Bone Oncology / Adult Oncology, 44 Binney Street, Shields-Warren Building, Room 530, Boston, MA 02115 (USA).	
Publication (references)	Samuels BL, Rushing D, Chawla SP, et al. Randomized 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.	
Study period: **.Date first patient included/treated** **.Cut-off date for interim data analysis**	12 May 2003 31 May 2005	**Phase of Development:** Phase II
Study objectives	**Primary:** • To compare the time to progression (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:** • To estimate the rate and duration of best overall objective response [complete responses (CRs) and partial responses (PRs)] of each schedule. • To compare progression-free survival (PFS) and overall survival (OS) in the two schedules • To characterize the safety profile, and • To estimate the pharmacokinetics of trabectedin.	
Methodology	This phase II, open-label, randomized, multicenter study was designed to evaluate the efficacy and safety of trabectedin, administered on two different treatment schedules in patients with locally advanced or metastatic L-sarcoma whose disease had relapsed or become refractory after treatment with an anthracycline and ifosfamide, given either in combination or in sequence. Trabectedin was administered through a central venous line either as a 3-hour infusion at the starting dose of 0.58 mg/m^2, every week for 3 consecutive weeks of a 4-week cycle (**qwk 3-h** schedule), or as a 24-hour intravenous infusion at the starting dose of 1.5 mg/m^2, once every 3 weeks (**q3wk 24-h** schedule) in an outpatient setting. Dexamethasone was administered intravenously 30 min before each trabectedin infusion.	
Number of patients (planned and analyzed)	**Planned number of patients:** The study was originally designed with the primary objective to demonstrate a clinical benefit rate of ≥20% in each schedule (5% significance level). Clinical benefit was defined as CR + PR + stable disease of at least 24 weeks' duration. The planned sample size was 45 evaluable patients in each group and no comparison of efficacy endpoints was initially planned between schedules. Preliminary promising data were publicly disclosed at the 2004 annual meeting of the American Society of Clinical Oncology (ASCO). These encouraging observations, along with the rarity of the disease, the small target population, the difficulty of patient accrual, and the lack of any other available therapy for this patient population, prompted to change the study design in order to enable a better assessment of	

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the effect of trabectedin therapy. Thus, the sample size was expanded to at least 130 randomly assigned patients in each arm and TTP was designated as the primary endpoint. An external, independent data monitoring committee (IDMC) was instituted. Measures to ensure symmetry in the assessments of TTP and duration of response were adopted. The handling of missing visits and censoring and imputation rules for non-radiographically-measurable or evaluable disease were specified.

By the random assignment of 260 evaluable patients and the observation of 217 TTP events of either disease progression or death due to progression, the study would have a greater than 90% power to detect a minimum of 60% improvement in median TTP at a 2-sided 5% significance level.

The IDMC monitored the study conduct and reviewed the results of the first interim analysis to monitor safety of treated patients, determine if a difference in efficacy and safety was evident between the two schedules, and provide the sponsor with advice on study conduct. Per protocol, the first interim analysis was conducted after the observation of approximately 150 events (scheduled cut-off date, 31 May 2005).

Patients analyzed:

From 13 May 2003 until the cut-off date, 266 patients had been randomized, 253 patients had been treated, 206 patients (199 per independent review) were evaluable for response, and 82 patients were ongoing. Patients were enrolled at investigative sites in the United States of America (n=181), Russia (n=26), Canada (n=24), France (n=17), Italy (n=8), Australia (n=4), Belgium (n=3) and Spain (n=3).

Diagnosis and main selection criteria

Inclusion Criteria:

1. Signed informed consent.
2. Male or female, and at least 18 years old.
3. Histologically-proven unresectable advanced or metastatic liposarcoma or leiomyosarcoma. Patients with gastrointestinal stromal tumors (GIST) were not eligible.
4. Pathology specimens of the tumor were required to be available for centralized review.
5. Relapse or progressive disease (PD) after treatment with an anthracycline and ifosfamide, administered either in combination or as sequential regimens.
6. Progressive, measurable disease as defined in the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. If the only indicator lesion was in a previously irradiated area, the recurrence had to be confirmed by biopsy examination.
7. Recovery from the toxic effects of prior therapies to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade ≤1.
8. An Eastern Cooperative Oncology group (ECOG) performance status score of either 0 or 1.
9. Hematological variables: hemoglobin (Hb) ≥9 g/dl, absolute neutrophil count (ANC) ≥1500/µl, and platelet count ≥100000/µl.
10. Serum creatinine ≤upper limit of normal (ULN).
11. Hepatic function variables: total bilirubin ≤ULN; serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) ≤2.5 × ULN; total alkaline phosphatase (AP) ≤ULN, or if >ULN, then AP liver fraction or 5' nucleotidase had to be ≤ULN, and albumin ≥2.5 g/dl.

Exclusion Criteria:

1. Pregnant or breast–feeding women or male or female patients who were not employing adequate contraception. Acceptable birth control measures included intrauterine devices, oral contraceptives, subdermal 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.

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	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.	
Test product, dose and mode of administration, batch No.	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) or its designated contractor provided trabectedin as vials containing a sterile lyophilized powder for reconstitution and infusion. Each vial contained a white to pale yellow amorphous powder containing 0.25 mg of trabectedin and 250 mg of mannitol, or 1.0 mg of trabectedin and 1,000 mg of mannitol. Sufficient quantities of mono-potassium phosphate and phosphoric acid were added to the process solution to adjust the pH before lyophilization. Each study medication shipment was to be shipped in a cold storage container with dry ice. Trabectedin was diluted to at least a 500-ml volume, and administered by a central venous catheter. For patients with a body mass index (BMI) of >30, the body surface area (BSA) was calculated by using their ideal body weight. Recalculation of BSA was required for patients who had a body weight change of >10% from baseline. **Trabectedin qwk 3-h:** patients in this group received trabectedin as a 3-hour infusion at the starting dose of 0.58 mg/m^2 every week for three weeks of a 4-week cycle (Days 1, 8, 15 of a 28-day cycle). **Trabectedin q3wk 24-h:** patients in this group received trabectedin as a 24-hour infusion at the starting dose of 1.5 mg/m^2 every three weeks (Day 1 of a 21-day cycle). Patients were randomly assigned to one of the two schedules in a 1:1 ratio. The permuted-block randomization method was used, with stratification by baseline ECOG performance status score of either 0 or 1. Randomization codes were generated by the sponsor and assigned to eligible patients through the Interactive Voice Response System (IVRS) before study treatment began. <u>Trabectedin batch numbers:</u> • 01D13, 01H07, 02F12, 02I06, 03G08 and 04C03 (0.25 mg/20 ml vial, trabectedin lyophilized powder/formulation). • 02F13, 02J09, 03H27, 04C04, 04J08 and 4D001A (1.0 mg/100 ml vial, trabectedin lyophilized powder/formulation).	
Duration of treatment	Treatment could be continued as long as disease progression was not evident, unacceptable toxicity had not occurred, and the patient did not withdraw informed consent. Treatment was permanently discontinued after the patient received two additional cycles of study treatment after a CR was confirmed. Patients who had disease progression during treatment in the dosage group to which they had been initially allocated were allowed to cross over to the alternate dosage group, at the discretion of the investigator.	
Evaluation criteria: **Efficacy**	TTP was defined as time between randomization and the first documentation of disease progression or death due to progressive disease. Secondary efficacy endpoints were objective response rate (ORR), duration of response, progression-free survival (PFS), and overall survival. The RECIST guidelines were used to determine ORR. Tumor assessments were performed for all patients up to 30 days before randomization, and every 8 weeks thereafter until disease progression. The timing of assessments was the same for all patients, irrespective of the actual treatment date, to ensure symmetry of progression-based outcomes in the two study arms. Additional tumor assessments could be scheduled, if clinically indicated. Efficacy analyses were conducted primarily based on the independent review of outcomes for all randomly assigned patients. These included the primary efficacy endpoint, TTP, and	

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	the secondary efficacy endpoints, ORR, PFS and overall survival. Duration of response was measured in evaluable patients who had an objective response. Sensitivity analyses were conducted in treated patients. Supportive analyses were done on the basis of data obtained from the investigators' assessments.	
Safety	Safety evaluations included adverse events (AEs), clinical laboratory data, the results of physical examination and vital signs findings, and deaths.	
Statistical methodology	The cut-off for the interim analysis (at 150 events) was prospectively defined as 31 May 2005. The results of this protocol-specified analysis are presented in this report. The "all randomized" analysis set comprised all patients who were randomly assigned to one of the two schedules, independent of whether they received trabectedin or not. The "all evaluable" analysis set comprised all randomly assigned patients with a diagnosis of L-sarcoma who received at least one dose of trabectedin, and for whom at least one post-baseline evaluation of response was available. The "all treated" analysis set comprised all patients who received at least one dose of trabectedin (patients who received dexamethasone only were not included). For TTP and overall survival, the overall significance level was 5%. The significance of efficacy was claimed if the p-value was less than or equal to the significance level, calculated on the basis of the specified alpha spending function and the observed number of events. For objective response, the significance of efficacy was considered if the lower limit of the exact 95% CI of the response rate was higher than 5%. Continuous variables were summarized and presented with summary statistics, which included mean, standard deviation (SDev), median and range. Categorical variables were summarized in frequency tables. Estimates of TTP and other time-to-event endpoints were calculated by the Kaplan-Meier (K-M) method for each schedule. Adverse events (AEs) were summarized by system organ class and overall. Imputation rules for incomplete dates are described in the SAP. 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.	
Results (1): <u>Patient characteristics</u>	Demographic characteristics were similarly distributed between study arms. Median age was 53 years (range, 20-80 years) and 63.2% of patients were female. All had a confirmed diagnosis of L-sarcoma: 65.8% leiomyosarcoma and 34.2% liposarcoma according to the institutions´ pathology reports. Primary tumors were most commonly located in the uterus (22.6%), retroperitoneal area (22.6%), or lower extremities (21.4%). Most metastases were located in the lungs (41.9%), liver (15.7%), abdomen (10.9%), pelvis (9.9%) and thorax (6.9%). Median number of metastatic sites per patient was 2 in each study arm (qwk 3-h, range 1-7; q3wk 24-h, range 1-5). Most patients (96.6%) had had previous surgery (median of three surgical procedures in each group) and approximately half had received radiotherapy. As specified by protocol, all patients had received prior systemic therapy (median of two lines and three agents in each group). A median of 1.3 months (range, 0.1-42.8 months) had elapsed between the documentation of disease progression with previous chemotherapy and randomization. The vast majority of patients (99.2%) had been previously treated with both anthracyclines and ifosfamide. The most common anthracycline administered was doxorubicin (93.6%). Besides anthracyclines and ifosfamide, gemcitabine (32.0%), docetaxel (24.1%) and dacarbazine (20.4%) were the most commonly administered previous chemotherapeutic agents.	

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Results (2):

Efficacy

A cut-off date was prospectively scheduled (31 May 2005) to provide for 150 progression events necessary for this interim analysis. Actually, 147 progression events were independently assessed at the cut-off date (155 events according to the investigator's assessment).

The interim results reported here show that both trabectedin schedules evaluated, qwk 3-h and q3wk 24-h, were effective in terms of time-to-event primary (TTP rates at 3 and 6 months) and secondary endpoints (PFS rates at 3 and 6 months). PFS rates at fixed time points were clearly better than the 3-month 39% and the 6-month 14% rates designated by the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTC STBSG) to declare an agent active in chemotherapy of pretreated STS. The antitumor activity reported in earlier phase II non-controlled studies with trabectedin in STS extensively pretreated patients is confirmed in the current randomized study for both trabectedin arms.

Primary efficacy endpoint- Time to progression (TTP)

Efficacy variables	**qwk 3-h** (n=134)	**q3wk 24-h** (n=132)	**LR*** **(p-value)** **HR*** **(p-value)**	**Total** (n=266)
TTP, months (independent review)				
Number of events, n (%)	77 (57.5%)	70 (53.0%)	.	147 (55.3%)
Median (95% CI)	2.1 (1.9-3.6)	3.8 (2.1-5.4)	LR: 4.297 (p=0.0382)** HR: 0.709 (p=0.0406)	3.0 (2.1-3.8)
TTP at 3 months, % (95% CI)	46.1% (35.9-56.4%)	53.1% (42.9-63.3%)	.	49.7% (42.5-56.9%)
TTP at 6 months, % (95% CI)	28.9% (19.0-38.7%)	37.1% (26.4-47.8%)	.	32.9% (25.6-40.2%)
TTP, months (investigator)				
Number of events	83 (61.9%)	72 (54.5%)	.	155 (58.3%)
Median (95% CI)	2.5 (2.1-3.5)	4.2 (2.5-7.9)	LR: 6.911 (p=0.0086)*** HR: 0.650 (p=0.0094)	3.4 (2.1-4.1)
TTP at 3 months, % (95% CI)	47.6% (37.6-57.5%)	56.6% (46.7-66.5%)	.	52.0% (44.9-59.0%)
TTP at 6 months, % (95% CI)	30.4% (21.0-39.9%)	42.6% (32.3-53.0%)	.	36.2% (29.1-43.3%)

Data for TTP are shown for all randomized patients. *Log rank and HR q3wk 24-h vs. qwk 3-h group. **Level of significance (log-rank) to be reached for 147 events=0.0246. ***Level of significance (log-rank) to be reached for 155 events=0.0273. CI, confidence interval; HR, hazard ratio; LR, log-rank; TTP, time to progression.

An increment of 81% (independent review) and 68% (investigator's assessment) was achieved in median TTP with the q3wk 24-h schedule compared to the qwk 3-h schedule. The differences between TTP curves approached statistical significance in the independent review data set (log-rank p=0.0382; level of significance to be reached for 147 progression events=0.0246) and were statistically significant in the investigator's assessment data set (log-rank p=0.0086; level of significance to be reached for 155 progression events=0.0273). The hazard ratios showed a consistent lower risk of progression for patients treated in the q3wk 24-h group: 29.1% and 35.0% reduction in the independent review and investigator's assessment, respectively.

Intrapatient comparison of TTP with trabectedin versus TTP with last prior chemotherapy (i.e., "growth modulation index") was used as patient-specific historical control. Of note, 36.8% of patients achieved a longer TTP with trabectedin than with prior chemotherapy for advanced/metastatic disease: 35.5% with the qwk 3-h schedule and 38.0% with the q3wk 24-h schedule, respectively. Most of these last prior chemotherapies were based on anthracyclines (mainly doxorubicin) and ifosfamide.

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Results (2):
Efficacy (continues)

Secondary efficacy endpoints

Efficacy variables	**qwk 3-h** (n=134)	**q3wk 24-h** (n=132)	**LR* (p-value) HR* (p-value)**	**Total** (n=266)
ORR and duration of response				
Independent review				
ORR, % (95%CI) all evaluable**	1.0% (0.0-5.5%)	4.0% (1.1-9.9%)	.	2.5% (0.8-5.8%)
Duration of response, months (95% CI)	.	6.1 (5.3-7.8)	.	6.1 (5.3-7.8)
Investigator				
ORR, % (95%CI) all evaluable***	1.9% (0.2-6.8%)	7.8% (3.4-14.9%)	.	4.9% (2.4-8.7%)
Duration of response, months (95% CI)	4.8 (.)	8.2 (5.3-11.5)	.	8.1 (4.8-8.4)
PFS, months				
Independent review				
Median (95% CI)	2.1 (1.9-3.4)	3.5 (2.0-4.5)	LR: 3.365 (p=0.0666) HR: 0.748 (p=0.0694)	2.5 (2.0-3.6)
PFS at 3 months, % (95% CI)	45.1% (35.2-55.0%)	50.2% (40.3-60.1%)	.	47.7% (40.7-54.7%)
PFS at 6 months, % (95% CI)	26.9% (17.6-36.2%)	34.6% (24.5-44.7%)	.	30.6% (23.7-37.5%)
Investigator				
Median (95% CI)	2.5 (2.0-3.5)	4.2 (2.3-6.2)	LR: 6.537 (p=0.0106) HR: 0.666 (p=0.0115)	3.2 (2.1-3.9)
PFS at 3 months, % (95% CI)	46.6% (36.8-56.5%)	54.8% (45.1-64.5%)	.	50.7% (43.8-57.6%)
PFS at 6 months, % (95% CI)	29.8% (20.5-39.1%)	40.4% (30.4-50.4%)	.	34.9% (28.0-41.8%)
OS, months				
Median (95% CI), all randomized	11.8 (8.9-14.9)	16.7 (12.2-nr)	LR: 2.778 (p=0.0956) HR: 0.709 (p=0.0977)	13.4 (11.1-15.9)
Median (95% CI), all treated	11.8 (8.9-14.9)	17.9 (12.5-nr)	LR: 3.884 (p=0.0487) HR: 0.656 (p=0.0505)	13.6 (11.4-17.9)

Data for ORR are shown for all evaluable patients. Data for PFS are shown for all randomized patients. Data for OS are shown for all randomized and all treated patients.*Log rank (LR) and hazard ratio (HR) q3wk 24-h vs. qwk 3-h group.**Evaluable patients (independent review): n=99 (qwk 3-h group), 100 (q3wk 24-h group) and 199 patients (total-both groups).***Evaluable patients (investigator assessment): n=104 (qwk 3-h group), 102 (q3wk 24-h group) and 206 patients (total-both groups). CI, confidence interval; HR, hazard ratio; nr, not reached; LR, log-rank; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

An increment of 66.7% (independent review) and 68% (investigator's assessment) was achieved in median PFS with the q3wk 24-h schedule (41.5% for median OS). As with TTP, the hazard ratio revealed a consistent relative risk reduction in PFS (25.2% and 33.4% as determined by the independent review and the investigator, respectively) and relative risk reduction of death (29.1% and 34.4% as determined in all randomized patients and in all treated patients, respectively) for patients treated in the q3wk 24-h group.

A multivariate analysis revealed the following main prognostic factors for a lower risk of disease progression (i.e., longer TTP): baseline performance status =0, time from diagnosis to randomization >24 months, age at diagnosis >50 years, and pretreatment with one line of systemic anticancer therapy. Some of these prognostic factors were significant in the multivariate analysis of overall survival: baseline performance status=0 and time from diagnosis to randomization >24 months were also associated with a low risk of death (i.e., longer overall survival). Sum of diameters of target lesions<100 mm also was a significant prognostic factor for a longer survival.

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Results (3):

Efficacy (continues)

Clinical benefit rate, the original primary endpoint, was no longer considered as an endpoint of this study once TTP was chosen after the amendment.

Safety

Most AEs associated with trabectedin treatment were mild or moderate (grade 1 or 2), and most patients were able to continue the study treatment. Overall, 46 (18.2%) of 253 treated patients experienced drug-related grade 3/4 AEs: 18 patients (14.1%) in the qwk 3-h group and 28 patients (22.4%) in the q3wk 24-h group. Only nine patients (3.6%) discontinued trabectedin treatment due to drug-related AEs: four patients (3.1%) in the qwk 3-h group and five patients (4.0%) in the q3wk 24-h group. Ten patients (4.0%) required hospitalization due to drug-related AEs: five patients (~4.0%) in each group.

The most common grade 3/4 AEs related to the study medication were fatigue, nausea and vomiting, each affecting less than 5% of patients and 1-2% of cycles. Only one drug-related AE (fatigue) reached grade 4 in one patient and one cycle in the q3wk 24-h group. Of particular interest is the rarity of many of the unpleasant effects typical of commonly used anticancer chemotherapeutic agents, such as alopecia, mucositis, skin/nail toxicities, neurotoxicity, cardiac toxicity or other major organ-related toxicities. Likewise, and in contrast to the most commonly used agent in STS, doxorubicin, the lack of any evidence of cumulative toxicities with trabectedin is noteworthy.

A total of 38 drug-related SAEs were reported: eight patients (6.3%) experienced 19 drug-related SAEs in the qwk 3-h group and 12 patients (9.6%) experienced 19 drug-related SAEs in the q3wk 24-h group. Vomiting/nausea were the most common drug-related SAEs in both groups.

A total of 89 patients (35.2% of all treated patients) had died at cut-off date: 51 patients (39.8%) in the qwk 3-h group and 38 patients (30.4%) in the q3wk 24-h group. The most common cause of death was disease progression in both study groups. Four patients had treatment-related deaths; therefore, the drug-related death rate in this study was 1.6% (identical rate in each study group).

The most common grade 3/4 hematological toxicity was neutropenia (qwk 3-h: 11.4% of patients and 5.6% of cycles; q3wk 24-h: 43.0% of patients and 21.8% of cycles), followed at a distance by thrombocytopenia (qwk 3-h: 5.6% of patients and 1.6% of cycles; q3wk 24-h: 10.6% of patients and 3.1% of cycles) and anemia (qwk 3-h: 9.7% of patients and 3.5% of cycles; q3wk 24-h: 5.7% of patients and 1.1% of cycles). The vast majority of these AEs were grade 3 events. The rates of hematological toxicity were higher in the q3wk 24-h group except for anemia. Neutropenia and thrombocytopenia had a transient pattern, with a short duration (median of 7 days) and a rapid recovery. Few cases of grade 3/4 drug-related febrile neutropenia occurred: two (1.6% of all treated patients) and one patient (0.8% of all treated patients) in the qwk 3-h and q3wk 24-h group, respectively. Likewise, virtually no instances of life-threatening neutropenic infections or bleeding complications were noticed.

The most common grade 3/4 biochemical toxicities were transient increases in AST or ALT levels with a median duration of 8-9 days. Grade 4 transaminase elevations were only reported in three patients (2.4%) from the q3wk 24-h group. Liver toxicity was non-cumulative and no signs/symptoms of hepatic failure were observed.

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Conclusions	This report includes results from a protocol-specified interim analysis of the randomized study ET-743-STS-201 with cut-off date of 31 May 2005 and 147 progression events recorded at that date per independent review. These results confirm trabectedin as an effective chemotherapeutic agent in patients with L-sarcoma extensively pretreated with the active agents clinically available, anthracyclines and ifosfamide, plus other experimental agents such as gemcitabine and docetaxel in a third of the population. The two schedules evaluated, qwk 3-h and q3wk 24-h, were efficacious. Clinical benefit of trabectedin was shown in this randomized study in terms of time-to-event efficacy outcomes, which are widely accepted as good surrogates of efficacy. The primary efficacy endpoint, TTP, confirmed both schedules as efficacious in this patient population, with longer median TTP, PFS and overall survival with the q3wk 24-h arm. The curves of these time-to-event variables showed a consistent separation between the two schedules. Although the differences in efficacy outcomes between study arms approached but did not reach statistical significance after alpha-spending adjustment, the substantial magnitude and consistency of the changes observed in all time-to-event variables were clinically meaningful in favor of the q3wk 24-h arm. Intrapatient comparison of TTP with trabectedin relative to TTP with the last prior chemotherapy regimen showed longer TTP with trabectedin in 35-38% of patients, although most of them had been previously treated with anthracyclines and/or ifosfamide. Overall survival with trabectedin was much longer than the expected 6 months in STS patients after failure of standard chemotherapy in the absence of an active treatment. Moreover, it was equal or longer than that reported with standard agents in first-line STS chemotherapy. Further evidence that both the qwk 3-h and q3wk 24-h trabectedin schedules were efficacious comes from the 3- and 6-month PFS rates in this study, which clearly exceeded those designated by the EORTC STBSG to declare an agent active in chemotherapy of pretreated STS. This last finding further reinforces the value of the qwk 3-h schedule as an appropriate active control arm, better than placebo or best supportive care. The safety profile was similar with both trabectedin schedules, except for a higher incidence of hematological toxicity and transaminase elevations in the q3wk 24-h schedule, albeit with shorter duration and without relevant clinical consequences. The incidence of transient hematological toxicities and transient transaminase increases in this study agreed with those reported in earlier studies, and these side effects were tolerable and manageable. The rates of toxic death, discontinuations, and hospitalizations due to serious adverse events were low in the context of such an advanced, poor prognosis patient population. In conclusion, the risk/benefit ratio for the q3wk 24-h trabectedin schedule appears to be the most favorable for the treatment of a rare population of heavily pretreated patients with L-sarcoma who have exhausted all available therapeutic options and, therefore, have a very poor prognosis in the absence of an active treatment. Trabectedin represents a beneficial therapeutic option for these patients with a highly unmet medical need.	
Date of Report (final version)	26 June 2006	

Pharma Mar
Colmenar Viejo, Madrid. Spain

UPDATED CLINICAL STUDY REPORT
(FINAL ANALYSIS OF THE PRIMARY ENDPOINT-TIME TO PROGRESSION)

ET743-STS-201

A RANDOMIZED, MULTICENTER, OPEN-LABEL STUDY OF YONDELIS (ET-743 ECTEINASCIDIN) ADMINISTERED BY 2 DIFFERENT SCHEDULES (WEEKLY FOR 3 OF 4 WEEKS *VS.* Q3 WEEKS) IN SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC LIPOSARCOMA OR LEIOMYOSARCOMA FOLLOWING TREATMENT WITH AN ANTHRACYCLINE AND IFOSFAMIDE

Compound Number:	ET-743
Name of Test Drug:	Trabectedin (YONDELIS)
Protocol Number:	ET743-STS-201
EudraCT:	2004-002106-29
Study Start Date:	12 May 2003 (First randomization date)
Cut-off Date for Final TTP Analysis:	31 May 2006
Principal Investigator Name and Affiliation:	George Demetri, M.D. Dana-Faber Cancer Institute, Center for Sarcoma and Bone Oncology/Adult Oncology 44 Binney Street, Shields-Warren Building, Room 530, Boston, MA 02115 (USA)
Responsible Medical Officer (for updated report production):	Miguel Angel Izquierdo, M.D., Ph.D. Director Clinical Research and Development. Pharma Mar, S.A. Colmenar Viejo, Madrid, Spain
Earlier Approved Reports:	Interim Report (dated 26 June 2006)
Version:	Final version
Approval Date:	28 February 2007

2. SYNOPSIS

Name of Sponsor/Company: Johnson & Johnson, Pharmaceutical Research and Development (J&JPRD) **Sponsor in Belgium, France, Germany, Italy and Spain:** Pharma Mar S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(*For National Authority Use only*)**
Name of finished product: YONDELIS		
Name of active ingredient(s): Trabectedin		
Protocol number	ET743-STS-201.	
EudraCT	2004-002106-29.	
Title of the study	A Randomized, Multicenter, Open-label Study of YONDELIS (ET-743 Ecteinascidin) Administered by 2 Different Schedules (Weekly for 3 of 4 weeks *vs.* q3 Weeks) in Subjects With Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma Following Treatment With an Anthracycline and Ifosfamide.	
Coordinating Investigator	George Demetri, M.D.	
Center (coordinating investigator)	Dana-Faber Cancer Institute, Center for Sarcoma and Bone Oncology / Adult Oncology, 44 Binney Street, Shields-Warren Building, Room 530, Boston, MA 02115 (USA).	
Publication (references)	Samuels BL, Rushing D, Chawla SP, et al. Randomized 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.	
Study period: **.Date first patient included/treated** **.Cut-off date for final TTP analysis**	12 May 2003 31 May 2006	**Phase of Development:** Phase II
Study objectives	**Primary:** • To compare the time to progression (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:** • To estimate the rate and duration of best overall objective response (OOR) [complete responses (CRs) and partial responses (PRs)] of each schedule. • To compare progression-free survival (PFS) and overall survival (OS) in the two schedules • To characterize the safety profile, and • To estimate the pharmacokinetics of trabectedin.	
Methodology	This phase II, open-label, randomized, multicenter study was designed to evaluate the efficacy and safety of trabectedin, administered on two different treatment schedules in patients with locally advanced or metastatic L-sarcoma whose disease had relapsed or become refractory after treatment with an anthracycline and ifosfamide, given either in combination or in sequence. Trabectedin was administered through a central venous line either as a 3-hour infusion at the starting dose of 0.58 mg/m^2, every week for 3 consecutive weeks of a 4-week cycle (**qwk 3-h** schedule), or as a 24-hour intravenous infusion at the starting dose of 1.5 mg/m^2, once every 3 weeks (**q3wk 24-h** schedule) in an outpatient setting. Dexamethasone was administered intravenously 30 min before each trabectedin infusion.	
Number of patients (planned and analyzed)	**Planned number of patients:** By the random assignment of 260 evaluable patients and the observation of 217 TTP events of either disease progression or death due to progression, the study would have a greater than 90% power to detect a minimum of 60% improvement in median TTP at a 2-sided 5% significance level. Per protocol, a first interim analysis was conducted with 147 events (31 May 2005; data shown in the Interim Study Report). Cut-off date for achieving 217 TTP events in the final TTP analysis was scheduled for 31 May 2006. **Patients analyzed:** From 12 May 2003 until the cut-off date for final TTP analysis, 270 patients had been randomized, 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. Patients were enrolled at investigational sites in the 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).	

Name of Sponsor/Company: Johnson & Johnson, Pharmaceutical Research and Development (J&JPRD) **Sponsor in Belgium, France, Germany, Italy and Spain:** Pharma Mar S.A. **Name of finished product:** YONDELIS **Name of active ingredient(s):** Trabectedin	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	(***For National Authority Use only***)
Diagnosis and main selection criteria	**Inclusion Criteria:** **(1)** Signed informed consent. **(2)** Male or female, and at least 18 years old. **(3)** Histologically-proven unresectable advanced or metastatic liposarcoma or leiomyosarcoma. Patients with gastrointestinal stromal tumors (GIST) were not eligible. (**4)** Pathology specimens of the tumor were required to be available for centralized review. (**5)** Relapse or progressive disease (PD) after treatment with an anthracycline and ifosfamide, administered either in combination or as sequential regimens. **(6)** Progressive, measurable disease as defined in the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. If the only indicator lesion was in a previously irradiated area, the recurrence had to be confirmed by biopsy examination. **(7)** Recovery from the toxic effects of prior therapies to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade ≤1. **(8)** An Eastern Cooperative Oncology group (ECOG) performance status score of either 0 or 1. **(9)** Hematological variables: hemoglobin (Hb) ≥9 g/dl, absolute neutrophil count (ANC) ≥1500/µl, and platelet count ≥100000/µl. **(10)** Serum creatinine ≤upper limit of normal (ULN). **(11)** Hepatic function variables: total bilirubin ≤ULN; serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) ≤2.5 × ULN; total alkaline phosphatase (AP) ≤ULN, or if >ULN, then AP liver fraction or 5' nucleotidase had to be ≤ULN, and albumin ≥2.5 g/dl. **Exclusion Criteria:** **(1)** Pregnant or breast–feeding women or male or female patients who were not employing adequate contraception. Acceptable birth control measures included intrauterine devices, oral contraceptives, subdermal 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.	
Test product, dose and mode of administration	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) or its designated contractor provided trabectedin as vials containing a sterile lyophilized powder for reconstitution and infusion. Each vial contained a white to pale yellow amorphous powder containing 0.25 mg of trabectedin and 250 mg of mannitol, or 1.0 mg of trabectedin and 1,000 mg of mannitol. Sufficient quantities of mono-potassium phosphate and phosphoric acid were added to the process solution to adjust the pH before lyophilization. Each study medication shipment was to be shipped in a cold storage container with dry ice. Trabectedin was diluted to at least a 500-ml volume, and administered by a central venous catheter. For patients with a body mass index (BMI) of >30, the body surface area (BSA) was calculated by using their ideal body weight. Recalculation of BSA was required for patients who had a body weight change of >10% from baseline. **Trabectedin qwk 3-h:** patients in this group received trabectedin as a 3-hour infusion at the starting dose of 0.58 mg/m^2 every week for three weeks of a 4-week cycle (Days 1, 8, 15 of a 28-day cycle). **Trabectedin q3wk 24-h:** patients in this group received trabectedin as a 24-hour infusion at the starting dose of 1.5 mg/m^2 every three weeks (Day 1 of a 21-day cycle). Patients were randomly assigned to one of the two schedules in a 1:1 ratio. The permuted-block randomization method was used, with stratification by baseline ECOG performance status score of either 0 or 1. Randomization codes were generated by the Sponsor and assigned to eligible patients through the Interactive Voice Response System (IVRS) before study treatment began.	
Duration of treatment	Treatment could be continued as long as disease progression was not evident, unacceptable toxicity had not occurred, and the patient did not withdraw informed consent. Treatment was permanently discontinued after the patient received two additional cycles of study treatment after a CR was confirmed. Patients who had disease progression during treatment in the dosage group to which they had been initially allocated were allowed to cross over to the alternate dosage group, at the discretion of the investigator.	
Evaluation criteria: **Efficacy**	TTP was defined as time between randomization and the first documentation of disease progression or death due to progressive disease. Secondary efficacy endpoints were objective response rate (ORR),	

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Safety	duration of response, progression-free survival (PFS), and overall survival according to protocol amendment ET743-STS-201 INT-3. The RECIST guidelines were used to determine ORR. Tumor assessments were performed for all patients up to 30 days before randomization, and every 8 weeks thereafter until disease progression. The timing of assessments was the same for all patients, irrespective of the actual treatment date, to ensure symmetry of progression-based outcomes in the two study arms. Additional tumor assessments could be scheduled, if clinically indicated. Efficacy analyses were conducted primarily based on the independent review of outcomes for all randomly assigned patients. These included the primary efficacy endpoint, TTP, and the secondary efficacy endpoints, ORR, PFS and overall survival. Duration of response was measured in evaluable patients who had an objective response. Sensitivity analyses were conducted in treated patients. Supportive analyses were done on the basis of data obtained from the investigators' assessments. Safety evaluations included adverse events (AEs), clinical laboratory data, the results of physical examination and vital signs findings, and deaths.	
Statistical methodology	The cut-off for the final TTP analysis (at approximately 217 events) was prospectively defined as 31 May 2006. The results of this protocol-specified analysis are presented in this report. The "all randomized" analysis set comprised all patients who were randomly assigned to one of the two schedules, independent of whether they received trabectedin or not. The "all evaluable" analysis set comprised all randomly assigned patients with a diagnosis of L-sarcoma who received at least one dose of trabectedin, and for whom at least one post-baseline evaluation of response was available. The "all treated" analysis set comprised all patients who received at least one dose of trabectedin (patients who received dexamethasone only were not included). The "confirmed L-sarcoma" analysis set comprised all patients with L-sarcoma as per independent central histopathological review. For TTP and overall survival, the overall significance level was 5%. The significance of efficacy was claimed if the p-value was less than or equal to the significance level, calculated on the basis of the specified alpha spending function and the observed number of events. Continuous variables were summarized and presented with summary statistics, which included mean, standard deviation (SDev), median and range. Categorical variables were summarized in frequency tables. Estimates of TTP and other time-to-event endpoints were calculated by the Kaplan-Meier (K-M) method for each schedule. 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.	
Results (1): <u>Patient characteristics</u>	Demographic characteristics were similarly distributed between study arms. The median age was 53 years (range, 20-80 years) and 63.0% of patients were female. All had a confirmed diagnosis of L-sarcoma: 65.6% leiomyosarcoma and 34.4% liposarcoma according to the institutions´ pathology reports. L-sarcoma was confirmed by the independent central histopathological review in 213 patients (78.9% of all randomized). Primary tumors were most commonly located in the retroperitoneal area (23.0%), the uterus (22.2%), or lower extremities (21.1%). Most metastases were located in the lungs (41.7%), liver (15.7%), abdomen (11.3%), pelvis (9.6%) or thorax (6.9%). Median number of metastatic sites per patient was 2 in each study arm. Most patients (96.7%) had had previous surgery (median of three surgical procedures in each group) and approximately half of them had received radiotherapy. As specified by protocol, all patients had received prior systemic therapy (median of two lines and three agents in each group). A median of 1.3 months (range, 0.1-42.8 months) had elapsed between the documentation of disease progression with previous chemotherapy and randomization. The vast majority of patients (99.3%) had been previously treated with both anthracyclines and ifosfamide. The most common anthracycline administered was doxorubicin (93.3%). Besides anthracyclines and ifosfamide, gemcitabine (31.9%), docetaxel (24.1%) and dacarbazine (20.4%) were the most commonly administered previous chemotherapeutic agents.	

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Results (2):
Efficacy

A cut-off date was prospectively scheduled (31 May 2006) to provide for 217 progression events necessary for final TTP analysis. Actually, 206 progression events were independently assessed at the cut-off date (216 events according to the investigator's assessment).

The differences between TTP curves reached statistical significance in the independent review data set (log-rank p=0.0302; level of significance to be reached for 206 progression events=0.0340) and in the investigator's assessment data set (log-rank p=0.0042; level of significance to be reached for 216 progression events=0.0370). Therefore, statistically significant longer TTP was found for patients treated in the q3wk 24-h arm, with an increment of 61% in median TTP with the q3wk 24-h schedule compared to the qwk 3-h schedule (independent review). The hazard ratios showed a consistent lower risk of progression in those patients treated in the q3wk 24-h group: 26.6% and 33.2% reduction in the independent review and investigator's assessment, respectively

Table 1. Primary efficacy endpoint - Time to progression (TTP)

Efficacy variables	**qwk 3-h** (n=134)	**q3wk 24-h** (n=136)	**LR* (p-value) HR* (p-value)**	**Total** (n=270)
TTP, months (independent review)				
Number of events, n (%)	102 (76.1%)	104 (76.5%)	.	206 (76.3%)
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)	2.7 (2.1-3.6)
TTP, months (investigator)				
Number of events	106 (79.1%)	110 (80.9%)	.	216 (80.0%)
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)	3.5 (2.5-4.1)

Data for TTP are shown for all randomized patients. *Log rank and HR q3wk 24-h *vs.* qwk 3-h group. **Lower than the level of significance (log-rank) to be reached for 206 events=0.0340. ***Lower than the level of significance (log-rank) to be reached for 216 events=0.0370. CI, confidence interval; HR, hazard ratio; LR, log-rank; TTP, time to progression.

All TTP sensitivity analyses were consistent in showing a reduction of the relative risk of progression for patients treated in the q3wk 24-h arm with the lowest risk reduction in patients with confirmed L-sarcoma. Treatment with the q3wk 24-h schedule was confirmed as an independent, statistically significant (p=0.0174) prognostic factor for lower risk of progression in the multivariate analysis.

Table 2. Time to progression (TTP): summary of primary and additional analyses.

Time to progression	**Number of events**	**HR (95% CI)***	**p-value****
Primary analysis			
All randomized	206	0.734 (0.554 - 0.974)	0.0302
Sensitivity analyses			
All treated	201	0.717 (0.538 - 0.954)	0.0208
Confirmed L-sarcoma	160	0.647 (0.468 - 0.895)	0.0076
Conservative analysis	231	0.736 (0.561 - 0.964)	0.0242
First imputation (midpoint)	225	0.716 (0.549 - 0.934)	0.0129
Second imputation (scheduled times)	225	0.784 (0.601 -1.021)	0.0210
Independent review-modified charter	194	0.768 (0.576 - 1.024)	0.0697
Multivariate analysis			
All randomized	206	0.680 (0.495-0.935)	0.0174

All analyses according to the independent review. *HR: q3wk 24-h compared to qwk 3-h group. *HR as determined by Cox regression, **Log-rank p value except for multivariate analysis where Pr>Chi square. HR, hazard ratio.

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Results (2):
Efficacy (continues)

The results of this final TTP analysis also show that both trabectedin schedules evaluated, qwk 3-h and q3wk 24-h, were effective in terms of time-to-event primary and secondary endpoints (including TTP and PFS rates at the 3- and 6-months fixed time points). PFS rates were clearly better than the 3-month 39% and the 6-month 14% rates designated by the Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer (EORTC STBSG) to declare an agent active in chemotherapy of pretreated STS. The antitumor activity reported in earlier phase II non-controlled studies with trabectedin in STS extensively pretreated patients is confirmed in the current randomized study for both trabectedin arms.

Table 3. Secondary efficacy endpoints

Efficacy variables	**qwk 3-h** (n=134)	**q3wk 24-h** (n=136)	**LR* (p-value) HR* (p-value)**	**Total** (n=270)
ORR and duration of response				
Independent review				
ORR, % (95%CI) all evaluable**	1.6% (0.2-5.8%)	5.6% (2.3-11.2%)	.	3.6% (1.7-6.8%)
Investigator				
ORR, % (95%CI) all evaluable***	2.4% (0.5-6.8%)	12.0% (6.9-19.0%)	.	7.2% (4.3-11.1%)
PFS, months				
Independent review				
Median (95% CI)	2.3 (2.0-3.4)	3.3 (2.1-4.6)	LR: 4.144 (p=0.0418) HR: 0.755 p=0.0438)	2.6 (2.1-3.6)
PFS at 3 months, % (95% CI)	44.7% (36.0-53.3%)	51.5% (43.0-60.1%)	.	48.1% (42.1-54.2%)
PFS at 6 months, % (95% CI)	27.5% (19.4-33.5%)	35.5% (27.1-43.9%)	.	31.4% (25.6-37.3%)
Investigator				
Median (95% CI)	2.5 (2.1-3.5)	4.2 (2.5-6.2)	LR: 7.628 (p=0.0057) HR: 0.685 (p=0.0063)	3.2 (2.3-4.0)
PFS at 3 months, % (95% CI)	46.7% (38.1-55.3%)	54.8% (46.3-63.2%)	.	50.8% (44.7-56.8%)
PFS at 6 months, % (95% CI)	28.8% (20.7-36.9%)	42.4% (33.9-50.9%)	.	35.8% (29.9-41.7%)
OS, months				
Median (95% CI), all randomized	11.8 (9.9-13.9)	13.8 (12.5-17.9)	LR: 1.654 (p=0.1984) HR: 0.823 (p=0.1985)	13.2 (11.6-14.0)
Median (95% CI), all treated	11.8 (9.9-14.3)	13.9 (12.7-18.3)	LR: 2.276 (p=0.1314) HR: 0.792 (p=0.1326)	13.3 (12.1-14.3)

Data for ORR are shown for all evaluable patients. Data for PFS are shown for all randomized patients. Data for OS are shown for all randomized and all treated patients.*Log rank (LR) and hazard ratio (HR) q3wk 24-h *vs.* qwk 3-h group.**Evaluable patients (independent review): n=123 (qwk 3-h group), 125 (q3wk 24-h group) and 248 patients (total-both groups).***Evaluable patients (investigator assessment): n=126 (qwk 3-h group), 125 (q3wk 24-h group) and 251 patients (total-both groups). CI, confidence interval; HR, hazard ratio; LR, log-rank; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

As with TTP, the hazard ratios revealed a consistent relative risk reduction in PFS (24.5% and 31.5% as determined by the independent review and the investigator, respectively) and in risk of death (17.7% and 20.8% as determined in all randomized patients and in all treated patients, respectively) for patients treated in the q3wk 24-h group.

The maximum magnitude of tumor variation in target lesions from baseline was calculated from each patient. About half of the evaluable patients from the q3wk 24-h arm (50.5%) had reduction of target tumor lesions at any time of treatment compared with a third of patients (32.4%) in the qwk 3-h arm. Intrapatient comparison of TTP with trabectedin versus TTP with last prior chemotherapy (i.e., "growth modulation index") was used as patient-specific historical control. Of note, 33.9% of patients achieved a longer TTP (>1.33) with trabectedin than with prior chemotherapy for advanced/metastatic disease: 31.2% with the qwk 3-h schedule and 36.7% with the q3wk 24-h schedule, respectively. Most of these last prior chemotherapies were based on anthracyclines (mainly doxorubicin) and ifosfamide.

Name of Sponsor/Company: Johnson & Johnson, Pharmaceutical Research and Development (J&JPRD) **Sponsor in Belgium, France, Germany, Italy and Spain:** Pharma Mar S.A. **Name of finished product:** YONDELIS **Name of active ingredient(s):** Trabectedin	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(*For National Authority Use only*)**
Results (2): Efficacy (continues)	Multivariate analyses in all randomized patients revealed the following prognostic factors for a lower risk of disease progression (i.e., longer TTP): q3wk 24-h schedule, baseline performance status =0, liposarcoma, time from diagnosis to randomization >24 months, more than 3 months between progression and randomization, liver metastases, no prior surgery, and moderate-low histological grade. Most of the prognostic factors for TTP were also significant in the multivariate analysis of ORR, PFS or OS. These findings are in line with the literature on prognostic factors in STS and denote that this was a representative patient population. Of note, except for OS, other multivariate analyses confirmed the q3wk 24-h schedule as a favorable prognostic factor. The consistency of these results with those of the primary TTP analysis supports a true treatment effect. The significantly better clinical benefit of trabectedin given as a q3wk 24-h regimen appears robust despite the suboptimal methodology after the implementation of the ET743-STS-201 INT-3 amendment. There were no statistically significant differences in TTP outcomes pre- *vs.* post-amendment. The HRs reflecting the greater benefit associated with the q3wk 24-h regimen over the qwk 3-h regimen were virtually identical in both cohorts (0.729 *vs.* 0.738) and consistent with the HR of 0.734 obtained in the ITT population of 270 randomized patients. The Cox regression analyses confirmed the significant treatment effect favoring the q3wk 24-h regimen in this patient population. Similar outcomes were obtained for the sensitivity analyses of the secondary endpoint PFS in the pre- *vs.* the post-amendment cohorts, showing consistently better outcomes with the q3wk 24-h regimen. Taken together, these results reinforce the conclusions and interpretability of the primary efficacy outcomes of the ET743-STS-201 study and support an unequivocal and consistently superior clinical benefit from trabectedin q3wk 24-h in this patient population with high unmet medical need.	
Results (3): Safety	In the current safety analysis, 260 treated patients (seven more than in the Interim Study Report) and 1473 cycles of trabectedin (407 additional cycles) were evaluated. Most AEs associated with trabectedin treatment were mild or moderate (grade 1 or 2), and most patients were able to continue the study treatment. Overall, 63 (24.2%) of 260 treated patients experienced drug-related grade 3/4 AEs: 21 patients (16.2%) in the qwk 3-h group and 42 patients (32.3%) in the q3wk 24-h group. Only 12 patients (4.6%) discontinued trabectedin treatment due to drug-related AEs: four patients (3.1%) in the qwk 3-h group and eight patients (6.2%) in the q3wk 24-h group. Thirteen patients (5.0%) required hospitalization due to drug-related AEs: six patients (4.6%) in the qwk 3-h group and seven patients (5.4%) in the q3wk 24-h group. The most common grade 3/4 AEs related to the study medication, apart from laboratory abnormalities, were fatigue, nausea and vomiting, each affecting less than 5% of patients (except for fatigue, 5.4%) and 1-2% of cycles. Virtually all were grade 3 events: only one (fatigue) reached grade 4 in one patient and one cycle in the q3wk 24-h group. Of particular interest is the rarity of many of the unpleasant effects typical of commonly used anticancer chemotherapeutic agents, such as alopecia, mucositis, skin/nail toxicities, neurotoxicity, cardiac toxicity or other major organ-related toxicities. Likewise, and in contrast to the most commonly used agent in STS, doxorubicin, the lack of any evidence of cumulative toxicities with trabectedin is noteworthy. A total of 54 drug-related SAEs were reported: 12 patients (9.2%) experienced 23 drug-related SAEs in the qwk 3-h group and 18 patients (13.8%) experienced 31 drug-related SAEs in the q3wk 24-h group. Vomiting/nausea were the most common drug-related SAEs in both groups. A total of 167 patients (64.2% of all treated patients) had died at cut-off date: 88 patients (67.7%) in the qwk 3-h group and 79 patients (60.8%) in the q3wk 24-h group. The most common cause of death was disease progression in both study groups. Seven patients had treatment-related deaths; therefore, the drug-related death rate in this study was 2.3% (3 patients) in the qwk 3-h group and 3.1% (4 patients) in the q3wk 24-h group.	

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Results (3): Safety (continues)	The most common grade 3/4 hematological toxicity was neutropenia (qwk 3-h: 13.3% of patients and 5.8% of cycles; q3wk 24-h: 47.0% of patients and 20.7% of cycles), followed at a distance by thrombocytopenia (qwk 3-h: 5.5% of patients and 1.3% of cycles; q3wk 24-h: 11.5% of patients and 2.4% of cycles) and anemia (qwk 3-h: 9.3% of patients and 2.9% of cycles; q3wk 24-h: 7.6% of patients and 1.1% of cycles). The vast majority of these were grade 3 events. The rates of hematological toxicity were higher in the q3wk 24-h group except for anemia. Neutropenia and thrombocytopenia had a transient pattern, with a short duration (median of 7 days for neutropenia and median of 5-7 days for thrombocytopenia) and a rapid recovery. Only two cases of drug-related febrile neutropenia occurred: one in each group (0.8% of treated patients). Likewise, no instances of life-threatening neutropenic infections or bleeding complications were noticed. The most common grade 3/4 biochemical toxicities were transient increases in AST or ALT levels with a median duration of 7-8 days. Grade 4 transaminase elevations occurred in only three patients (2.3%) from the q3wk 24-h group. Liver toxicity was non-cumulative and no signs/symptoms of hepatic failure were observed.	
Conclusions	This report includes results from the protocol-specified final TTP analysis of the ET-743-STS-201 randomized study, with cut-off date of 31 May 2006 and 206 progression events recorded on that date per independent review. The primary final analysis of TTP showed a significant longer TTP in those patients treated in the q3wk 24-h arm, with a 26.6% reduction in the relative risk of progression relative to the control arm (qwk 3-h). The magnitude of this reduction in the risk of disease progression was very consistent among various sensitivity analyses performed on the primary efficacy endpoint, TTP, and with the analyses of secondary endpoints such as PFS. Consistency of results across several analyses and consistent better outcomes in the main secondary efficacy endpoints support a true treatment effect obtained with the trabectedin q3wk 24-h regimen. The consistent difference in favor of the q3wk 24-h regimen is clinically relevant in the context of heavily pretreated patients with advanced/metastatic L-sarcoma and having progressed after therapy with the two available standard of care agents, doxorubicin and ifosfamide (in addition to failure to various experimental agents, which included gemcitabine and/or docetaxel in a third of the patient population). Analysis of maximum tumor shrinkage or intrapatient TTP comparison added biological plausibility to the significant findings in the primary study endpoint. About half of patients with trabectedin q3wk 24-h regimen showed tumor shrinkage compared to a third of patients with qwk 3-h regimen. Moreover, a higher percentage of patients obtained a longer TTP with trabectedin than TTP with prior chemotherapy for advanced disease (ratio >1.33; i.e., increment of TTP greater than 33% as compared with TTP to prior chemotherapy) with the q3wk 24-h schedule compared with the qwk 3-h schedule. The potential bias generated by the implementation of the ET743-STS-201 INT-3 protocol amendment appears to have caused negligible effects on the primary endpoint TTP per independent review, as well as in the secondary time-to-event endpoint PFS. There were no statistically significant differences in TTP outcomes pre- *vs.* post-amendment. The substantial crossover from the qwk 3-h to the q3w 24-h arm, which mostly occurred after the implementation of the amendment (due to the amendment itself and to the IDMC recommendations), may have introduced a confounding factor for the evaluation of OS. Overall, despite the confounding effect of crossover, which may preclude that OS would become statistically significant with more mature data, an overall trend in favor of the q3wk 24-h regimen was still maintained. In spite of the acknowledged limitations of historical comparisons, a) the median survival (11.8 months) reported with the trabectedin qwk 3-h regimen when compared with survival after failure of anthracycline-based chemotherapy or even from the beginning of first-line anthracycline based-chemotherapy, b) the rate of PFS at 3 and 6 months (44.7% and 27.5%, respectively), and c) the large magnitude of the separation among the PFS and OS curves for inactive or active agents and the curves for trabectedin qwk 3-h suggest that efficacy outcomes with the least performing trabectedin regimen (qwk 3-h) are highly unlikely to be inferior to those with inactive or even active agents in STS. Overall, these results provide confidence that trabectedin qwk 3-h is active against L-sarcoma, not a placebo-like treatment, and therefore an appropriate control arm in ET743-STS-201 randomized study.	

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Name of finished product: YONDELIS		
Name of active ingredient(s): Trabectedin		
Conclusions (continues)	The safety profile was similar with both trabectedin schedules, except for a higher incidence of hematological toxicity and transaminase elevations in the q3wk 24-h schedule, albeit of shorter duration and without relevant clinical consequences. The low rates of transient hematological toxicities and transient transaminase changes agreed with those reported in earlier studies and these effects were tolerable and manageable. The rates of toxic death, discontinuations, and hospitalizations due to serious adverse events were low in the context of such an advanced, poor prognosis patient population. In conclusion, the results of the final analysis of ET743-STS-201 primary endpoint TTP as well as the consistency of results in all supportive and sensitivity analyses indicate that trabectedin provides substantial clinical benefit (26.6% decreased risk of progression and 61% increase in median TTP compared to control arm) to patients with L-sarcoma in need of active palliation after failure of all available therapeutic options, thus representing a highly unmet medical need. The risk/benefit ratio appears more favorable with the q3wk 24-h trabectedin schedule in the target population.	
Date of report (final version)	28 February 2007	

Pharma Mar
Colmenar Viejo, Madrid. Spain

FINAL STUDY REPORT
(FINAL ANALYSIS OF OVERALL SURVIVAL)

ET743-STS-201

A RANDOMIZED, MULTICENTER, OPEN-LABEL STUDY OF YONDELIS (ET-743 ECTEINASCIDIN) ADMINISTERED BY 2 DIFFERENT SCHEDULES (WEEKLY FOR 3 OF 4 WEEKS *VS.* Q3 WEEKS) IN SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC LIPOSARCOMA OR LEIOMYOSARCOMA FOLLOWING TREATMENT WITH AN ANTHRACYCLINE AND IFOSFAMIDE

Compound Number:	ET-743
Name of Test Drug:	Trabectedin (YONDELIS®)
Protocol Number:	ET743-STS-201
EudraCT:	2004-002106-29
Study Start Date:	12 May 2003 (First randomization date)
Cut-off Date for Final Analysis of Survival:	23 April 2008
Principal Investigator Name and Affiliation:	**George Demetri, M.D.** Dana-Faber Cancer Institute, Center for Sarcoma and Bone Oncology/Adult Oncology 44 Binney Street, Shields-Warren Building, Room 530, Boston, MA 02115 (USA)
Responsible Medical Officer (for this report production):	**Alejandro Yovine, M.D.** Clinical Research and Development Director Pharma Mar, S.A. (mentioned as Pharma Mar in this report) Avenida de los Reyes, 1; Polígono Industrial La Mina-Norte 28770 Colmenar Viejo, Madrid, Spain Phone: +34 91 846 60 76 Fax: +34 91 823 45 04 E-mail: ayovine@pharmamar.com
Earlier Approved Reports:	Interim report (dated 26 June 2006) Final TTP analysis (dated 28 February 2007)
Version:	Final version
Approval Date:	12 June 2008

This study was conducted in compliance with Good Clinical Practice (GCP)

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Johnson & Johnson, Pharmaceutical Research and Development (J&JPRD)
Sponsor in Belgium, France, Germany, Italy and Spain:
Pharma Mar S.A.</td><td>Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td>(For National Authority Use only)</td></tr>
<tr><td>Name of finished product:
YONDELIS®</td><td></td><td></td></tr>
<tr><td>Name of active ingredient(s):
Trabectedin</td><td></td><td></td></tr>
<tr><td>Protocol number</td><td colspan="2">ET743-STS-201</td></tr>
<tr><td>EudraCT</td><td colspan="2">2004-002106-29</td></tr>
<tr><td>Title of the study</td><td colspan="2">A Randomized, Multicenter, Open-label Study of YONDELIS (ET-743 Ecteinascidin) Administered by 2 Different Schedules (Weekly for 3 of 4 weeks vs. q3 Weeks) in Subjects With Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma Following Treatment With an Anthracycline and Ifosfamide.</td></tr>
<tr><td>Coordinating Investigator</td><td colspan="2">George Demetri, M.D.</td></tr>
<tr><td>Center (coordinating investigator)</td><td colspan="2">Dana-Faber Cancer Institute, Center for Sarcoma and Bone Oncology / Adult Oncology, 44 Binney Street, Shields-Warren Building, Room 530, Boston, MA 02115 (USA).</td></tr>
<tr><td>Publication (references)</td><td colspan="2">• Samuels BL, Rushing D, Chawla SP, Schuetze SM, Von Mehren M, Leohan ML, O'Donovan M, Wei X, Sternas LA and Demetri GD. Randomized 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 randomized 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 tumor 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.</td></tr>
<tr><td>Study period:
.Date first patient included/treated
.Cutoff date for final analysis of survival</td><td>12 May 2003

23 April 2008</td><td>Phase of Development:

Phase II</td></tr>
</table>

Name of Sponsor/Company: Johnson & Johnson, Pharmaceutical Research and Development (J&JPRD) **Sponsor in Belgium, France, Germany, Italy and Spain:** Pharma Mar S.A. **Name of finished product:** YONDELIS® **Name of active ingredient(s):** Trabectedin	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(*For National Authority Use only*)**
Study objectives	**Primary:** • To compare the time to progression (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:** • To estimate the rate and duration of best overall objective response (complete responses and partial responses) of each schedule. • To compare progression-free survival and overall survival (OS) in the two schedules • To characterize the safety profile, and • To estimate the pharmacokinetics (PK) of trabectedin.	
Methodology	This phase II, open-label, randomized, multicenter study was designed to evaluate the efficacy and safety of trabectedin, administered on two different treatment schedules in patients with locally advanced or metastatic L-sarcoma whose disease had relapsed or become refractory after treatment with an anthracycline and ifosfamide, given either in combination or in sequence. Trabectedin was administered through a central venous line either as a 3-hour infusion at the starting dose of 0.58 mg/m^2, every week for 3 consecutive weeks of a 4-week cycle (**qwk 3-h** schedule), or as a 24-hour intravenous infusion at the starting dose of 1.5 mg/m^2, once every 3 weeks (**q3wk 24-h** schedule) in an outpatient setting. Dexamethasone was administered intravenously 30 minutes before each trabectedin infusion.	
Number of patients (planned and analyzed)	**Planned number of patients:** Three OS analyses were planned by protocol in the ET743-STS-201 study: two interim OS analyses (shown in previous reports) were scheduled at the same time as the analyses of TTP and the current final OS analysis was planned at 234 deaths. This will allow for a greater than 80% power to detect a minimum 45% improvement in median overall survival at a 2-sided 5% significance level. **Patients analyzed:** From 12 May 2003 (date of first patient included) until the cutoff date for final OS analysis (23 April 2008), 270 patients had been randomized and 260 patients had been treated (i.e., no changes with respect to the previous report dated 28 February 2007).	
Diagnosis and main selection criteria	**<u>Inclusion Criteria:</u>** **(1)** Signed informed consent. **(2)** Male or female, and at least 18 years old. **(3)** Histologically-proven unresectable advanced or metastatic liposarcoma or leiomyosarcoma. Patients with gastrointestinal stromal tumors (GIST) were not eligible. (**4)** Pathology specimens of the tumor were required to be available for centralized review. (**5)** Relapse or progressive disease (PD) after treatment with an anthracycline and ifosfamide, administered either in combination or as sequential regimens. **(6)** Progressive, measurable disease as defined in the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. If the only indicator lesion was in a previously irradiated area, the recurrence had to be confirmed by biopsy examination. **(7)** Recovery from the toxic effects of prior therapies to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) grade ≤ 1. **(8)** An Eastern Cooperative Oncology group (ECOG) performance status score of either 0 or 1. **(9)** Hematological variables: hemoglobin (Hb) ≥9 g/dl, absolute neutrophil count (ANC) ≥1500/µl, and platelet count ≥100000/µl. **(10)** Serum creatinine ≤ upper limit of normal (ULN). **(11)** Hepatic function variables: total bilirubin ≤ULN; serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) ≤2.5 × ULN; total alkaline phosphatase (AP) ≤ ULN, or if > ULN, then AP liver fraction or 5' nucleotidase had to be ≤ULN, and albumin ≥2.5 g/dl.	

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Name of finished product: YONDELIS®		
Name of active ingredient(s): Trabectedin		
	<u>Exclusion Criteria:</u> **(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, subdermal 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.	
Test product, dose and mode of administration	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) or its designated contractor provided trabectedin as vials containing a sterile lyophilized powder for reconstitution and infusion. Each vial contained a white to pale yellow amorphous powder containing 0.25 mg of trabectedin and 250 mg of mannitol, or 1.0 mg of trabectedin and 1,000 mg of mannitol. Sufficient quantities of mono-potassium phosphate and phosphoric acid were added to the process solution to adjust the pH before lyophilization. Each study medication shipment was to be shipped in a cold storage container with dry ice. Trabectedin was diluted to at least a 500-ml volume, and administered by a central venous catheter. For patients with a body mass index of >30, the body surface area (BSA) was calculated by using their ideal body weight. Recalculation of BSA was required for patients who had a body weight change of >10% from baseline. **Trabectedin qwk 3-h:** patients in this group received trabectedin as a 3-hour infusion at the starting dose of 0.58 mg/m^2 every week for three weeks of a 4-week cycle (Days 1, 8, 15 of a 28-day cycle). **Trabectedin q3wk 24-h:** patients in this group received trabectedin as a 24-hour infusion at the starting dose of 1.5 mg/m^2 every three weeks (Day 1 of a 21-day cycle). Patients were randomly assigned to one of the two schedules in a 1:1 ratio. The permuted-block randomization method was used, with stratification by baseline ECOG performance status score of either 0 or 1. Randomization codes were generated by the Sponsor and assigned to eligible patients through the Interactive Voice Response System before study treatment began.	
Duration of treatment	Treatment could be continued as long as disease progression was not evident, unacceptable toxicity had not occurred, and the patient did not withdraw informed consent. Treatment was permanently discontinued after the patient received two additional cycles of study treatment after a complete response was confirmed. Patients who had disease progression during treatment in the dosage group to which they had been initially allocated were allowed to cross over to the alternate dosage group, at the discretion of the investigator.	
Evaluation criteria for overall survival	This Final Study Report shows the results of the final OS analysis planned by protocol and prospectively scheduled at 234 events. OS, a secondary endpoint of efficacy, was defined as the time between randomization 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.	

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Trabectedin</td><td></td><td></td></tr>
<tr><td>Statistical methodology</td><td colspan="2">Analyses were performed with standard statistical SAS procedures (SAS, version 8.02) and conducted primarily on all randomly assigned patients. A sensitivity analysis was conducted in treated patients. Estimates of OS were determined using the Kaplan-Meier (K-M) method. Tabular summaries present the number of events, the number of patients censored, estimates of the median and the 95% CI for the median. These results are also presented graphically in K-M plots. An unstratified 2-sided log-rank test was used to compare estimates of OS between the two schedules.</td></tr>
<tr><td>Results
<u>Overall survival</u></td><td colspan="2">At the cutoff date (23 April 2008), 35 (13.0%) of the patients were censored in the final OS analysis. 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.
For the primary OS analysis, all randomized patients, the hazard ratio (HR) showed a 15.7% reduction in the relative risk of death for patients treated in the q3wk 24-h group (HR=0.843; p=0.1931). The median OS was 11.8 months (95% CI, 9.9-14.9) in the qwk 3-h group and 13.9 months (95% CI, 12.5-18.6) in the q3wk 24-h group (log-rank p=0.1920). The overall survival rate at 12 months was 50.0% in the qwk 3-h group and 60.3% in the q3wk 24-h group, respectively.
All final OS analyses showed that patients from the q3wk 24-h arm had a trend to reduction in the relative risk of death, which was not statistically significant (Table 1). The trend for a better OS outcome with trabectedin q3wk 24-h increased when patients crossing over to the alternate treatment arm were censored at the time of crossover.

Table 1. Summary of main results for final OS analysis.
<table><tr><th>Efficacy variables</th><th>Number of events</th><th>HR (95% CI)*</th><th>LR p-value</th></tr><tr><td>Overall survival (OS)</td><td></td><td></td><td></td></tr><tr><td>All randomized</td><td>235</td><td>0.843 (0.653-1.090)</td><td>0.1920</td></tr><tr><td>All randomized (censored at crossover)</td><td>194</td><td>0.783 (0.587-1.046)</td><td>0.0965</td></tr><tr><td>All treated</td><td>227</td><td>0.820 (0.632-1.065)</td><td>0.1352</td></tr><tr><td>All treated (censored at crossover)</td><td>186</td><td>0.755 (0.563-1.014)</td><td>0.0608</td></tr></table>*HR: q3wk 24-h compared to qwk 3-h group. HR and p-value as determined by Cox regression.
HR, hazard ratio; LR, unstratified log-rank.</td></tr>
<tr><td>Conclusions</td><td colspan="2">The final analysis of OS, a secondary endpoint of efficacy, confirms the previously shown trend towards better survival with trabectedin q3wk 24-h, although, as anticipated, the difference between schedules was not statistically significant. Such a positive trend persists in the final OS analysis despite the substantial crossover (i.e., 32.1% of patients from the qwk 3-h crossed over to the q3wk 24-h arm) allowed per protocol. The sensitivity analyses (censoring at crossover) conducted to assess the impact of crossover on survival data further strengthened this trend. Additionally, the one-year survival rates, less likely to be affected by crossover, consistently favored the q3wk 24-h schedule.
In conclusion, the final survival data reinforce the internal consistency of the set of data from all efficacy-related endpoints showing a better outcome for the trabectedin q3wk 24-h schedule in the study ET743-STS-201. The finding of a similar benefit in survival, a secondary but robust endpoint, provides additional reassurance for the results in the primary endpoint TTP (26.6% reduction in the relative risk of progression and 61% increase in median TTP relative to the control arm).</td></tr>
<tr><td>Date of report (final version)</td><td colspan="2">12 June 2008</td></tr>
</table>