2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
PharmaMar S.A., Sociedad Unipersonal
J&JPRD</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">ET-B-027-06</td></tr>
<tr><td>Title of the study</td><td colspan="2">Phase II, multicenter, open-label, clinical trial of Trabectedin (Yondelis®) in Metastatic Breast Cancer Patients with triple negative profile (ER-, PR-, HER2-), HER2 overexpressing tumors and BRCA1 or BRCA2 mutation carriers.</td></tr>
<tr><td>Coordinating investigator</td><td colspan="2">Suzette Delaloge, M.D.
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Karen Tedesco, M.D. Amsterdam Community Cancer Program, Amsterdam, NY, U.S.
Beatrice Uziely, M.D. Hadassah Medical Organization, Jerusalem, Israel.</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) 45th Annual Meeting (Orlando, May 29-June 2). “Delaloge S, Tedesco KL, Blum J, Gonçalves A, Lubinski J, Efrat N, Osborne C, Lebedinsky C, Tercero JC, Holmes FA. Preliminary safety and activity results of trabectedin in a phase II trial dedicated to triple-negative (ER-, PR-, HER2-), HER2+++, or BRCA1/2 germ-line-mutated metastatic breast cancer (MBC) patients (pts). J Clin Oncol 2009, 27(15 Supl): Abstract 1010”.</td></tr>
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<tr><td>Name of finished product:
YONDELIS®</td><td colspan="3"></td></tr>
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Trabectedin</td><td colspan="3"></td></tr>
<tr><td></td><td colspan="3">• American Society of Clinical Oncology (ASCO) 46th Annual Meeting (Chicago, June 4-8). “Tedesco KL, Blum JL, Goncalves A, Lubinski J, Ben-Baruch N, Osborne CR, Lardelli P, Tercero JC, Holmes FA, Delaloge S. A phase II trial of trabectedin (T) in patients (pts) with HER2-positive and BRCA1/2 germ-line-mutated metastatic breast cancer (MBC). J Clin Oncol 2010, 28(15 Supl): Abstract 1038”.
• American Society of Clinical Oncology (ASCO) 47th Annual Meeting (Chicago, June 3-7). “Tedesco KL, Blum JL, Gonçalves A, Lubinski J, Osborne C, Lardelli P, Tercero JC, Flórez A, Holmes FA, Delaloge S. Final results of a phase II trial of trabectedin (T) in triple negative, HER2 positive and RCA1/2 germ-line-mutated metastatic breast cancer (MBC) patients. J Clin Oncol 2011, 29(Supl): Abstract 1125”.</td></tr>
<tr><td>Study period:
. First consent signed
. Last consent signed
. First dose first cycle
. First dose last cycle
. Last follow-up
. Date of completion reported to authorities</td><td colspan="2">13 June 2007
28 December 2010
2 July 2007
27 June 2011
11 July 2011
11 August 2011</td><td>Phase of Development:

Phase II</td></tr>
<tr><td>Study objectives</td><td colspan="3">Primary:
• To determine the objective response rate by Response Evaluation Criteria In Solid Tumors (RECIST) [complete and partial response (CR + PR)] with trabectedin in patients with the following metastatic breast cancer subtypes:
o Group A: triple negative profile [estrogen receptor (ER)-, progesterone receptor (PR)-, human epidermal growth factor receptor-2 (HER-2)-].
o Group B: HER-2 overexpressing tumors (HER-2+).
o Group C: familial BRCA1 or BRCA2 mutation carriers.
Secondary:
To assess the following in each group:
• Duration of response (DR).
• Progression-free survival (PFS).
• Exploratory evaluation of changes in tumor volume (three dimensional analysis) and changes in tumoral radiological density.
• Safety profile in this patient population.
• Exploratory, hypothesis-generating pharmacogenomic (PGx) analyses to correlate molecular parameters in patient samples with clinical outcomes (objective response and PFS) within and across patient strata.</td></tr>
<tr><td>Methodology</td><td colspan="3">Open-label, prospective, multicenter, phase II clinical trial.</td></tr>
<tr><td>Number of patients (planned and analyzed)</td><td colspan="3">Planned number of patients:
One hundred and seven evaluable patients for the primary endpoint (confirmed objective tumor response rate) were to be recruited into each group, therefore giving a total of 321 evaluable patients. A futility analysis based on the primary endpoint was conducted after 36 evaluable patients had been recruited in each group. Recruitment into each group was to be stopped if there were five or less responses at the time of the analysis.
Patients analyzed:
A total of 127 patients were included; of these, 124 were evaluable for safety and 112 for efficacy. The futility analyses showed no confirmed responses in Group A, four in Group B, and six in Group C. The results were positive for Group C, but the recruitment rate was extremely slow (<10 patients per year). As a result, patient accrual into all three groups was stopped.</td></tr>
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Name of active ingredient(s): Trabectedin		

Diagnosis and main selection criteria

<u>Inclusion Criteria</u>

Patients who met all following criteria participated in the study:

1. Patient's written informed consent before any clinical trial-specific procedure.
2. Woman 18-years-of age, or older.
3. Histologically proven diagnosis of progressive metastatic breast cancer, either in documented:
   - <u>Group A:</u> triple negative phenotype [ER, PR and HER-2 negative status (surrogate of basal-like type)]. Patients were eligible if they had received prior therapy with an anthracycline and taxanes, including adjuvant or neoadjuvant therapy, but no more than three prior chemotherapy regimens for metastatic disease. NOTE: re-treatment with the same regimen or its components after a progression-free interval of six months or longer was considered a second regimen.
   - <u>Group B:</u> HER-2 overexpressing breast cancer. Patients were eligible if they had progressive metastatic disease following treatment with trastuzumab-based regimens or other HER-2 targeted therapy containing regimens, but no more than three prior regimens that contain HER-2 directed therapy and chemotherapy for metastatic disease were allowed. NOTE: re-treatment with the same regimen or its components after a progression-free interval of six months or longer was considered a second regimen.
   - <u>Group C:</u> familial BRCA1 or BRCA2 mutation carriers. Patients were eligible if they had developed progressive metastatic disease after at least one prior chemotherapy regimen in the adjuvant or metastatic setting. There was no limit to the maximal number of prior therapies allowed.
4. Measurable disease as defined in the RECIST guidelines. If the only indicator lesion was in a previously irradiated area, the recurrence had to be biopsy proven.
5. Patients with bone metastases currently receiving bisphosphonates for palliation were eligible if other sites of measurable disease were present.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
7. Hematologic variables:
   - Hemoglobin ≥ 9 g/dl.
   - Absolute neutrophil count (ANC) ≥ 1,500/µl, and
   - Platelet count ≥ 100,000/µl.
8. Serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 30 ml/min.
9. Creatine phosphokinase (CPK) ≤ 2.5 x upper limit of normal (ULN).
10. Hepatic function variables:
    - Total bilirubin ≤ ULN.
    - Total alkaline phosphatase (AP) ≤ 2.5 x ULN, or if > 2.5 x ULN, the AP liver fraction had to be considered or gamma-glutamyltransferase (GGT) or 5' nucleotidase had to be ≤ ULN, if the elevation could be osseous in origin.
    - AST (serum aspartate aminotransferase) and ALT (serum alanine aminotransferase) had to be ≤ 2.5 x ULN.
11. Albumin ≥ 25 g/l.
12. Complete recovery from the acute toxicity of any prior treatment. The presence of alopecia or National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 1 symptomatic peripheral neuropathy was allowed.
13. Patients could have central nervous system (CNS) metastases if stable (no evidence of progression) for at least three months after local therapy.

<u>Exclusion Criteria</u>

Patients who met any of the following criteria were to be excluded from participating in the study:

1. Prior exposure to trabectedin.
2. Known hypersensitivity to any of the components of the trabectedin intravenous (i.v.) formulation or dexamethasone.

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	3. More than three prior chemotherapy regimens for metastatic disease for Groups A and B. NOTE: re-treatment with the same regimen or its components after a progression-free interval of six months or more was considered a second regimen. **4.** Pregnant or lactating women or any women of childbearing potential who was not employing adequate contraception. Acceptable methods of contraception included intrauterine device (IUD) and double barrier (condom with a contraceptive sponge or contraceptive suppository). Use of hormonal contraception was not acceptable during this clinical trial. **5.** Completion of prior therapy: less than two weeks from radiation therapy (radiated lesions could not serve as measurable disease) or last dose of hormonal therapy, less than three weeks from prior chemotherapy or biological therapy (all acute toxicities had to be adequately recovered as per inclusion criteria #12), less than four weeks with any investigational agent. **6.** History of another neoplastic disease (except basal cell carcinoma or squamous cell carcinoma of the skin or cervical carcinoma *in situ* adequately treated) unless in remission for five years or longer. Group C patients could be enrolled with less than five years remission from another neoplastic disease; however, appropriate biopsy confirming current metastasic breast cancer was mandatory. **7.** Patients with known leptomeningeal disease. **8.** Other serious illnesses, such as: • Congestive heart failure or angina pectoris; myocardial infarction within one year before enrolment; uncontrolled arterial hypertension or arrhythmias. • Psychiatric disorder that prevents compliance with protocol. • Active viral hepatitis; or chronic liver disease. • Active infection. • Any other unstable medical conditions. **9.** Patients with a life expectancy of less than three months.	
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. It was administered as a **1.3 mg/m^2 3-hour every three weeks (q3wk) i.v. infusion.** The following batches were used: • **0.25-mg vial batches:** #05C09, #05I01, #05I20, #06L14, #07A19, #08A16, #09J14 and #10G09. • **1-mg vial batches:** #06K16, #07A10, #07I13, #07J18, #08A22, #08C31, #08D07, #08D24, #08F19, #08I11, #08K18, #09A14, #09C04, #09C11, #09K03, #09L17 and #9K217A.	
Duration of treatment	Trabectedin treatment was administered until disease progression, unmanageable toxicity, patient refusal or treatment delay longer than three weeks due to toxicity (except in case of obvious patient benefit). In case of objective response and acceptable toxicity, no maximum number of cycles of treatment was defined. The clinical trial could also be discontinued due to major protocol deviations, administrative reasons, or Sponsor's decision.	
Criteria for evaluation **Efficacy**	Patients who had received a minimum of two trabectedin infusions and had at least one disease assessment after baseline (performed at least six weeks after the start of trabectedin administration) were evaluable for efficacy. In addition, any eligible patient who experienced early disease progression or died of progressive disease prior to response evaluation was considered evaluable for response. The primary analysis of efficacy was based on the confirmed objective tumor response (i.e., CR or PR) rate in each group of patients. Secondary endpoints of efficacy were DR, PFS and exploratory evaluation of changes in tumor volume and in tumoral radiological density. The tumor response rate, DR and PFS were evaluated according to the RECIST v.1.0.	

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Safety **Pharmacogenomics**	All patients who had received at least part of one trabectedin infusion were evaluable for safety. Safety parameters included the description of adverse events (AEs), serious adverse events (SAEs), laboratory measurements and clinical examinations. Pharmacogenomic analyses were conducted to correlate molecular parameters in patients' tumor samples with clinical outcome (objective response and PFS).	
Statistical methodology	Descriptive statistics were used for this open, non-comparative study. Non-continuous variables were described in frequency tables using counts and percentages. Continuous variables were described by median, minimum and maximum. **Efficacy** For evaluation of the primary endpoint (objective tumor response rate), binomial exact estimator and its 95% confidence interval (CI) were calculated. Median time-to-event parameters (DR and PFS) and their fixed-time estimates were analyzed using the Kaplan-Meier method. Changes in tumor volume (three-dimensional analysis) and tumor radiological density were calculated by the independent central review and were assessed based on preestablished thresholds. **Safety** Descriptive statistics were used to characterize the toxicity, drug-related deaths, SAEs and toxicity-related treatment discontinuation profiles. AEs were graded according to the NCI-CTC v.3.0 and coded with the Medical Dictionary for Regulatory Activities (MedDRA) v.6.1. **Pharmacogenomics** All pharmacogenomic analyses were hypothesis-generating and exploratory. The first of these analyses was to be conducted on the futility analysis population (see below). **Futility Analysis** A futility analysis was conducted after 36 evaluable patients had been recruited in each group to give advice to the Sponsor regarding the conduct of the clinical trial. The cut-off date for each futility analysis was 16 weeks after the first infusion date of the 36th evaluable patient in each group. At that time, the analyses were based on the primary endpoint (objective tumor response rate). The O'Brien Fleming boundary was used for each analysis. If there were five or less responses at the time of analysis, according to boundaries and sample size assumptions, the alternative hypothesis would be rejected and the recruitment of that group would be stopped.	
Results (1): Patient characteristics	**Group A (triple negative profile)** Most patients (n=36, 72.0%) were Caucasian, their median age was 51 years (range, 27-77 years), and 26 (52.0%) had ECOG PS = 1. Most primary tumors were ductal carcinomas (n=44, 88.0%). The most frequent stages at diagnosis were II (n=23, 46.0%) and III (n=19, 38.0%). All patients were negative for ER, PR and HER-2 expression. The median number of sites involved per patient was 2 (range, 1-6 sites). The most common disease locations were lymph nodes (n=31, 62.0%), lung (n=21, 42.0%), liver (n=20, 40.0%) and bone (n=10, 20.0%). Forty-four patients (88.0%) had previously received radiotherapy. All patients had undergone previous surgery and received prior chemotherapy alone (n=26, 52.0%) or combined with biological therapy (n=21, 42.0%). The median number of lines and agents of prior chemotherapy (including adjuvant and neoadjuvant therapies) was three (range, 1-5 lines) and five (range, 3-10 agents), respectively. As defined per protocol, all patients had received prior anthracyclines and taxanes. **Group B (HER-2 overexpressing tumors)** Most patients (n=35, 94.6%) were Caucasian, their median age was 54 years (range, 38-75 years), and 16 (43.2%) had ECOG PS = 1. Most primary tumors were ductal carcinomas (n=32, 86.5%). The most frequent stages at diagnosis were II and III (n=15 each, 40.5%). All were positive for HER-2 expression. The median number of sites involved per patient was 2 (range, 1-5 sites).	

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	The most common disease locations were lymph nodes (n=20, 54.1%), liver (n=17, 45.9%), lung (n=16, 43.2%) and bone (n=16, 43.2%). Twenty-seven patients (73.0%) had previously received radiotherapy. All patients had undergone previous surgery and received prior chemotherapy combined with anti-HER-2 therapy alone (n=20, 54.1%) or with anti-HER-2 and hormone therapy (n=17, 45.9%). The median number of lines and agents of prior chemotherapy (including adjuvant and neoadjuvant therapies) was three (range, 1-7 lines) and five (range, 1-7 agents), respectively. The most frequent prior anticancer agents were taxanes (n=35, 94.6%), anthracyclines (n=32, 86.5%), and pyrimidine analogues (n=30, 81.1%). **<u>Group C (BRCA1/2 mutation carriers)</u>** Most patients (n=38, 95.0%) were Caucasian, their median age was 47 years (range, 30-59 years), and 23 (57.5%) had ECOG PS = 1. Most primary tumors were ductal carcinomas (n=35, 87.5%). Twelve patients (30.0%) had stage II disease and 15 (37.5%) had stage III disease at diagnosis. Fourteen patients (35.0%) were positive for ER expression and 12 (30.0%) were positive for PR expression. Seven patients (17.5%) were positive for HER-2 expression. All patients in this group were positive for BRCA1 and/or BRCA2 mutation. The median number of sites involved per patient was 2 (range, 1-6 sites). The most common disease locations were lymph nodes (n=26, 65.0%), lung (n=19, 47.5%), liver (n=18, 45.0%) and bone (n=15, 37.5%). Thirty-three patients (82.5%) had previously received radiotherapy. All patients had undergone previous surgery and received prior chemotherapy alone (n=12, 30.0%) or combined with biological therapy (n=13, 32.5%), with hormone therapy (n=9, 22.5%), or with biological and hormone therapy (n=6, 15.0%). The median number of lines and agents of prior chemotherapy was four (range, 1-10 lines) and six (range, 1-10 agents), respectively. The most frequent prior anticancer agents were anthracyclines (n=37, 92.5%) and taxanes (n=37, 92.5%).	
Results (2): <u>Efficacy</u>	A total of 112 enrolled and treated patients in all three groups were evaluable for the primary efficacy endpoint (confirmed objective tumor response rate) by an independent expert review. No confirmed objective responses were obtained in 43 evaluable patients in Group A (triple negative profile). In Group B (HER-2 overexpressing tumors), four of 34 evaluable patients showed PR, thereby giving a confirmed objective tumor response rate of 11.8% (95% CI: 3.3%-27.5%). Six of 35 evaluable patients in Group C (BRCA1/2 mutation carriers) achieved PR, which resulted in a confirmed objective tumor response rate of 17.1% (95% CI: 6.6%-33.6%). Concerning the secondary efficacy endpoints, median DR was 12.5 months (95% CI: 6.2-14.7 months) in Group B, and was not reached (95% CI: 4.1 months – upper limit not reached) in Group C. The longest median PFS was observed in Group C (3.9 months; 95% CI, 1.6-5.5 months). In Group B it was 3.8 months (95% CI, 1.8-5.5 months) and Group A had the shortest median PFS (2.2 months; 95% CI, 1.3-2.7 months). Likewise, changes in tumor volume and tumor radiological density according to the independent central review were less common in Group A compared to the other two groups. Changes in tumor volume were found in 4.0% of patients in Group A, 19.4% in Group B and 21.1% in Group C, while changes in tumoral radiological density occurred in 32.0% of patients in Group A, 47.2% in group B and 44.7% in Group C.	
Results (3): <u>Safety</u>	One hundred and twenty-four patients received at least one infusion of trabectedin in this study and therefore were evaluable for safety. The median number of cycles administered per patient was 3 (range, 1-29). The most common AEs related to trabectedin were general and gastrointestinal disorders: fatigue (66 patients, 53.2%; grade 3/4 in 12 patients, 9.7%), nausea (60 patients, 48.4%; grade 3 in two patients, 1.6%), constipation (32 patients, 25.8%; grade 3 in two patients, 1.6%) and vomiting (31 patients, 25.0%; grade 3 in six	

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<tr><td></td><td colspan="2">patients, 4.8%). Thirty-eight patients (30.6%) had trabectedin-related grade ≥3 AEs, the most frequent being fatigue (n=12, 9.7%), febrile neutropenia (n=8, 6.5%), and vomiting (n=6, 4.8%). Most patients were able to continue treatment. Six patients discontinued treatment due to trabectedin-related AEs: grade 3 muscular weakness and grade 1 fatigue; grade 2 nausea, grade 2 anorexia, grade 2 dizziness, grade 3 fall (associated with the aforementioned grade 2 dizziness), grade 3 dehydration and grade 4 fatigue; grade 2 hepatotoxicity; grade 3 congestive cardiac failure; and grade 3 cardiac failure; and liver toxicity (reported as transient grade 1 ALT/AST increase; see below).
No deaths occurred due to trabectedin-related AEs.
Nineteen patients had trabectedin-related SAEs. They comprised grade 3/4 febrile neutropenia (n=4), grade 3/4 neutropenia (n=3), grade 2/3 anemia, grade 4 pancytopenia, grade 4 thrombocytopenia, grade 2/3 congestive cardiac failure (n=2 each), grade 3 aplasia, grade 4 leukopenia, grade 3 cardiac failure, grade 2 palpitations, grade 3 nausea, grade 4 fatigue, grade 4 hepatotoxicity, grade 3 ejection fraction decreased, grade 4 transaminases increased, grade 3 dehydration, grade 3 renal failure acute, grade 3 deep venous thrombosis, grade 3 thrombosis, and grade 3 phlebitis (n=1 each). Most of these SAEs resolved without having any effects on trabectedin treatment: only four patients required cycle delays and/or dose reductions, and only three patients discontinued treatment.
The most common hematological abnormality was leukopenia (108 patients), followed by lymphopenia (106 patients) and anemia (103 patients). No dose reductions resulted from these abnormalities. Neutropenia was reported in 92 patients and reached grade 4 in 31 of them. In addition, nine patients had febrile neutropenia. Severe neutropenia appeared on Day 15 (range, 8-34) after dosing; most cases lasted 15 days or less and returned to grade ≤ 2 between Day 22 and Day 28. Transient neutropenia alone or concomitant with other adverse events or abnormalities was the most common cause of treatment-related cycle delay and dose reduction in this study. Febrile neutropenia also caused cycle delays and dose reductions in one and three patients, respectively. Thrombocytopenia occurred in 53 patients and reached grade 4 in ten patients. Severe thrombocytopenia appeared on Day 15 (range, 8-22) after dosing, mostly lasted 15 or less days, and returned to >100 x 10^9/l at >28 days after administration. Thrombocytopenia was the reason for dose delay in nine patients and for dose reduction in five patients. No treatment discontinuations occurred due to hematological abnormalities.
The most frequent biochemical abnormality was transaminases increases. ALT increases were found in 106 patients (grade 3/4 in 51 patients), and AST increases in 99 patients (grade 3 in 20 patients). Severe transaminase increases appeared on Day 8 (range, 4-23 days for ALT and 4-15 days for AST) after dosing and mostly lasted 15 days or less, returning to grade 1 before Day 22. Transaminase increases caused cycle delays in six patients and dose reductions in seven patients. In addition, one patient discontinued treatment due to transient grade 1 ALT/AST increase. Other biochemical abnormalities were less common and were mostly grade 1 or 2. Grade 3/4 CPK increases occurred in seven patients, and alone or concomitantly with transaminase increases were the cause of delays in two patients and dose reductions in three patients. Grade 3 AP increase was reported in one patient only, concomitantly with grade 3 ALT/AST increase and grade 4 GGT increase, and had no effects on treatment. Grade 3 bilirubin increases occurred in four patients; one of these patients fulfilled Hy's Law criteria. Nevertheless, she developed bilirubin increase after completion of concomitant intensive treatment with several antibiotic agents known to produce liver dysfunction. Two patients had dose reduction due to bilirubin increase.</td></tr>
<tr><td>Results (4):
<u>Pharmacogenomics</u></td><td colspan="2">Seventy-nine treated patients consented to undergo the PGx substudy. Paraffin-embedded tumor tissue samples were obtained from 65 of these patients. No tumor was detected in samples from 16 patients, and the amount and quality of extracted RNA was too low for analysis in samples from five other. Thus, RNA expression data</td></tr>
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	was available for tumor samples from 44 patients: 22 from Group A, 12 from Group B, and 10 from Group C. High XPG mRNA expression was associated with a better outcome after trabectedin treatment. All responder patients evaluated in the PGx substudy had XPG mRNA expression > 2.54. Furthermore, patients with XPG mRNA expression > 2.54 had longer median PFS compared to patients with XPG mRNA expression ≤ 2.54 both in the overall PGx population (4.0 *vs.* 1.6 months) and in each group (Group A: 2.6 *vs.* 1.8 months; Groups B and C together: 4.9 *vs.* 1.6 months).
Conclusions	No recommendation is given for further evaluation of trabectedin 1.3 mg/m^2 3-hour q3wk as treatment of patients with metastatic breast cancer negative for ER, PR and HER-2 expression. Evidence of antitumor activity has been found for this trabectedin dose and schedule in patients overexpressing HER-2 or with BRCA1 or BRCA2 mutations. XPG mRNA overexpression was associated with a better clinical outcome. This trabectedin schedule has an acceptable tolerability, and most adverse reactions are mild or moderate, reversible and predictable. No new safety issues were identified.
Date of report (final version)	11 March 2013.

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