2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
PharmaMar, S.A.
J&JPRD</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

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<tr><td>Name of finished product:
YONDELIS®</td></tr>
<tr><td>Name of active ingredient(s):
Trabectedin</td></tr>
<tr><td>Protocol number</td><td colspan="2">ET-B-025-02</td></tr>
<tr><td>Title of the study</td><td colspan="2">Phase II study of Yondelis® in men with advanced prostate carcinoma.</td></tr>
<tr><td>Coordinating Investigator</td><td colspan="2">Dror Michaelson, M.D.
Dana-Farber Cancer Institute / Massachusetts General Hospital, Boston MA, USA.</td></tr>
<tr><td>Co-investigators / Study centers</td><td colspan="2">Gary R. Hudes, M.D. Fox Chase Cancer Center, Philadelphia PA, USA.
Nancy L. Lewis, M.D. Fox Chase Cancer Center, Philadelphia PA, USA
Joaquim Bellmunt, M.D. Hospital del Mar, Barcelona, Spain.
Sanjay Goel, M.D. Montefiore Medical Center, New York NY, USA.</td></tr>
<tr><td>Publication (references)</td><td colspan="2">At the time of this report no articles have been published on the study described herein. Preliminary results of this study were presented at:
American Society of Clinical Oncology (ASCO) 2005 Meeting. “Michaelson MD, Gilligan T, Oh W, Kartoff P, Taplin M, Izquierdo MA, Flores L, Smith MR. Phase II Study of Three Hour, Weekly Infusion of Trabectedin (ET-743) in Men with Metastatic, Androgen-Independent Prostate Carcinoma (AIPC). J Clin Oncol 2005; ASCO Annual Meeting Proceedings Part I. Vol 23 (No. 16S – June 1 Supplement): 4517”.
2009 Genitourinary Cancers Symposium. “Michaelson D, Bellmunt J, Lewis N, Goel S, Lee RJ, Kaufman DS, Lebedinsky C, Nieto A, Bayever E, Smith MR. Phase II study of trabectedin in men with castration resistant prostate cancer (CRPC). Abstract 175”.
X Congreso de la Sociedad Española de Oncología Médica (SEOM). “Michaelson MD, Kantoff P, Oh W, Gilligan T, López Martín JA, Flores L, Zintl P, Izquierdo MA, Smith MR. Trabectedin (Yondelis, ET-743) en el tratamiento de pacientes (PTS) con cáncer de próstata hormono-independiente (CPHI). Clin Transl Oncol 2005, 7(Suppl. 1): Abstract PD-50”.</td></tr>
<tr><td>Study period:
. First consent signed
. Last consent signed
. First infusion administered
. Last infusion administered
. Last follow-up</td><td>
2 January 2004
1 April 2008

8 January 2004

29 September 2008
10 November 2008</td><td>Phase of Development:

Phase II</td></tr>
<tr><td>Study objectives</td><td colspan="2">Primary:
<u>Cohort A (3-hour infusion weekly)</u>
To measure prostate-specific antigen (PSA) response in men with androgen-independent prostate cancer (AIPC) treated with trabectedin.
<u>Cohort B (applies both to Cohort B1 and to Cohort B2) (24-hour infusion q3wk)</u>
To measure PSA response, duration of response and time to progression in an additional cohort of 16 prostate cancer patients previously treated with docetaxel that will be treated with trabectedin administered as a 24-hour infusion every three weeks (q3wk).
Secondary:
<u>Cohort A (3-hour infusion weekly)</u>
To assess the safety of administration of trabectedin as a weekly, three-hour infusion in this population of patients.
To measure duration of response and time to progression in men with AIPC treated with trabectedin.
<u>Cohort B (24-hour infusion q3wk)</u>
To assess the safety of administration of trabectedin as a 24-hour infusion every three weeks in these patients.</td></tr>
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	- Exploratory and hypothesis-generating pharmacogenomics (PGx) analysis associating molecular parameters measured in the patient's samples with the clinical outcome [objective response and progression-free survival (PFS)] of trabectedin treatment. The results of the proposed molecular analyses will be correlated with the clinical outcome of the patients. The following parameters were to be determined in the patient samples: ▪ mRNA expression of ERCC1, XPD, BRCA1, BRCA2 and XPG genes in tumor tissue samples. ▪ Protein expression of DNA repair proteins in tissue microarrays. ▪ Fluorescence *in situ* hybridization (FISH) analysis of chromosomal translocations affecting transcription factors such as TMPRSS2-ETV1 and TMPSS2-ERG. ▪ Methylation status of BRCA1 promoter in tumor DNA circulating in serum and tumor samples. Hypothesis-generating analysis of methylation status of FANCF and Sigma 14-3-3 promoters.	
Methodology	This open-label, single-arm, non-randomized, multicenter, phase II clinical trial was designed to explore the benefit/risk ratio of trabectedin as single-agent chemotherapy in AIPC patients. Initially, patients were to be treated with a trabectedin weekly schedule (0.58 mg/m^2 as a 3-hour infusion weekly for three weeks of a 4-week cycle) in Cohort A. Later, new findings in the setting of AIPC chemotherapy that occurred during the course of this clinical trial prompted the interest to find new chemotherapeutic agents active in AIPC patients pretreated with docetaxel-based regimens. Furthermore, emerging evidence from the trabectedin clinical development program showed that the trabectedin dose and schedule originally tested in this study could be safe but less active than other dose and schedule (1.5 mg/m^2 as a 24-hour infusion every three weeks) successfully tested in randomized phase II clinical trials. Therefore, a new cohort of docetaxel-pretreated patients receiving therapy with the every-3-week trabectedin schedule was to be evaluated (Cohort B1). However, safety findings from the first five patients treated in this new cohort showed that co-morbidities usually associated to prostate cancer might result in an increased risk of having serious adverse events (SAEs). Accordingly, the starting dose was reduced from 1.5 mg/m^2 to 1.2 mg/m^2 in the further docetaxel-pretreated patients to be treated in a new cohort (Cohort B2).	
Number of patients (planned and analyzed)	**Planned number of patients:** **<u>Cohort A</u>** A Simon's two-stage phase II study design was used. The null hypothesis was 5% PSA response rate and a PSA response rate of 25% was the alternative hypothesis. The expected enrollment was 33 patients, of whom 30 were expected to be eligible. In the first stage, 17 patients were to be enrolled, 15 of whom were expected to be evaluable for response. If fewer than two patients achieved the primary endpoint of PSA response, the study was to be terminated due to lack of efficacy. The probability of early termination if the null hypothesis was truly correct (a response rate of 5%) was 83%. If two or more patients achieved the primary endpoint, the study was to proceed to its expected total accrual of 30 eligible patients. The treatment was to be declared promising if four or more patients achieved the primary endpoint. Using this design, there was a 9.6% probability of rejecting a promising treatment (β) and a 4.5% probability of accepting an uninteresting treatment (α). **<u>Cohort B</u>** No statistical hypotheses were formulated for patients in Cohort B1. In Cohort B2, 16 patients previously treated with docetaxel were to be treated with trabectedin 1.2 mg/m^2 as a 24-hour infusion every three weeks. If three or more responses were observed, the trial would be finished with the conclusion that the drug should be further investigated. This ensured a <20% probability (β=0.197) of rejecting the treatment for further evaluation while showing an actual response rate that was promising (25% or higher). Besides, there would be a <5% probability (α=0.043) of accepting the treatment for further evaluation with an actual response rate that was non-interesting (i.e., 5% or	

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	lower). **Patients analyzed:** A total of 59 patients were enrolled at five investigational sites in the U.S. and in Spain. Of these, 58 patients were enrolled and treated at five investigational sites in the U.S. and in Spain: 33 in Cohort A, five in Cohort B1 and 20 in Cohort B2. One patient in each cohort had no PSA measurements available and was excluded from the primary analysis of efficacy. Therefore, 32 patients in Cohort A, four in Cohort B1 and 19 in Cohort B2 were evaluable for efficacy.	
Diagnosis and main selection criteria	**Inclusion Criteria** • Signed informed consent. • Histologically confirmed adenocarcinoma of the prostate. • Radiographically documented metastatic disease. • Surgical or chemical castration (and testosterone < 50 ng/ml for Cohort B only). • PSA > 5 ng/ml. • Androgen-independent disease, as defined by detectable rising PSA in two consecutive measurements at least one week apart, with a minimum increment of at least 5 ng/ml above the nadir. • No more than one previous chemotherapy regimen (for Cohort A only), or previous treatment with one docetaxel-based chemotherapy regimen (for Cohort B only). • Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) performance status (PS) of 0, 1 or 2. • Adequate bone marrow reserve(s): - Neutrophil count > 1,500/µl. - Platelet count > 100,000/µl. • Adequate hepatic function: - Serum bilirubin < 1.0 x upper limit of normal (ULN). - Serum alkaline phosphatase (AP) < 1.5 x ULN. NOTE: If serum AP was elevated, measurement of 5' nucleotidase (5'NT) and gamma-glutamyltransferase (GGT) or AP liver fraction had to be performed, and if either of these was within normal limits (suggesting a bone origin for abnormal AP), the patient could be included. - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) < 2.5 x ULN. - Albumin > 2.5 g/dl. • Adequate renal function, with serum creatinine < 1.5 x ULN. **Exclusion Criteria** • Small cell carcinoma of the prostate. • Current treatment with chemotherapy or radiation therapy (for Cohort A only). • Treatment with chemotherapy or radiation therapy was terminated at least four weeks before study entry (for Cohort B only). • Treatment with extensive external beam radiation therapy or radionuclide therapy within six weeks of study entry. Palliative radiation involving less than 20% of bone marrow reserves had to have been completed within four weeks of entry (for Cohort A only) or at least four weeks before study entry (for Cohort B only). • Treatment with chemotherapy within four weeks of study entry (for Cohort A only) or terminated at least four weeks before study entry (for Cohort B only). • Patient not employing adequate contraception. • Other serious illness or medical conditions, specifically: - Uncontrolled congestive heart failure or history of myocardial infection or active angina pectoris within six months preceding registration. - Active infectious process. - Chronic active liver disease, including chronic hepatitis B, chronic hepatitis C, or cirrhosis.	

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	• Current anticancer treatment with any other non-Food and Drug Administration (FDA)-approved investigational drug. • ECOG performance status of 3 or worse.	
Test product, dose and mode of administration	Trabectedin was supplied by PharmaMar (Colmenar Viejo, Madrid, Spain) as a sterile lyophilized powder for concentrate for solution for infusion, available in vials with two strengths: 0.25 mg or 1 mg. The 0.25-mg and 1-mg vials had to be reconstituted by adding 5 ml (0.25-mg vials) or 20 ml (1-mg vials) of sterile water for injection. From a microbiological point of view the reconstituted solution had to be used immediately. If not used immediately, in-use storage times and conditions prior to use could not be longer than 24 hours at 2ºC to 8ºC (or 28 hours for a 24-hour infusion). The reconstituted solution had to be further diluted in at least 500 ml of normal saline (0.9% NaCl for injection) or 5% glucose and had to be administered using a central line. Trabectedin was administered **as a 3-hour intravenous (i.v.) infusion of 0.58 mg/m^2 weekly on days 1, 8 and 15 in 4-week cycles (Cohort A)**, or **as a 24-hour i.v. infusion of 1.5 mg/m^2 (Cohort B1)** or **1.2 mg/m^2 (Cohort B2) every three weeks (q3wk)**. The numbers of the trabectedin batches were as follows: • **0.25-mg vial batches:** 03G08, 04C03, 05B10, 05C09, 05I20 and 06L14. • **1-mg vial batches:** 02J09, 03H27, 04C04, 04K18, 05E31, 05F01, 05I01, 05I20, 07A10, 07I13 and 07J18.	
Duration of treatment	Treatment was to be administered until progressive disease or until major toxicity occurred. Progressive disease was to be evidenced by serially rising PSA values, worsening symptoms, or new radiographic findings, at which point patients were to be withdrawn from the study. All surviving patients were to be fully evaluated after three months (Cohort A) or after six months (Cohort B) for each endpoint, regardless of whether they have continued therapy or not. In Cohort B, patients with clinical benefit from trabectedin after the 6-month period could continue receiving the medication off-study. After the end of study treatment (regardless of the reason for discontinuation), patients had to be followed during the last cycle for which a set of procedures were to be conducted. Toxicity, hematology and biochemistry assessments had to be done for 30 days after the administration of the last study treatment and until the resolution of all toxicities that occurred during protocol treatment. In the event of toxicity persisting after the end of treatment, the patient had to be followed until resolution. All SAEs occurring within 30 days of the last study drug administration had to be reported. Beyond this time limit, only trabectedin-related SAEs were to be reported.	
Criteria for evaluation **Efficacy** **Safety** **Pharmacogenomics**	The primary efficacy endpoint in all cohorts was the PSA response, based on serum PSA levels measured once monthly and following the criteria of the National Cancer Institute PSA Working Group. All eligible patients who had at least one PSA determination after treatment onset were to be considered evaluable for efficacy. Secondary efficacy endpoints were duration of response and time to progression (TTP). In addition, although the overall response rate (ORR) was not to be used as a formal endpoint, patients with measurable visceral disease could be assessed in a standard fashion according to the WHO criteria All patients who had received any trabectedin infusion were evaluable for safety. Safety parameters included the description of drug-related deaths, premature withdrawals from treatment due to toxicity, and description of adverse events (AEs) and serious adverse events (SAEs). Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0. Paraffin-embedded tumor tissue samples and blood/serum samples were prospectively collected from patients of Cohort B consenting for the PGx testing. In addition, paraffin-embedded tumor tissue samples were obtained retrospectively from patients of Cohort A.	
Statistical methodology	No formal comparison for efficacy or safety was foreseen between Cohorts A and B, given the small sample size and the exploratory nature of the study. The two dosing subgroups in Cohort B (Cohort B1: 1.5 mg/m^2, Cohort B2: 1.2 mg/m^2) also were to be	

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	analyzed separately. Summary tables, data listings and statistical analyses were to be generated using the SAS statistical package (version 8.2). Non-continuous variables were to be described in frequency tables using counts and percentages. Continuous variables were to be described by median, minimum and maximum. Baseline data such as demographics, histology, number of organs involved and sites of disease, prior hormonal therapy, other prior anticancer therapy, biological values, prior relevant history, signs and symptoms, electrocardiogram and concomitant medication [coded according to the Anatomical Therapeutic Chemical Classification System (ATC)] were to be described following standard tables. Performance status and weight gain-loss during the study were to be summarized by frequency tabulation. For the evaluation of the primary endpoint, PSA response was to be calculated with binomial exact estimator and the confidence interval at 95% (95% CI). PSA outcomes were to be reported at post-treatment intervals: 3, 6, 12, 18 and 24 months. Median time-dependent parameters (duration of response, TTP) and their fix time estimations were to be analyzed according to the Kaplan-Meier method. For rates, the binomial exact estimator and its 95% CI were to be shown. Response rates, duration of radiological response and time to progression by WHO criteria in patients with measurable disease also were to be calculated using rates, binomial exact confidence intervals and Kaplan-Meier analysis. In those cases where testing of efficacy parameters *vs.* baseline covariates of interest was considered relevant, the appropriate test was to be used (i.e., Fisher's exact test for categorical variables, log-rank test or Cox regression for time to event variables, etc.). All AEs were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 5.0). Toxicities were to be coded using the NCI-CTC (version 2.0). All deaths, and deaths during treatment or within 30 days from the last treatment administration were to be tabulated, as well as the primary cause of death. Other SAEs and events resulting in study discontinuation also were to be tabulated. Additional safety analyses could be determined at any time in order to most clearly enumerate the rates of toxicities and to further define the safety profile of trabectedin.	
Results (1): Patient characteristics	**Cohort A (n=33)** The median age was 68.0 years (range, 43-83 years) and most patients (n=30, 90.9%) had an ECOG PS score of 0 or 1. Twenty-two patients (66.7%) had a total Gleason score ≥ 8 at baseline. All patients had metastatic disease. The median time from initial diagnosis was 84.6 months (range, 7.0-200.2 months). Median PSA level at inclusion into the study was 117.0 ng/ml (range, 14.5-2280 ng/ml). The median number of sites involved per patient was 2 (range, 1-4 sites). The most common disease locations at baseline were bone (n=26, 78.8%) and lymph nodes (n=22, 66.7%). The vast majority of patients (n=32, 97.0%) had had previous surgery, mostly diagnostic/exploratory (n=29, 87.9%) or radical (n=20, 60.6%). In addition, a total of 25 patients (75.8%) were given radiotherapy, mostly in the radical (i.e., mostly prostate and pelvis) setting (n=17, 51.5%). All 33 patients received prior hormone therapy. Of these, 22 (66.7%) were also given chemotherapy, four patients (12.1%) also received chemotherapy and biological therapy, and one patient (3.0%) was also given biological therapy. Patients received a median of 2 lines (range, 1-5) of hormone therapy; the agents most commonly administered were leuprorelin acetate (n=29, 87.9%) and bicalutamide (n=27, 81.8%). Twenty-six patients received previous chemotherapy, mostly in the advanced setting (n=25, 75.8%), with a median of one line (range, 0-2) and one agent (range, 0-3) each. The chemotherapy agents most commonly administered were docetaxel (n=24, 72.7%) and estramustine (n=9, 27.3%). The median time from end of last treatment to trabectedin was 5.4 months (range, 0.9-89.9 months) and the median time from end of last docetaxel treatment to trabectedin was 1.9 months (range, 0.9-44.1 months). **Cohort B1 (n=5)** The median age was 67.0 years (range, 49-78 years) and all patients had an ECOG PS	

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	score of 0 or 1. Three patients (60.0%) had a total Gleason score of ≥ 8 at baseline. All patients had metastatic disease. The median time from initial diagnosis was 28.6 months (range, 19.6-139.9 months). Median PSA level at inclusion into the study was 212.0 ng/ml (range, 147.6-603.1 ng/ml). The median number of sites involved per patient was 3 (range, 1-3 sites). The most common disease locations at baseline were bone (n=4, 80.0%) and lymph nodes (n=4, 80.0%). All five patients in this cohort had had previous diagnostic/exploratory surgery, and one had also had previous radical surgery. In addition, three patients (60.0%) were given radiotherapy. All patients received prior hormone therapy followed by chemotherapy. In addition, three patients (60.0%) were also given previous biological therapy. Patients received a median of 2 lines (range, 1-2) of hormone therapy. The agents most commonly administered were bicalutamide (n=4, 80.0%) and leuprorelin (n=4, 80.0%). All five patients received previous chemotherapy, mostly in the advanced setting (n=4, 80.0%), with a median of one line and one agent each. Docetaxel was the only chemotherapy agent given to patients in this cohort. The median time from end of last treatment to trabectedin was 2.6 months (range, 1.8-12.5 months) and the median time from end of last docetaxel treatment to trabectedin was 4.2 months (range, 1.8-12.5 months). **Cohort B2 (n=20)** The median age was 68.0 years (range, 53-81 years) and most patients (n=19, 95.0%) had an ECOG PS score of 0 or 1. Thirteen patients (65.0%) had a total Gleason score of ≥ 8 at baseline. All patients had metastatic disease. The median time from initial diagnosis was 46.9 months (range, 18.8-159.5 months). Median PSA level at inclusion into the study was 128.0 ng/ml (range, 12.8-2113 ng/ml). The median number of sites involved per patient was 1.5 (range, 1-4 sites). The most common disease locations at baseline were bone (n=16, 80.0%) and lymph nodes (n=11, 55.0%). Nineteen patients (95.0%) in this cohort had had previous surgery, mostly diagnostic/exploratory (n=15, 75.0%) or radical (n=6, 30.0%). In addition, 13 patients (65.0%) were given radiotherapy. All 20 patients received prior hormone therapy and chemotherapy. Of these, six patients (30.0%) also received biological therapy. Patients received a median of 2 lines (range, 1-5) of hormone therapy. The agents most commonly administered were bicalutamide (n=20, 100.0%) and leuprorelin (n=14, 70.0%). All 20 patients received previous chemotherapy, always in the advanced setting, with a median of one line (range, 1-4) and one agent (range, 1-2) each. Docetaxel (n=20, 100.0%) was the most common chemotherapy agent administered. The median time from end of last treatment to trabectedin was 4.2 months (range, 0.2-122.8 months) and the median time from end of last docetaxel treatment to trabectedin was 4.7 months (range, 1.1-32.2 months).
Results (2): Efficacy	**Cohort A (0.58 mg/m^2 weekly)** Confirmed PSA decline of ≥ 50% was observed in 12.5% of patients (n=4); these patients were pre-treated with chemotherapy, including taxanes. The PSA responses obtained were durable (4.5-6.4 months). Furthermore, one patient had unconfirmed PSA decline of ≥ 50%, and 21.9% of patients (n=7) had confirmed PSA decrease ≥ 30%. The median TTP was 1.5 months (95% CI, 0.9-1.8 months). Twenty-two of 33 treated patients were classified as taxane-resistant (i.e., they had confirmed progression during or within 60 days after stopping taxane chemotherapy). Of note, in this subset of taxane-resistant patients, 13.6% of them had confirmed PSA decline of ≥ 50%. According to the Simon two-stage optimal design followed in Cohort A, the four patients with PSA response found in this cohort confirmed trabectedin as an agent of interest for its development in the AIPC second-line setting. **Cohort B1 (1.5 mg/m^2 q3wk)** Three disease stabilizations were found among the five patients treated in this cohort. However, no efficacy conclusions may be drawn due to the low number of patients

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	treated. **<u>Cohort B2 (1.2 mg/m^2 q3wk)</u>** Confirmed PSA decline of ≥ 50% was observed in 10.5% of patients (n=2); both patients had previously received docetaxel-based regimens. Duration of response was 4.11 months and 8.59 months in each of these patients. Additionally, two patients (10.5%) had unconfirmed PSA decline of ≥ 50% (one of whom also showed PR in measurable disease as per WHO criteria) and 31.6% of patients (n=6) had confirmed PSA decrease ≥ 30%. The median TTP was 1.9 months (95% CI, 1.2-3.5 months). Thirteen of 20 treated patients were classified as taxane-resistant. Of note, two patients (15.4%) in this subset had confirmed PSA decline of ≥ 50%. The number of confirmed PSA responses in Cohort B2 (n=2) was lower than the three or more PSA responses established by the statistical plan for Cohort B2 to conclude that trabectedin should be further investigated in AIPC patients.	
Results (3): <u>Safety</u>	**<u>Cohort A (0.58 mg/m^2 weekly)</u>** A total of 110 cycles of trabectedin were administered to patients in Cohort A. The median number of cycles administered per patient was 2 (range, 1-19), with five patients receiving more than four trabectedin cycles. The median relative dose intensity was high (88.2%). Most treatment-related AEs were mild or moderate (grade 1 or 2) in severity; the most common were nausea (60.6% of patients/34.5% of cycles), fatigue (45.5% of patients/50.9% of cycles), anorexia (24.2% of patients/13.6% of cycles), vomiting (21.2% of patients/7.3% of cycles), insomnia (15.2% of patients/8.2% of cycles) and constipation (15.2% of patients/8.2% of cycles). Overall, three (9.1%) of the 33 patients treated in this cohort had severe (grade 3) treatment-related AEs; these comprised fatigue (n=2 in one cycle each), weakness (n=1 in one cycle) and tachycardia (n=1 in one cycle). Of note, no treatment-related AEs reached grade 4. Most patients were able to continue receiving this trabectedin schedule. Only two patients discontinued the treatment due to trabectedin-related AEs: grade 3 tachycardia, and grade 3 fatigue (n=1 each). In addition, no patients in Cohort A died as a result of treatment-related AEs. Four patients (12.1%) had trabectedin-related SAEs. These comprised grade 3 hyponatremia, grade 3 fatigue, grade 3 tachycardia, grade 2 nausea, grade 2 vomiting and grade 2 hypocalcemia. All SAEs resolved. Four patients (12.1%) had died at the cutoff date (date of last follow-up for this cohort, 10 April 2007). Three died due to disease progression, and the other one died as a result of a stroke unrelated to trabectedin. No grade 4 hematological abnormalities were found with this schedule. The most common grade 3 abnormality was lymphopenia (9.1% of patients/3.7% of cycles). Only one patient in this cohort had grade 3 neutropenia, leukopenia and thrombocytopenia, and was withdrawn from the study after receiving two trabectedin cycles due to disease-related fatigue and failure to thrive. No cases of febrile neutropenia were found. The most common grade 3/4 biochemical abnormality was serum AP increase (21.2% of patients/12.0% of patients). Transient severe transaminase increases were found in one patient (3.0%) and one cycle (0.9%) each. GGT increase only reached grade 3 in one patient (3.0%) and one cycle (0.9%). No cases of severe creatinine and total bilirubin increases were found. A total of 12 dose delays occurred in this cohort. Seven delays were due to hematological toxicity: neutropenia (n=6) and thrombocytopenia concomitant with unrelated neuropathy (n=1). Two delays were the result of non-hematological toxicity: grade 2 transaminase increase, and hypocalcemia (n=1 each). The other three delays were due to reasons unrelated to the treatment. Overall, 12 patients had one dose reduction and one had two dose reductions. All dose reductions were due to non-hematological toxicity. Reasons for dose reduction comprised GGT increase alone (n=7); transaminase increase alone (n=2); GGT increase concomitant with AP increase or transaminase increase (n=2); AP increase alone; bilirubin increase; and hyponatremia with hypocalcemia (n=1 each).	

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Cohort B1 (1.5 mg/m^2 q3wk)

A total of 11 cycles of trabectedin were administered to patients in Cohort B1. The five AIPC patients in this cohort received a median of 2 cycles (range, 1-4), with a median relative dose intensity of 82.3%.

The AEs most commonly related to this trabectedin schedule were fatigue (60.0% of patients/45.5% of cycles), anorexia (60.0% of patients/54.5% of cycles), nausea (40.0% of patients/36.4% of cycles) and vomiting (40.0% of patients/36.4% of cycles). Treatment-related SAEs occurred in 80.0% of the patients and comprised febrile neutropenia, myocardial infarction, pulmonary edema, diarrhea, nausea, vomiting, fatigue, increased lipase, dyspnea and phlebothrombosis (one patient and one cycle each). Most of them were grade 3, with the exception of one case of grade 4 myocardial infarction. Most treatment-related SAEs resolved.

Two patients (40.0%) were withdrawn from the study due to treatment-related AEs: one patient with grade 3 dyspnea, grade 3 pulmonary edema and grade 4 myocardial infarction; and one with grade 3 increased lipase (concomitant with treatment-related grade 2 amylase increase and grade 3 transaminase increases). In addition, a third patient with grade 3 febrile neutropenia concomitant with unrelated respiratory failure and atrial fibrillation was to be withdrawn but died shortly afterwards due to the respiratory failure.

Overall, 14 trabectedin-related SAEs were reported in four patients (80.0%). Three of these SAEs were considered SUSARs (grade 4 myocardial infarction, grade 3 lipase increase and grade 2 blood amylase increase). All treatment-related SAEs resolved except for two: grade 3 dyspnea and grade 3 febrile neutropenia.

Two patients in Cohort B1 had died at the cutoff date (date of last follow-up for this cohort, 14 December 2007): one due to disease progression and the other one to respiratory failure unrelated to trabectedin (see above).

Severe hematological abnormalities were common and comprised grade 3/4 leukopenia, grade 3/4 neutropenia, grade 3 lymphopenia (each in 80.0% of patients/54.5% of cycles), and grade 3/4 thrombocytopenia (60.0% of patients/36.4% of cycles). Severe neutropenia was transient and most cases returned to grade < 2 levels within 15 days. In addition, one patient had two episodes of febrile neutropenia, both of which were reported as SAEs.

The most frequent severe biochemical abnormality was grade 3 GGT increase (50.0% of patients/33.3% of cycles), followed by transient grade 3/4 transaminase increases (each in 40.0% of patients/18.2% of cycles each). Severe ALT increase appeared at a median of 7.5 days (range, 7-8 days) after dosing and returned to grade < 1 within 21-28 days, while grade 3 AST increase also appeared at a median of 7.5 days (range, 7-8 days) after dosing and returned to grade < 1 within 15 days. Other biochemical abnormalities were less common and did not reach grade 3/4.

A total of four cycle delays occurred in this cohort. All four were due to hematological toxicity: neutropenia (n=3) and a combination of thrombocytopenia and febrile neutropenia (n=1).

There were a total of three dose reductions in this cohort. Two reductions were due to non-hematological toxicity: GGT increase and bilirubin increase (n=1 each). The other reduction was due to hematological toxicity (thrombocytopenia and febrile neutropenia).

Cohort B2 (1.2 mg/m^2 q3wk)

A total of 105 cycles of trabectedin were administered to patients in Cohort B2. The median number of cycles per patient was 4 (range, 1-15), and nine patients (45.0%) were able to receive more than four treatment cycles each. The median relative dose intensity was 93.4%.

The AEs most frequently related with this dose and schedule were nausea (55.0% of patients/41.0% of cycles), vomiting (45.0% of patients/14.3% of cycles), fatigue (40.0% of patients/32.4% of cycles), anorexia (30.0% of patients/13.3% of cycles) and diarrhea (20.0% of patients/16.2% of cycles). Most treatment-related AEs were mild or moderate, and most patients were able to remain on study. Grade 3/4 AEs were found in 15.0% of patients and consisted of grade 4 pneumonia, grade 4 neutropenic sepsis, grade 3 vomiting and grade 3 fatigue (n=1 each). One patient died as a result of a related event (grade 4 neutropenic sepsis) and another one was withdrawn from the study due to related

Name of Sponsor/Company: PharmaMar, S.A. J&JPRD **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*)**
	grade 2 pancytopenia. A total of ten related SAEs were reported in four patients (20.0%). These consisted of grade 4 neutropenic sepsis, grade 4 neutropenia, grade 2 anorexia, grade 2 fatigue, grade 2 nausea (n=2), grade 2 pancytopenia, grade 2 vomiting (n=2) and grade 3 thrombocytopenia. Most (n=9) related SAEs resolved, but one (grade 4 neutropenic sepsis) resulted in death. Four patients in Cohort B2 had died at the cutoff date (date of last follow-up for this cohort, 10 November 2008). Two patients died due to disease progression, one due to trabectedin-related grade 4 neutropenic sepsis (see above), and one died suddenly due to reasons unknown but unrelated to trabectedin. Severe hematological abnormalities were mostly grade 3 and consisted of lymphopenia (40.0% of patients/12.5% of cycles), neutropenia (25.0% of patients/7.7% of cycles), leukopenia (25.0% of patients/5.8% of cycles) and thrombocytopenia (10.0% of patients/2.9% of cycles). Most cases of severe neutropenia returned to grade < 2 levels within 15 days. Of note, no cases of febrile neutropenia were found. Grade 3/4 AP increase was the most common severe biochemical abnormality (20.0% of patients/10.6% of cycles); however, two of the four patients with severe AP increase in this cohort already had grade 2/3 AP increase at baseline. The second most common was grade 3 transaminase increase (ALT increase: 20.0% of patients/3.8% of cycles; AST increase: 15.0% of patients/2.9% of cycles). Grade 3 ALT increase appeared at a median of 8.0 days (range, 5-8 days) after infusion and returned to grade < 1 within 21-28 days, while grade 3 AST increase appeared at a median of 8.0 days (range, 5-9 days) after infusion and returned to grade < 1 within 15-25 days. Other biochemical abnormalities were less common and did not reach grade 3/4. A total of 20 cycle delays occurred in this cohort. Of these, 11 delays were due to hematological toxicity (neutropenia). Two delays were due to non-hematological toxicity: grade 3 hypokalemia and catheter phlebitis (n=1 each). One delay was the result of both hematological (neutropenia and thrombocytopenia) and non-hematological toxicity (nausea and vomiting). The remaining six delays were due to reasons unrelated to the treatment. There were seven dose reductions in this cohort. Five reductions were due to non-hematological toxicity: AP increase (n=2); GGT increase (n=2); and a combination of ALT, AP and GGT increases (n=1). One was due to hematological toxicity (neutropenia). In addition, one reduction was due to both hematological and non-hematological toxicity (neutropenia, thrombocytopenia, nausea and vomiting).	
Results (4): Pharmacogenomics	The results of the PGx substudy will be described in a separate report.	
Conclusions	Trabectedin administered weekly (0.58 mg/m^2 given as a 3-hour i.v. infusion on days 1, 8 and 15 in 4-week cycles) and every three weeks (at 1.2 mg/m^2 given as a 24-hour infusion) were generally well tolerated and associated with a moderate antitumor activity against AIPC, as reflected in these small-size cohorts by PSA declines ≥ 50% in 12.5% (weekly regimen) and 10.5% of patients (q3wk regimen). Of note, PSA responses in patients with proven resistance to previous taxanes was 13.6% (weekly regimen) and 15.4% (q3wk regimen). Safety results discard further evaluations in pretreated AIPC patients of the 24-hour q3wk regimen at the approved dose (1.5 mg/m^2) for soft tissue sarcoma.	
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