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CLINICAL TRIAL PROTOCOL

Phase II Clinical and Pharmacokinetic Trial of PM00104 (Zalypsis®) in Patients with Advanced and/or Metastatic Endometrial or Cervical Cancer Previously Treated with One Line of Systemic Chemotherapy

INVESTIGATIONAL MEDICINAL PRODUCTS: PM00104 (Zalypsis®)
Protocol No.: PM104-B-001-09
NCT Code: 00900562

Version 2.0 including Amendment #1 – 30 September 2010

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INVESTIGATIONAL MEDICINAL PRODUCT: PM00104 (Zalypsis®)

Protocol No.: PM104-B-001-09

Final Version 1.0 – 27 January 2009
Version 2.0 including Amendment #1 – 30 September 2010

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

Confidentiality Statement

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[1] Abbreviated as PharmaMar S.A. in the rest of the protocol.

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INVESTIGATORS

A complete list of investigators will be available as a separate document.

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APPENDIX 5. DECLARATION OF HELSINKI 94

SYNOPSIS

TITLE	Phase II Clinical and Pharmacokinetic Trial of PM00104 (Zalypsis®) in Patients with Advanced and/or Metastatic Endometrial or Cervical Cancer Previously Treated with One Line of Systemic Chemotherapy.
PROTOCOL CODE	PM104-B-001-09
INVESTIGATORS / TRIAL LOCATION	About 10 centers worldwide will participate in this trial. A full list of investigators will be available as a separate document.
STUDY OBJECTIVES **Primary**	• To evaluate the antitumor activity of PM00104 administered as a 1-hour intravenous (i.v.) infusion on Day 1, 8 and 15 every four weeks (d1, d8 and d15; q4wk) to patients with advanced and/or metastatic endometrial or cervical cancer previously treated with one line of systemic chemotherapy.
Secondary	• To determine the safety profile of this PM00104 regimen in these patients. • To determine the pharmacokinetic (PK) profile of this PM00104 regimen in these patients. • To determine the pharmacogenomic (PGx) profile of this PM00104 regimen in these patients. Hypothesis-generating exploratory PGx analyses will be conducted to correlate the molecular parameters found in the tumor and blood samples of the patients with the clinical results achieved with PM00104.
STUDY DESIGN	Multicenter, open label, phase II clinical trial with single-agent PM00104 given as a 1-hour i.v. infusion on d1, d8 and d15 q4wk to patients with advanced and/or metastatic endometrial or cervical cancer in progression. The primary endpoint of the study is the overall response rate (ORR), defined as the percentage of patients with objective response (OR; complete or partial response) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST). Treatment will be administered in the absence of disease progression and/or unacceptable toxicity. In case of obtaining a complete response, two additional cycles will be administered and then the treatment will be stopped.

STUDY POPULATION	Adult female patients with endometrial or cervical cancer progressing after one previous line of systemic chemotherapy are eligible for this trial. To be included in the study, patients have to fulfill all inclusion criteria and none of the exclusion criteria.
INCLUSION CRITERIA	1. Voluntary written informed consent, obtained from the patient before the beginning of any specific study procedures. 2. Group 1 (endometrial cancer): histologically confirmed advanced and/or metastatic endometrial cancer (any grade, including endometroid, clear cell, serous and mixed types) with documented disease progression as per RECIST at study entry. Group 2 (cervical cancer): histologically confirmed advanced and/or metastatic cervical cancer with documented disease progression as per RECIST at study entry. 3. Group 1 (endometrial cancer): patients must have failed one prior systemic chemotherapy line for advanced/metastatic disease (excluding chemosensitizing chemotherapy); prior hormone therapy and biological therapy are allowed. Group 2 (cervical cancer): patients must have failed one prior systemic chemotherapy line for advanced/metastatic disease (excluding chemosensitizing chemotherapy); prior hormone therapy and biological therapy are allowed. 4. Complete recovery from the effects of prior radiotherapy and from any drug-related adverse events (AEs) derived from previous treatments, excluding alopecia and grade 1 peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v. 3.0). 5. At least one measurable lesion ("target lesion" according to the RECIST), located in a non-irradiated area and adequately measured less than four weeks before study entry. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is clearly documented or biopsy proven. 6. Age ≥ 18 years. 7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 1. 8. Life expectancy ≥ 3 months. 9. Appropriate bone marrow reserve, renal and hepatic functions. a. Platelet count ≥ 100 x 10^9/l, hemoglobin ≥ 9 g/dl and absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l. b. Alkaline phosphatase (AP) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 x ULN in case of extensive bone metastases). c. Alanine aminotransferase (ALT), aspartate

	aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN in case of hepatic metastases). d. Total bilirubin ≤ 1.5 x ULN, unless due to Gilbert's syndrome. e. Renal function: patients with calculated creatinine clearance (using Cockcroft and Gault formula) ≥ 30 ml/min. f. Albumin ≥ 2.5 g/dl. 10. Left ventricular ejection fraction (LVEF) within normal limits (LVEF of at least 50%). 11. Women of childbearing potential must have a negative serum pregnancy test before study entry. In case of childbearing potential, the patients and their partners must agree to use a medically acceptable method of contraception throughout the treatment period and for three months after discontinuation of treatment. Acceptable methods of contraception include complete abstinence, intrauterine contraceptive device (IUD), oral contraceptive, subdermal implant and double barrier (condom with a contraceptive sponge or contraceptive suppository).
EXCLUSION CRITERIA	1. Prior therapy with PM00104. 2. Uterine sarcomas, adenosarcoma, and malignant Mullerian tumors. 3. Cervical neuroendocrine or small cell carcinomas, non-epithelial cervical neoplasms such as sarcomas. 4. Patients who have isolated recurrences (vaginal, pelvic or para-aortic) potentially curative with radiation therapy or surgery. 5. Pregnant or lactating women, or in case of childbearing potential, women not using an appropriate contraceptive method. 6. Less than three weeks from prior radiation therapy, biological therapy or chemotherapy. Less than six weeks from prior nitrosourea, mitomycin C, high-dose chemotherapy or radiotherapy involving the whole pelvis or over 50% of the spine, provided that acute effects of radiation treatment have resolved. Hormonal therapy and palliative radiation therapy (i.e., for control of pain from bone metastases) must be discontinued before study entry. 7. <u>Group 1 (endometrial cancer):</u> more than one line of prior systemic chemotherapy for advanced/metastatic disease (excluding chemosensitizing chemotherapy). <u>Group 2 (cervical cancer):</u> more than one line of prior systemic chemotherapy for advanced/metastatic disease (excluding chemosensitizing chemotherapy. 8. Patients with a prior invasive malignancy (except non-melanoma skin cancer) who have had any evidence of disease within the last five years or whose prior malignancy treatment contraindicates the current protocol therapy.

	9. Patients with serious non-healing wound, ulcer, or bone fracture. This includes history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess for which an interval of three to six months must pass before study entry. In addition, the patient must have undergone correction (or spontaneous healing) of the perforation/fistula and/or the underlying process causing the fistula/perforation. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations. 10. Evidence of progressive or symptomatic central nervous system (CNS) metastases or leptomeningeal metastases. 11. Other diseases or serious conditions: a. Increased cardiac risk as defined by: • Unstable angina or myocardial infarction within 12 months before inclusion in the study. • New York Heart Association (NYHA) grade II or greater congestive heart failure. • Symptomatic arrhythmia or any arrhythmia requiring ongoing treatment. • Abnormal electrocardiogram (ECG), i.e., patients with the following are excluded: QT prolongation - QTc > 480 msec; signs of cardiac enlargement or hypertrophy; bundle branch block; partial blocks; signs of ischemia or necrosis, and Wolff Parkinson White patterns. • History or presence of valvular heart disease. • Uncontrolled arterial hypertension despite optimal medical therapy. • Previous mediastinal radiotherapy. • Previous treatment with doxorubicin at cumulative doses exceeding 400 mg/m^2. b. History of significant neurological or psychiatric disorders. c. Active infection requiring systemic treatment. d. Significant non-neoplastic liver disease (e.g., cirrhosis, active chronic hepatitis). e. Immunocompromised patients, including those known to be infected with the human immunodeficiency virus (HIV). f. Uncontrolled (i.e., requiring relevant changes in medication within the last month or hospital admission within the last three months) endocrine diseases (e.g., diabetes mellitus, hypo- or hyperthyroidism, adrenal disorder). 12. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in the study. The investigator should feel free to consult the Study Coordinator or the Sponsor for

	uncertainty in this regard. 13. Limitation of the patient's ability to comply with the treatment or to follow-up at a participating center. Patients enrolled into this trial must be treated and followed at a participating center. 14. Treatment with any investigational product within 30 days prior to inclusion in the study. 15. Known hypersensitivity to any component of PM00104.
No. of patients	A total of 62 evaluable patients are expected to participate in the study: • 30 patients in Group 1 (endometrial cancer), and • 32 patients in Group 2 (cervical cancer).
No. of sites	About 10 sites.
STUDY DRUG **Formulation**	Zalypsis® (PM00104). PM00104 is provided as a lyophilized powder for concentrate for solution for infusion in strength of 2.5 mg/vial.
Route of administration	Intravenous as a 1-h infusion by central catheter.
Administered dose	2 mg/m^2.
Treatment schedule	A treatment cycle consists of the drug administration on Day 1, 8 and 15 and all the study evaluations done before the next cycle. Treatment cycles will be repeated every four weeks.
Concomitant medication	Antiemetic prophylaxis: patients will receive prophylactic treatment for emesis consisting of dexamethasone 8 mg i.v. and 5-HT3 antagonists (ondansetron 8 mg i.v. or granisetron 1 mg i.v. or tropisetron 5 mg i.v.) before the infusion of PM00104 and according to the American Society for Clinical Oncology (ASCO) guidelines for drugs with moderate emetic risk. If necessary, in addition to the above, 10 mg of metoclopramide orally every 8 hours may be administered, or the duration of treatment with 5-HT3 antagonists and/or dexamethasone can be extended. Secondary prophylaxis with colony-stimulating factors such as granulocyte (G-CSF) or granulocyte-macrophage (GM-CSF) colony-stimulating factors are allowed according to the ASCO guidelines.

Criteria for continuation of treatment and for re-treatment	In order to be re-treated on Day 1 of a new cycle, the patients will have to fulfill the same criteria as at study entry. If these criteria are not met on Day 1 of a new cycle, treatment administration should be delayed up to two weeks and reevaluated weekly. The new cycle will start upon recovery of these parameters, according to these same criteria. A maximum delay of two weeks is allowed for recovery from drug-related AEs. If toxicities have not recovered after a maximum delay of two weeks, the patient should discontinue the treatment. In the event of obvious clinical benefit, the patient will remain on treatment only after having discussed and agreed upon the case with the Sponsor, and upon recovery of all parameters according to the aforementioned criteria. In order to be re-treated on Day 8 and Day 15 of each cycle, the patients will have to fulfill the following criteria: a) Platelet count $\geq$ 75 x 10^9/l, hemoglobin $\geq$ 9 g/dl and ANC $\geq$ 1.0 x 10^9/l. b) ALT and AST $\leq$ 2.5 x ULN ($\leq$ 5 x ULN in case of hepatic metastases). c) Other non-hematological toxicities, including renal function, $\leq$ grade 1 ($\leq$ grade 2 in case of asthenia). If these criteria are not met on Day 8 or Day 15, the respective infusion will be skipped. If both Day 8 and Day 15 infusions cannot be administered for any reason, the patient should discontinue the treatment, except in the event of obvious clinical benefit, in which case the patient will be allowed to remain on treatment only after having discussed and agreed upon the case with the Sponsor, and upon subsequent recovery of all parameters according to the aforementioned criteria.
Dose reduction	Dose reductions will take place based on the worst drug-related toxicity found since the last dose administration. No more than two dose reductions per patient (from 2 mg/m^2 to 1.6 mg/m^2 and then to 1.3 mg/m^2) will be allowed during the study. Patients requiring more than two dose reductions should discontinue the treatment, except in the event of obvious clinical benefit, in which case the patient could be allowed to remain on treatment after having discussed and agreed upon the case with the Sponsor. No dose escalations will be allowed in this study.
EFFICACY EVALUATIONS	To be evaluable for efficacy, patients must have: • Received at least four of the six infusions in the first two cycles (i.e., two infusions in each cycle, or three infusions in Cycle 1 and one infusion in Cycle 2), and • At least one disease measurement recorded not less than six weeks after treatment onset.

	In addition, any eligible patient who receive at least two of the three infusions in one treatment cycle and experience disease progression or die due to progressive disease (PD) prior to response evaluation will be considered evaluable for the main endpoint (ORR) and will be categorized as an "early progression". Patients withdrawn due to toxicity without any tumor assessment after the start of study treatment will be considered as "treatment failures" and will not be replaced. Patients withdrawn due to significant clinical deterioration of unknown reason, hypersensitivity reactions, refusal to continue on study for any reason or unrelated AEs without any tumor assessment after the start of study treatment will be considered not evaluable for efficacy and will be replaced. Assessment of efficacy will be done using the RECIST and will be essentially based on a set of measurable lesions identified at baseline as target lesions and followed until disease progression. A comprehensive workup will be performed at baseline and every other cycle (± 1 week) until evidence of PD. The same procedure will be used to evaluate each identified lesion both at baseline and throughout the treatment period. In case of detection of an objective response (complete or partial response), a confirmation assessment has to be performed four weeks after the first documentation of the response.
SAFETY EVALUATIONS	Patients will be evaluable for safety if they have received at least one total or partial infusion of PM00104. Safety will be evaluated using clinical examinations, which will comprise vital signs analysis, clinical assessment of AEs, changes in laboratory parameters (hematological and biochemical, including liver function tests) and any other analyses that may be considered necessary. All AEs will be classified according to the NCI-CTCAE, v. 3.0.
PHARMACOKINETIC EVALUATIONS	The PK of plasma PM00104 will be evaluated during the first two infusions of the first cycle with a limited sampling schedule of eight samples. The schedule of sampling per each infusion will be as follows: • T0 (before infusion). • T1 [5 min before the end of the infusion (EOI)]. • T1.5 (1.5 hours after the EOI). • T3 (3 hours after EOI). • T7 (7 hours after EOI). • T24 (24 hours after EOI). • T48 (48 hours after EOI). • T168 (168 hours after EOI).

	PK parameters will be calculated using population methods, after pooling data from this study with data obtained during phase I studies.
PHARMACOGENOMIC EVALUATIONS (only on samples collected in the U.S.)	Inclusion criteria for the PGx substudy: • All patients included in trial PM104-B-001-09 will be eligible. • Only those patients with available tissue samples that voluntarily sign the Informed Consent Form for the PGx substudy will participate. Exclusion criteria for the PGx substudy: • Patients who do not consent to participate in this substudy. Refusal to participate in the PGx substudy will not affect participation in the main trial PM104-B-001-09. The aim of this investigation is to identify and validate molecular markers whose expression may be associated with the clinical outcome of patients treated with PM00104. These molecular markers might allow the identification of those patients who will benefit from the treatment with PM00104, thus improving the health care by an individualized medicine. The following analyses will be done on tumor and blood samples from consenting patients treated with PM00104: ◆ Quantitation of mRNA expression in paraffin-embedded tumor tissue by real-time quantitative reverse transcriptase polymerase chain reaction (PCR) of genes identified during *in vitro* studies as potential biomarkers of response to PM00104. These genes will be selected from BRCA1, ERCC1, XPG, RAD51, TOP2A and TOP1 and other genes related to the mechanism of action of PM00104. ◆ Quantitation of protein expression by immunohistochemistry in tissue microarrays constructed from the patient's paraffin-embedded tumor tissue blocks. The proteins to be determined include XPG, ERCC1, XPA, BRCA1, RAD51, BRCA2, ATM, CDK7, CHK1, MDM2, DNApola, CHK2, DNA-PK, p16, p21, p53, and other proteins related to the mechanism of action of PM00104. ◆ Analysis of single nucleotide polymorphisms (SNP) at the gene XPG will be done, including those at positions 1104, 1080 and 1053 and SNPs of other genes related to the mechanism of action of PM00104.
STATISTICAL METHODS	**Primary Endpoint:** • Overall response rate (ORR), defined as the percentage of patients with confirmed objective response (OR), either complete (CR) or partial (PR) response according to the RECIST.

	Secondary Endpoints: • Progression-free survival rate at four months (PFS4), defined as the percentage of patients who are alive and with no evidence of disease progression at four months after the first study drug administration. • Progression-free survival rate at six months (PFS6), defined as the percentage of patients who are alive and with no evidence of disease progression at six months after the first study drug administration. • Duration of response (DR), defined as the time between the date when the response criteria (PR or CR, the first that is reached) are fulfilled and the first date when disease progression, recurrence or death is objectively documented (taking the smallest measurements documented since the treatment started as reference for progressive disease). • Progression-free survival (PFS), defined as the time from the first day of study treatment to the day of negative assessment (progression or death) or last tumor evaluation. • Overall survival (OS), defined as the time from the first day of treatment to the date of death (or the last day when the patient is known to be alive). Survival will be followed for up to six months after the treatment discontinuation of the last patient. • Safety profile. • PK profile. • PGx profile. **Sample Size Considerations:** In this phase II trial, efficacy of PM00104 will be evaluated in two different groups of patients with endometrial or cervical cancer. Group 1 (endometrial cancer): patients with endometrial cancer who have received one previous systemic chemotherapy line for advanced/metastatic disease (excluding chemosensitizing chemotherapy). A Simon two-stage design will be adopted in this group to test the null hypothesis that the ORR by RECIST is ≤ 10% *versus* the alternative that ORR ≥ 30% (two-sided test; alpha=0.1 and beta=0.1). A maximum of 30 evaluable patients will be included in this group. In a first stage, 10 evaluable patients will be recruited. If one or more (≥ 1) patients achieve an objective response, the accrual in this group will be expanded with 20 additional evaluable patients. If the total number of patients with objective response is 6 or more (≥ 6) in 30 evaluable patients (i.e., an ORR in the whole study of at least 20%), the null hypothesis will be rejected and PM00104 will be considered for further clinical development in endometrial cancer.

	Group 2 (cervical cancer): patients with cervical cancer who have received one previous systemic chemotherapy line for advanced/metastatic disease (excluding chemosensitizing chemotherapy). A Simon two-stage design will be adopted in this group to test the null hypothesis that the ORR by RECIST is ≤ 5% *versus* the alternative that ORR ≥ 20% (two-sided test; alpha=0.1 and beta=0.1). A maximum of 32 evaluable patients will be included in this group. In a first stage, 18 evaluable patients will be recruited. If one or more (≥ 1) patients achieve an objective response, the accrual in this group will be expanded with 14 additional evaluable patients. If the total number of patients with objective response is 4 or more (≥ 4) in 32 evaluable patients (i.e., an ORR in the whole study of at least 12.5%), the null hypothesis will be rejected and PM00104 will be considered for further clinical development in cervical cancer. **Methods of Analysis:** Binomial estimates with exact 95% confidence intervals will be calculated for the analysis of the main endpoint (ORR) and PFS4 and PFS6 rates. Time-to-event endpoints (DR, PFS and OS) will be analyzed according to the Kaplan-Meier method. If relevant, efficacy parameters *versus* baseline covariates will be analyzed and appropriate test will be used (i.e., the Fisher exact test for categorical variables, the log-rank test or Cox regression for time to event variables, etc.). Baseline characteristics, AEs, serious adverse events (SAEs), laboratory evaluations, deaths and the reason for study discontinuations will be analyzed. Continuous variables will be tabulated and presented with summary statistics (i.e., mean, standard deviation, median and range). Categorical variables will be summarized in frequency tables by means of counts and percentages.
DURATION OF STUDY PERIOD (per patient)	Patients will be evaluated at scheduled visits in up to three study periods: • **Pre-treatment:** from signature of informed consent to the first infusion of PM00104. • **Treatment:** from the first infusion of PM00104 to treatment discontinuation plus 30 days. • **Follow-up:** after treatment discontinuation, patients will be followed until all toxicities or their sequelae resolve or stabilize at a level acceptable to the Investigator and the Sponsor. Patients who discontinue treatment without progression will be followed every three months until disease progression, other antitumor therapy or death or until the date of study termination, whichever occurs first. After

	disease progression or after other antitumor therapy, patients will be followed every three months until death or until the date of study termination, whichever occurs first. Patients will be considered to be **on-study** from the signature of the informed consent to the end of follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and in the first 30 days following treatment discontinuation. **Treatment discontinuation** is defined as the day of the last study drug dose administration. Patients will receive PM00104 while it is considered to be in their best interest. Specifically, treatment will continue until: • Disease progression. • Unacceptable toxicity (including any toxicity leading to the need for a third dose reduction or severe hypersensitivity reactions). • Patient refusal. • Intercurrent serious illness. • Protocol deviation with an effect on the risk/benefit ratio of the clinical trial. • Treatment delay > two weeks or impossibility to administer both Day 8 and Day 15 dose on a given cycle (except in case of clear clinical benefit, with the Sponsor's approval). Any subsequent therapies for the patients may be provided off-study according to the Investigator's criteria.
REPLACEMENT OF PATIENTS	Patients must be replaced if they are considered not evaluable for efficacy, i.e., if they are withdrawn from the study due to significant clinical deterioration of unknown reason, hypersensitivity reactions, patient refusal or unrelated AEs without any tumor assessments after the start of study treatment.
PLANNED TRIAL PERIODS	The total duration of the study will be approximately 33 months, including approximately 24 months of active enrolment. Consenting patients will be followed until death, or until the date of study termination, whichever occurs first. • Planned start date (first patient on study): 3Q09. • Planned enrolment period: 24 months. • Planned study termination (clinical cutoff): six months after the last treatment visit of the last evaluable patient included in the study or nine months after the last patient is included, whichever occurs first.

SCHEDULE OF ASSESSMENTS AND PROCEDURES

	Screening	**Treatment (cycle 1 and further cycles)**					**Follow-up (1)**
Study day	**D–28 to D1**	**D1**	**D8 D15**	**D22**	**D28 (=D1 of the next cycle)**	**End of treatment (last dose + 30 days)**	
Study visit window			Within 2 days of pre-specified day				
Written informed consent	Before any study procedure						
Medical history	•						
Complete physical examination	•	•	Repeat if clinically indicated			•	• (9)
ECOG PS	•	•	Repeat if clinically indicated			•	• (9)
Vital signs	•	•	•		•	•	• (9)
Weight and height	•	Repeat if clinically indicated			•	Repeat if clinically indicated	
Hematology	• (2)	• (2)	• (7)	• (7)	• (7)	•	•
Biochemistry A	• (2)	• (2)	• (7)	• (7)	• (7)	•	•
Biochemistry B	• (2)	Repeat if clinically indicated			• (7)	•	•
Calculated creatinine clearance	• (2)	Repeat if clinically indicated			•	Repeat if clinically indicated	
Pregnancy test	• (3)	Repeat if clinically indicated					
ECG	**• (10)**	Repeat if clinically indicated			•	•	•
LVEF (cardiac ultrasound)	**• (10)**	Repeat if clinically indicated			• (8)	•	•
Intercurrent events, concomitant disease and treatments	•	Throughout the “on treatment” period					• (1,9)
Adverse events	NA	Throughout the “on treatment” period					• (1)
Tumor assessment	• (4)	Every other cycle (± 1 week) until PD				•	• (9)
Other tests	•	When indicated, according to the clinical and laboratory context					• (9)
Pharmacokinetics		• (5)	• (5)				
PGx substudy, if patient consented	• (6)						

1. Patients withdrawn with PM00104-related ongoing AEs should be followed with the appropriate tests until their resolution. Beyond 30 days after the last administration of study drug, only those procedures that are relevant to any remaining toxicities need to be performed.

2. Within one week prior to the first administration of PM00104. Repeat on Day 1 of Cycle 1 prior to treatment with PM00104, if the treatment is administered more than one week after the screening test.

   Hematology: differential WBC (neutrophils, lymphocytes), hemoglobin and platelets.

   Biochemistry A: liver function test (ALT, AP, AST, LDH, total and direct bilirubin), creatinine, CPK, troponin I , glucose and serum electrolytes (Na^+, Cl^-, K^+, Ca^{++}, Mg^{++}).

   Biochemistry B: total protein, albumin, amylase and lipase. CPK-MB fraction to be analyzed if CPK and/or troponin I are abnormal. In the case of grade ≥ 3 increase in serum cardiac troponin I, an ECG and cardiac ultrasound will be performed as soon as possible.

3. Pregnancy test, if applicable, within two weeks prior to registration
4. CT-scan or MRI of all measurable/evaluable sites of disease, as per RECIST. Within four weeks prior to the first dose of PM00104. Documentation of PD is mandatory.
5. First two infusions of the first cycle only.
6. Tissue block collection. Additionally, one blood sample will be taken prior to the first infusion of PM00104.
7. To be performed within the two prior days. If NCI-CTCAE grade ≥ 3 occurs, the appropriate chemistry test(s) should be done at least every 2-3 days until recovery.
8. To be performed every other cycle.
9. After discontinuation, patients taken off study without PD should be monitored every three months until PD, death, other antitumor therapy or the predefined date for study termination. After PD, patients should be monitored every three months until death or the predefined date for study termination.
10. All ECGs and LVEFs (ultrasound) will be reviewed by an external cardiologist.

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase-fraction MB; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NA, not applicable; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors; WBC, white blood cells.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ΔT/ΔC	% Ratio of Treated *versus* Control Tumor Volumes
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
βhCGs	Beta Human Chorionic Gonadotrophins
BSA	Body Surface Area
Cmax	Maximum Plasma Concentration
CNIO	Centro Nacional de Investigaciones Oncológicas (Spain)
CNS	Central Nervous System
Cp	Plasma Concentrations
CPK	Creatine Phosphokinase
CPK-MB	Creatine Phosphokinase-Fraction MB
CR	Complete Response
CRF	Case Report Form
CT	Computerized Tomography
CTRT	Chemoradiotherapy
d	Day
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EOI	End of Infusion
EVA	Ethylene Vinyl Acetate
FDA	Food and Drug Administration (United States)
FUP	Follow-up
G-CSF	Granulocyte Colony Stimulating Factor
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage Colony Stimulating Factor
GMT	Greenwich Meridian Time
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
hERG	Human ERG Potassium Channel
HR	Homologous Recombination
i.v.	Intravenous
IB	Investigator's Brochure
IC_{50}	Half-maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Investigational Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intrauterine Device
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction

MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
NA	Non Available-Non Applicable
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NER	Nucleotide Excision Repair
NYHA	New York Heart Association
OR	Objective Response
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PE	Polyethylene
PFS	Progression-free Survival
PFS4	Progression-free Survival Rate at Four Months
PFS6	Progression-free Survival Rate at Six Months
PGx	Pharmacogenomic(s)
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PM00104	Zalypsis®
PP	Polypropylene
PR	Partial Response
PRE TT	Pre-treatment
PS	Performance Status
PTEN	Phosphatase and Tensin Homolog
PU	Polyurethane
PVC	Polyvinyl Chloride
q3wk	Every Three Weeks
q4wk	Every Four Weeks
q.d.	Every Day
q.s.	Quantum Sufficit
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
SAE(s)	Serious Adverse Event(s)
SNP	Single Nucleotide Polymorphism
SOI	Start of Infusion
SPC	Summary of Product Characteristics
STR	Serious Toxicity Rate
TT	Treatment
ULN	Upper Limit of Normality
UPSC	Uterine Papillary Serous Carcinoma
US	Ultrasound
USPI	United States Package Insert
U.S./USA	United States/United States of America
vs.	*Versus*
WBC	White Blood Cells
Wk(s)	Week(s)
WMA	World Medical Association
XPG	Xeroderma Pigmentosum, Complementation group G

1. INTRODUCTION

1.1. ENDOMETRIAL CANCER

Uterine corpus cancer includes endometrial carcinoma (90%) and mixed histology (10%) (1). The 75-80% of endometrial carcinomas are endometrioid adenocarcinomas, with variants such as adenosquamous, villoglandular, ciliated and secretory subtypes. Rare cell types, including uterine papillary serous carcinoma (UPSC), clear cell carcinoma, papillary endometroid carcinoma, and mucinous carcinoma have a later age of onset, greater risk for extrauterine metastases, and poorer prognosis compared with typical low grade adenocarcinomas.

Table 1 outlines the incidence and mortality figures for uterine corpus cancer in the USA and Europe (no statistics are available for endometrial cancer alone). In 2008, it was estimated that 40,100 new cases of uterine corpus cancer will be found in the USA and 7,470 deaths will occur due to this disease (2). Thus, uterine corpus is the first genital cancer in females with respect to estimated new cases in the USA (6% of all cancer cases), and the second cause of gynecologic cancer mortality (3% of deaths due to cancer), immediately after ovarian cancer.

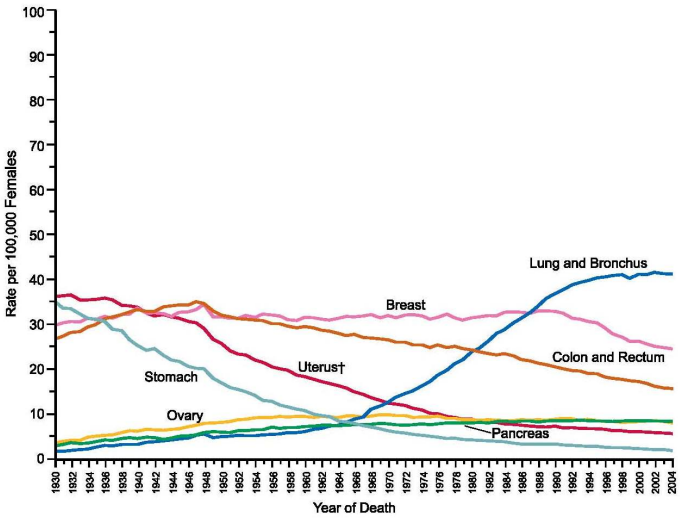
Table 1. Incidence and mortality due to cancer of the uterus (corpus and cervix)§.

	Incidence*	**Mortality****
Uterine corpus cancer		
USA†	40,100	7,470
European Union ††	82,230	25,740
Uterine cervix cancer		
USA†	11,070	3,870
European Union ††	30,560	13,650

*Number of new cases per year.
**Number of deaths per year.
†Source: Jemal *et al.* Cancer statistics, 2008. *CA Cancer J Clin.* 58:71-96 (2008) (2).
††Source: Arbyn *et al*. Burden of cervical cancer in Europe: estimates for 2004 *Ann Oncol* 18:1708-1715 (2007) (3).
§In both statistical analyses/databases, no data for endometrial cancer alone are provided. They are included with other types of cancer characteristic of uterine corpus cancer (uterine sarcoma, etc.).

Cancer of the uterus is among the cancers for which survival has not improved substantially over the past 25 years (Figure 1), making its treatment an important public health issue. The 5-year survival rates are drastically reduced in those patients with regional disease at diagnosis (56%) or with distant disease (17%) (2). Therefore, patients with metastatic disease have a dismal survival.

Figure 1. Annual age-adjusted* cancer death rates among females for selected cancers (USA, from 1930 to 2004).



*Rates are age-adjusted to the 2000 USA standard population. †"Uterus" includes uterine corpus and uterine cervix. Figure drawn from Jemal *et al.* Cancer Statistics 2008.*CA Cancer J Clin.* 58:71-96 (2008) (2)

Most patients with endometrial cancer have stage I disease at diagnosis and, therefore, surgery (usually total abdominal hysterectomy, with bilateral salpingo-oophorectomy) is the treatment of choice (1). Primary radiotherapy is administered for medically inoperable patients and adjuvant radiotherapy is offered for those patients at high risk of recurrence.

For metastatic extra-abdominal disease, palliative therapy including radiotherapy, hormonal therapy, or chemotherapy is generally used with poor results (4).

1.1.1. Treatment of Advanced/Metastatic Endometrial Cancer

Surgery (with or without radiotherapy) is recommended for patients with recurrence at sites without prior radiotherapy or with previous brachytherapy only. Recommended salvage therapy for patients with recurrence at sites previously irradiated includes pelvic exenteration with or without intraoperative radiotherapy, hormonal therapy or chemotherapy (4). Treatment with systemic agents should be considered for those patients with advanced or recurrent disease not amenable to radiation or surgery.

Hormonal therapy for metastatic disease involves mainly the use of progestational agents, although aromatase inhibitors are also being used (4).

Although phase II/III data is limited, chemotherapy for endometrial cancer includes different single agents, such as cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel and doxorubicin (5, 6). Response rates in first-line chemotherapy with these compounds range 20-30% for single-agent regimens and 40-60% for combinations. However, despite these relatively high response rates, most patients progress after a median of 6-9 months and are candidates for second-line therapy. Results of second-

line chemotherapy are generally poor, and only taxanes (e.g., paclitaxel) have shown response rates greater than 20% in this disease setting (Table 2).

Table 2. Antitumor activity of different single-agent therapies administered as second-line chemotherapy in recurrent, advanced endometrial carcinoma.

Agent	Reference	No of patients	Schedule (dose)	Median ORR (%)
Cisplatin	Thigpen *et al.* (7)	25	q3wk (50 mg/m^2)	4.0
Docetaxel	García *et al.* (8)	27	1-hour Day 1, 8 and 15 q4wk (36 mg/m^2)	7.7
Flavopiridol	Grendys *et al.* (9)	26	i.v. bolus Day 1, 2 and 3 q3wk (50 mg/m^2/day)	0.0
Ifosfamide	Sutton *et al.* (10)	52	Daily for 5 days q4wk (1.2 g/m^2)	15.0
Irofulven	Schilder *et al.* (11)	25	Daily for 4 days (11 mg/m^2)	4.0
Ixabepilone	Dizon et al. (12)	NA	NA	12.0
Liposomal doxorubicin	Muggia *et al.* (13)	46	1-hour q4wk (50 mg/m^2)	9.5
Oxaliplatin	Fracasso *et al.* (14)	44	2-hour q3wk (130 mg/m^2)	13.5
Paclitaxel	Lincoln *et al.* (15)	44	3-hour q3wk (200 mg/m^2)	27.3
	Homesley *et al.* (16)	16	1-hour weekly (80 mg/m^2)	26.7
Pyrazoloacridine	Plaxe *et al.*(17)	23*	3-hour q3wk (750 mg/m^2)	4.3
Topotecan	Miller *et al.*(18)	29	Daily for 5 days q3wk (0.5-1.5 mg/m^2)	9.0

*11 of 23 patients pretreated.

NA, non available; ORR; overall response rate; q3wk; every three weeks; q4wk, every four weeks.

Two combination regimens of chemotherapy have been tested in phase III clinical trials in the first line: doxorubicin/cisplatin/paclitaxel (19)) and cisplatin/doxorubicin (19-23)(19-23). The first regimen was the most active, but also the most toxic, in particular with respect to neurotoxicity (24). Overall response rate (ORR) ranged from 42% (cisplatin/doxorubicin) to 57% (doxorubicin/cisplatin/placlitaxel), but the duration of response was relatively short, and the median survival was approximately one year (4). The combination of carboplatin plus paclitaxel has also been investigated in phase II trials, with response rates of 56% to 63% (25, 26). However, all these combinations have not yet proven an improvement in survival or quality of life of patients. In fact, combination chemotherapy regimens in endometrial carcinoma should be approached with care with respect to toxicity. Many women with endometrial cancer are elderly (median age at diagnosis is 60 to 65 years), obese and diabetic. All these factors increase the risk of complications with more intensive chemotherapy. In addition, many of them have had adjuvant pelvic radiotherapy with the consequent limited hematological reserve, and therefore dose-intense regimens should be administered with caution.

Biologic and molecular-targeted therapies have no proven role at this time in the treatment or relapsed or metastatic endometrial carcinoma. The most tantalizing results have been obtained with mTOR inhibitors [temsirolimus (5, 27-29), everolimus (30) and deforolimus (31)], with a response rate in chemotherapy-naïve patients of up to 26% for temsirolimus. Results in pretreated patients are less encouraging, with a clinical benefit rate of 44%, but objective response rate equal or lower than 7% (29, 30).

In summary, despite the use of combinations or novel agents and therapies, responses in patients with advanced/metastatic endometrial cancer are of short duration. Thus, progression-free survival (PFS) of 6-9 months and overall survival (OS) of 12-15 months have been found with first-line chemotherapy (6). As expected, shorter PFS (2 months) and OS (6-8 months) have been found with second-line regimens (8, 13). Therefore, treatment of advanced/metastatic endometrial cancer is a clearly unmet medical need and investigation of new agents is warranted. Results found in phase I studies with PM00104 (Zalypsis®; see Section 1.3.5.4.2) suggest that this novel chemotherapeutic agent can be of value as chemotherapy in this disease setting.

1.2. CERVICAL CANCER

Cervical cancer is a common cancer in women. Squamous cell carcinomas account for about 80% of all cervical cancers (32). Other usual histologies are adenosquamous carcinoma and adenocarcinoma of the cervix.

Advanced cervical cancer is a public health problem even in those countries where screening and treatment of precursor lesions have had a positive impact on this disease. Table 1 shows the incidence and mortality figures for cervical cancer in the USA and Europe. In 2008, it was estimated that 11,070 new cases will be found in the USA and 3,870 deaths will be caused by cervical cancer (2). Despite the figures for new cases of cervical cancer are lower than those of uterine corpus cancer (11,070 *vs.* 40,100), mortality remains higher in this particular cancer type (35% and 45% of all new cases in USA and the European Union will die of their disease, respectively) (2, 3).

Either surgery or radiation therapy are the mainstay of treatment for most cases of cervical carcinoma (32). Surgery is typically reserved for lower-stage disease and smaller lesions. However, despite the efforts in screening and early detection, carcinoma of the uterine cervix continues to present at a relatively locally advanced stage in certain populations, and cisplatin-based concurrent chemoradiation is the current standard therapy for locally advanced disease (32). A large population-based pattern-of-care study conducted in 4,069 patients confirmed a better survival outcome with platinum-based chemoradiotherapy with respect to radiotherapy alone (33).

As mentioned above, survival in patients with uterine (endometrial or cervical) cancer has not improved over the past 25 years despite new treatments. As has been shown for endometrial cancer, the 5-year survival rates in patients with cervical cancer are drastically reduced in those patients with regional disease at diagnosis (67%), but particularly in patients with metastatic disease who have a dismal survival (5-year rate of 23%, and median survival of 6-8 months). In those cases, no potentially curative therapy exists and the focus of treatment is palliation with chemotherapy.

Therefore, there is an unmet need for new active agents to treat patients with advanced/metastatic cervical cancer.

1.2.1. Treatment of Advanced/Metastatic Cervical Cancer

Patients with a localized recurrence of cervical cancer after surgery should be evaluated for radiotherapy for relapse, with salvage rates of 40% in such cases (34). For patients with pelvic recurrence with no prior radiotherapy or with relapsed site outside the previously irradiated field, therapy for relapse includes definitive pelvic radiation and platinum-based chemotherapy with (or without) brachytherapy. Patients with advanced, recurrent cervical cancer or with extrapelvic metastases are the most difficult to treat, and chemotherapy constitutes the best treatment for these patients (32, 35).

Many attempts have been made to identify active agents in advanced, recurrent or persistent cervical cancer: these trials have shown cisplatin as the most active agent (36, 37). However, cisplatin is still capable of generating an objective response rate in only 20-30% of the patients treated, complete responses are rare, and responses are usually partial and of short duration (36). Carboplatin, topotecan and paclitaxel have also been reported as tolerable and efficacious in recurrent cervical cancer (32) and combinations of these agents have been evaluated: the most usual are cisplatin/topotecan (38) and cisplatin/paclitaxel (39). Cisplatin-based combination regimens have produced higher progression-free survival rates over cisplatin alone, and one combination (cisplatin/topotecan) has even prolonged survival without impairment in the quality of life, making these combinations new standard regimens in the setting of advanced, recurrent cervical cancer (38). However, newer agents are needed to move from palliation to cure. Other agents listed in the National Comprehensive Cancer Network (NCCN) Clinical Guidelines for cervical cancer (32) as having shown a partial response and that could be useful as second-line therapy include ifosfamide (40, 41), irinotecan (42) or vinorelbine (43-45) (Table 3). However, antitumor activity is limited and generally of short duration (46). The median PFS with second-line regimens is 2 months, with a dismal median survival of 6 months (35).

Table 3. Antitumor activity of different single-agent therapies in recurrent, advanced cervical cancer.

Agent	Reference	No of patients	Chemotherapy setting	Histology	Schedule (dose)	Median ORR (%)
Etoposide	Rose *et al.* (47)	25	First-line, n=3 Second-line, n=22	Squamous	Single dose, daily 1-21 q4wk (50 mg/m^2/day)	11.8
	Morris et al. (48)	44	First-line, n=25 Second-line, n=19	Squamous (40) Non-squamous (4)	Single dose, daily 1-21 q4wk (37.5 mg/m^2/day)	9.1
Gemcitabine	Schilder et al. (49)	27	First-line, n=13 Second-line, n=14	Squamous	30-min weekly x 3wks +1wke or rest (800 mg/m^2)	8.0
Ifosfamide	Sutton *et al.* (40)	30	First-line, n=1 Second-line, n=29	Squamous	Daily for 5 days q4wk (1.2 g/m^2)	11.1
	Sutton *et al.* (41)	46	NA	Non-squamous	Daily for 5 days q4wk (1.5 g/m^2)	15.0

Agent	Reference	No of patients	Chemotherapy setting	Histology	Schedule (dose)	Median ORR (%)
Irinotecan	Look *et al.* (50)	44	First-line	Squamous	90-min weekly x 4 wks + 2wks of rest (125 mg/m^2)	13.3
	Lhommé *et al.* (51)	55	First-line	Squamous	30-min q3wk (350 mg/m^2)	15.7
	Verschraegen *et al.* (42)	42	Second-line	Squamous	90-min q4wk every 6 wks (125 mg/m^2)	21.0
	Irvin *et al.* (52)	16	Second-line	Squamous	q4wk + 2wks of rest (125 mg/m^2)	0.0
Paclitaxel	McGuire *et al.* (53)	30	First-line	Squamous	24-hour q3wk (170 mg/m^2)	17.0
	Curtin *et al.* (54)	42	First-line, n=37 Second-line, n=5	Non-squamous	24-hour q3wk (170 mg/m^2)	31.0
	Kudelka *et al.* (55)	26	First-line, n=22 Second-line, n=4	Squamous	3-hour q3wk (250 mg/m^2)	21.0
	Homesley *et al.* (16)	28	Second-line	Squamous	1-hour weekly (80 mg/m^2)	10.0
Pemetrexed	Miller *et al.* (56)	29	Second-line	Squamous (19) Non-squamous (10)	10-min q3wk (900 mg/m^2)	15.0
	Ferrandina *et al.* (57)	18*	Second-line	NA	10-min q3wk (500 mg/m^2)	16.7
Topotecan	Muderspach et al. (58)	49	First-line	Squamous	30-min daily x 5 consecutive days q4wk (1.5 mg/m^2)	18.6
	Bookman *et al.* (59)	45	First-line, n=11 Second-line, n=34	Squamous	30-min daily x 5 consecutive days q3wk (1.5 mg/m^2)	12.5
Vinorelbine	Morris *et al.* (44)	35	First-line	Squamous	20-min weekly (30 mg/m^2)	18.0
	Lhommé et al. (60)	46	First-line	Squamous/ adenocarcinoma	20-min weekly (30 mg/m^2)	17.8
	Muggia *et al.* (45)	30	First-line, n=18 Second-line, n=12	Non-squamous	Day 1 and 8 q3wk (30 mg/m^2)	7.1
	Muggia *et al.* (43)	44	Second-line	Squamous	Day 1 and 8 q3wk (30 mg/m^2)	13.7

*Preliminary data after a first stage.
No of patients refers to enrolled patients.
NA, non available; ORR; overall response rate; q3wk; every three weeks; q4wk, every four weeks.

With respect to cisplatin-based combinations, chemotherapy regimens such as cisplatin/topotecan or cisplatin/paclitaxel have been extensively investigated in clinical studies. Both topotecan and paclitaxel in combination with cisplatin have yielded superior response rates and longer PFS without diminishing patient quality of life. However, only the combination of cisplatin and topotecan has improved OS and has received regulatory approval both in the USA and the European Union in this setting (61, 62). A randomized phase III study investigated the combination of cisplatin plus topotecan *vs.* cisplatin alone in recurrent or persistent cervical cancer and found the combination regimen superior to single-agent cisplatin with respect to ORR (27% vs. 13%), PFS (4.6 *vs.* 2.9 months) and median OS (9.4 *vs.* 6.5 months) (38). Other randomized phase III study compared cisplatin plus paclitaxel *vs.* cisplatin alone and showed a higher ORR (36% *vs.* 19%) and longer PFS (4.8 *vs.* 2.8 months), although no improvement was seen in median survival (39).

Despite the therapeutic benefit obtained with the cisplatin/topotecan combination, most patients do not respond to treatment and median survival is still less than one year (9 months). Therefore, investigation of new agents is clearly necessary to incorporate new agents to existing chemotherapy in order to improve the treatment

results of advanced, persistent or recurrent cervical cancer. Results found in phase I studies with PM00104 (Zalypsis®; see Section 1.3.5.4.2) suggest that this novel chemotherapeutic agent can be of value as chemotherapy in this disease setting.

1.3. PM00104 (ZALYPSIS®)

PM00104 (Zalypsis®) is a new synthetic alkaloid, which was selected for clinical development as an antineoplastic agent because of its broad *in vitro* cytotoxic activity against human solid and non-solid tumor cell lines, its *in vivo* activity in human tumor xenografts, as well as an acceptable non-clinical toxicology profile. The main bases for the preclinical and clinical development of PM00104 are shown here, although complete details and references can be found in the Investigator Brochure (IB), provided in a separate folder.

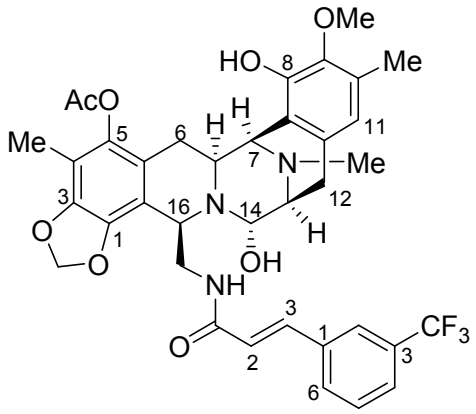
1.3.1. Chemical Structure and Formulation

PM00104 (Figure 2) is currently produced by chemical synthesis.

Molecular formula: $C_{37}H_{38}F_3N_3O_8$.

Molecular weight: 709.708

Figure 2. Chemical structure of PM00104.



1.3.2. Mechanism of Action

Preliminary data on mechanism of action suggest that PM00104 exhibits effects on the cell cycle, and displays DNA-binding properties as well as transcriptional inhibition.

Structure-activity relationship studies have led to the notion that the binding of PM00104 to DNA is a critical event in its cytotoxic action, but that an additional non-DNA target may be required to elicit an optimal antitumor response.

PM00104 displayed strong inhibition of the transcriptional response, with a similar pattern at all the concentrations studied. In addition, PM00104 strongly inhibited the activation of the transcription of other genes such as MDR1, a gene critically involved in resistance to many chemotherapeutic agents, without affecting constitutive transcription.

More details on mechanism of action can be found in Section 1.3.6.1 (Rationale for the pharmacogenomic substudy).

1.3.3. Preclinical Data

In vitro, PM00104 showed strong anti-proliferative activity against most tumor types at nano-to-picomolar concentrations (Table 4).

Table 4. *In vitro* activity of PM00104.

Type	Tumor	Cell line	IC_{50} (M)
Solid	**Bladder**	5637	$8.6 \cdot 10^{-09} – 1.1 \cdot 10^{-09}$
	Breast	BT-474	$6.2 \cdot 10^{-07} – 8.2 \cdot 10^{-07}$
		MX-1	$4.7 \cdot 10^{-06} – 8.5 \cdot 10^{-06}$
	Colon	HT-29	$1.1 \cdot 10^{-08} – 7.7 \cdot 10^{-07}$
	Gastric	Hs746T	$2.1 \cdot 10^{-08} – 5.5 \cdot 10^{-11}$
	Kidney	768-O	$1.0 \cdot 10^{-08} – 2.1 \cdot 10^{-09}$
	Liver	SK-HEP-1	$2.2 \cdot 10^{-07} – 2.3 \cdot 10^{-07}$
	Lung	A459	$3.0 \cdot 10^{-06} – 4.8 \cdot 10^{-06}$
	Melanoma	SK-MEL-28	$1.7 \cdot 10^{-08} – 2.0 \cdot 10^{-09}$
	Ovarian	SK-OV-3	$1.7 \cdot 10^{-06} – 1.5 \cdot 10^{-05}$
	Pancreas	PANC-1	$7.9 \cdot 10^{-08} – 2.3 \cdot 10^{-09}$
	Prostate	DU-145	$2.7 \cdot 10^{-06} – 4.2 \cdot 10^{-06}$
		LNCaP	$7.5 \cdot 10^{-08} – 1.1 \cdot 10^{-08}$
		PC-3	$4.2 \cdot 10^{-08} – 6.8 \cdot 10^{-07}$
	Sarcoma	A-673	$1.6 \cdot 10^{-12} – 2.0 \cdot 10^{-12}$
		CHSA	$1.8 \cdot 10^{-08} – 1.0 \cdot 10^{-09}$
		OSA-FH	$1.5 \cdot 10^{-08} – 4.1 \cdot 10^{-07}$
		SK-LMS-1	$8.7 \cdot 10^{-07} – 2.2 \cdot 10^{-06}$
		SW-684	$2.7 \cdot 10^{-06} – 3.7 \cdot 10^{-06}$
	Thyroid	SW-579	$1.1 \cdot 10^{-08} – 2.3 \cdot 10^{-09}$
Non-solid	**Leukemia**	HL-60	$5.4 \cdot 10^{-08} – 8.6 \cdot 10^{-08}$
		K-562	$9.4 \cdot 10^{-09} – 1.3 \cdot 10^{-08}$
	Lymphoma	H9	$3.7 \cdot 10^{-11} – 2.0 \cdot 10^{-9}$
		MC116	$3.9 \cdot 10^{-08} – 2.5 \cdot 10^{-08}$
		U937	$1.4 \cdot 10^{-07} – 2.1 \cdot 10^{-07}$

Source: Investigator's Brochure.

Antitumor activity of PM00104 was confirmed *in vivo* in most cell lines (Table 5).

Table 5. Antitumor activity of PM00104 in human athymic mouse xenografts

Tumor type, cell line	Route and schedule	Dose levels mg/kg (mg/m^2)	Antitumor effect (optimal day)
Breast, MX-1	i.v., q.d. x 1	0.75 (2.25)	-64% ΔT/ΔC (Day 9)*
Colon, HT-29	i.v., q.d. x 1	0.75 (2.25)	47% ΔT/ΔC (Day 7)§
Kidney, MRI-H-121	i.v., q.d. x 1	0.75 (2.25)	7% ΔT/ΔC (Day 6)*
Ovary, SK-OV-3	i.v., q.d. x 1	0.75 (2.25)	60% ΔT/ΔC (Day 6)
Prostate, PC-3	i.v., q.d. x 1	0.75 (2.25)	2% ΔT/ΔC (Day 7)*
Gastric, MRI-H-254	i.v., q.d. x 1	0.75 (2.25)	14% ΔT/ΔC (Day 15)*

*$p < 0.05$, statistically significant compared to control cohort. §$p < 0.06$, trend to significance.
q.d., every day; ΔT/ΔC = % ratio of treated versus control tumor volumes.
Source: Investigator's Brochure.

PM00104, given by intravenous (i.v.) injection, produced toxicological effects typical of cytotoxic antitumor agents. Tissues containing cells with a high turnover rate were especially targeted in rats and dogs, i.e., bone marrow, reticuloendothelial system, and gastrointestinal tract, as well as the liver, the reproductive system and lesions in the injection site. Most toxicities were reversible or in repair at the end of an acute toxicity evaluation. Toxicological effects were more severe when the compound was given as a multicycle 24-hour infusion in rats and dogs. In the fractionated dose studies performed so far, PM00104 was well tolerated when administered to rats and dogs at levels based on dividing the maximum tolerated dose (MTD) calculated after single administration by a factor of five or three, for five consecutive days or three consecutive weeks, respectively. PM00104 displayed less liver toxicity when administered using fractionated daily doses compared to single bolus administration. In rats receiving PM00104 at MTD levels (single administration), increases in liver function markers as well as histology findings related to liver injury were seen. However, these findings were not detected in those animals which received an equivalent total dose but in a fractionated five consecutive daily schedule of PM00104. Regardless of the dosing schedule, toxicity related to hematopoietic and thymus systems were observed.

With respect to the safety pharmacology of PM00104, none of the observations regarding the alterations triggered by PM00104 on either neurotoxicity, cardiovascular or respiratory function, raised any concern. For multicycle studies, PM00104 was well tolerated in rats and dogs at the MTD values when administered as a bolus. However, the administration of two (on Days 1 and 15) 24-hour infusions of PM00104 in rats resulted in deaths occurring at the higher dose levels studied. Histology evaluation revealed hemorrhage, necrosis and mineralization of the heart in many of the early dead animals, accompanied by degeneration in the animals treated at the highest doses. PM00104 appears to be more toxic after multiple 24-h administration compared to either single 24-h or single/multiple bolus administration in rats and dogs.

In the human ERG potassium channel (hERG) assay, after a 5 min exposure of HEK293 cells stably transfected with hERG cDNA to a concentration of 15μM of PM00104, inhibition of the hERG tail current was complete. Increasing concentrations of PM00104 (0.01, 0.03, 0.1, 0.3 and 3 μM) produced changes which were fitted into a sigmoidal function, with a calculated IC_{50} of 0.4 μM (0.28 μg/mL), well above the C_{max} found in animals.

As a measure of precaution and to ensure the safety of the patients, closer cardiac monitoring was performed during the phase I clinical development.

1.3.4. Metabolism

In the early stages of drug development, several *in vitro* studies were carried out to assess the biotransformation pathways of PM00104 in humans and other animals (63). These studies indicated that PM00104 underwent extensive hepatic microsomal-mediated metabolism in all animal species, including man. Measurement of PM00104 in urine samples was not possible due to the instability of this drug in this medium.

1.3.5. Clinical Data

The clinical development program includes four phase I clinical trials aimed to assess five different schedules of administration in patients with solid malignancies or lymphoma for which no standard therapy would reasonably be expected to result in cure or palliation.

The recommended doses for phase II studies and dose-limiting toxicities (DLTs) found in these four phase I studies are summarized in Table 6. The recommended dose [b] for phase II studies found in the study PM104-A-004-05 for the schedule (PM00104 administered on Day 1, 8 and 15 every four weeks; d1, d8 and d15; q4wk) to be used in the current clinical trial (PM104-B-001-09) was 2 mg/m^2.

Table 6. Summary of the clinical program of PM00104.

Protocol (schedule)	Sites	Included patients	RD (mg/m^2)	Dose intensity at the recommended dose (mg/m^2/week)	DLTs	Status
PM104-A-001-04 (1-hour and 3-hour Day 1 q3wk)	2 (Europe)	27	3.0 (1-hour)	1.0	• Dose level 6 (3.6 mg/m^2, MTD): grade 3 nausea, grade 3 vomiting despite antiemetic treatment, grade 3 asthenia, grade 4 thrombocytopenia, grade 4 neutropenia and grade 3 transaminase increase*. •	Cohort closed. (64)
		15	Not reached** (3-hour)	***	• Dose level 1 (1.8 mg/m^2): grade 3 hypotension.	Cohort ongoing.

[b] Doses in phase I trials were expressed in μg/m^2, while for phase II development, doses will be expressed in mg/m^2 for simplification.

Protocol (schedule)	Sites	Included patients	RD (mg/m^2)	Dose intensity at the recommended dose (mg/m^2/week)	DLTs	Status
PM104-A-002-05 (1-hour Day 1-5 q3wk)	2 (USA)	12	Not reached†	-	• No DLTs were found.	Prematurely closed****.
PM104-A-003-05 (24-hour Day 1 q3wk)	2 (Europe)	37	4.0	1.3	• Dose level 2 (2.6 mg/m^2): grade 3 transaminase increase • Dose level 6 (3.2 mg/m^2): grade 3 tumor and muscle pain and stiffness • Dose level 7 (4 mg/m^2, RD): grade 3 asthenia and grade 4 neutropenia and thrombocytopenia • Dose level 8 (5 mg/m^2, MTD): grade 4 thrombocytopenia, grade 4 neutropenia > 5 days of duration, grade 3 nausea and vomiting.	Closed
PM104-A-004-05§ (1-hour Day 1, 8 and 15 q4wk)	2 (Europe)	49	2.0	1.5	• Dose level 7 (2 mg/m^2, RD): grade 4 lipase increase. • Dose level 8 and 9 (2.5 and 3.0 mg/m^2, MTD): grade 3/4 asthenia, grade 3 nausea, grade 1 neutropenia and thrombocytopenia leading to two missing infusions, grade 3 febrile neutropenia, grade 3 anemia, grade 4 neutropenia, grade 4 thrombocytopenia and grade 4 leukopenia.	Closed (65)

* Additionally, grade 4 troponin I increase without cardiac symptoms or ECG alterations was also reported (no DLT).
**The highest dose level reached up to December 2008 was 3.5 mg/m^2 (three patients enrolled).
***Recommended dose not achieved; dose intensity is expected to be 1.3 mg/m^2/week.
****Prematurely closed due to low recruitment and unpractical dosing schedule.
†The highest dose level reached was 0.475 mg/m^2/day.
§This schedule is the same than that used in the current phase II study: PM104-B-001-09.
In all studies, escalating dose cohorts are 1 to 3-6 patients per dose level. DLT, dose-limiting toxicities; ECG, electrocardiogram; MTD, maximum tolerated dose; RD, recommended dose; q3wk, every 3 weeks; q4wk, every 4 weeks

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1.3.5.1. Clinical Safety Data

One hundred and forty patients have been included in phase I trials with PM00104 as of December 2008. Safety data collected from these patients registered in these four phase I clinical trials show gastrointestinal and general disorders (nausea, asthenia, vomiting, anorexia, injection site reactions and diarrhea) as the most frequent PM00104-related adverse events (AEs). Most of these AEs were mild to moderate (i.e., grade ≤2) and recovered without sequelae. Prophylactic antiemetic therapy with dexamethasone plus metoclopramide before the infusions was mandatory, after the emetic events and the DLT observed in the clinical trial PM104-A-001-04 (Table 6).

With respect to hematological events, decrease in blood cell counts have been observed (a toxicity expected according to preclinical toxicology results), especially at the highest dose levels. In most cases, these hematological events were mild to moderate, transient and not associated with clinical manifestations, such as fever, infection or hemorrhages.

With respect to biochemical events, severe increases in liver transaminases were rare and no grade 4 cases were reported. The laboratory abnormalities usually recovered within few days and no concomitant symptoms were reported.

As previously mentioned, closer cardiac monitoring was included in the clinical phase I program as a measure of precaution due to some findings in preclinical studies. Cardiac-related disorders found in these phase I studies have consisted of elevations of cardiac troponin I without other symptoms or relevant electrocardiogram (ECG)/echocardiography (ECHO) alterations. Four patients treated in the study PM104-A-004-05 (1-hour Day 1, 8 and 15 q4wk) had grade 4 troponin I increase at the highest dose levels: 2.0 mg/m^2 (n=2), 2.5 mg/m^2 (n=1) and 3.0 mg/m^2 (n=1). None of them had cardiac AEs, abnormal ECG or decrease in left ventricular ejection fraction (LVEF) at the same time than troponin I increase, except one patient treated with 3.0 mg/m^2 who had grade 1 sinus tachycardia and a slight shortening of the QT interval in the ECG, which recovered by the next cycle. These events were considered not relevant by the investigators and by an external cardiologist who evaluated these cases. ECGs performed as per study protocols before and after each infusion of PM00104 have been reviewed by an external cardiologist and no evidence of cardiotoxicity has been reported. However, close clinical and investigational monitoring of cardiac safety will be continued in subsequent studies with PM00104.

No toxic deaths have occurred in the phase I studies with PM00104.

1.3.5.2. Results of PM104-A-004-05 trial

This phase I study evaluated the PM00104 schedule (d1, d8 and d15; q4wk) to be used in the current phase II clinical trial (PM104-B-001-09). As of December 2008, 49 patients with malignant solid tumors have been enrolled and treated at the participating institutions (Institut Gustave Roussy, Paris, France and Newcastle General Hospital-Northern Centre for Cancer, Newcastle, United Kingdom). The starting dose was 0.075 mg/m^2. The dose escalation was increasing at a 100% rate from levels 1 to 4, and at 50% thereafter. No DLTs were documented until dose level 9 (3.0 mg/m^2), in which two DLTs were reported. Upon agreement with the investigators, an intermediate dose between this level and the next lowest (2.0 mg/m^2) was proposed and subsequent patients were enrolled and treated with a dose of 2.5 mg/m^2. Three out of eight patients treated with this dose had DLT; therefore, this level and the previously tested next highest were considered maximum tolerated dose (MTD) and the dose of 2.0 mg/m^2 was defined as the recommended dose (RD). See detail of DLTs in Table 6.

1.3.5.3. Clinical Efficacy Data

Out of 140 patients evaluated, no objective response as per the Response Evaluation Criteria in Solid Tumors (RECIST) was observed; however, 20 disease stabilizations lasting longer than 3 months have been documented, most of them of clinical value due to being observed in heavily pretreated patients with progressive disease before

treatment. Indeed, some patients experienced reduction of tumor mass although not enough to be qualified as tumor response (i.e., with tumor shrinkage <20%). All patients had previously received chemotherapy and many of them had been heavily pretreated. The proportion of disease stabilizations was similar in all five schedules analyzed; thus, the antitumor activity of PM00104 appears to be independent of the administration regimen used. Remarkably, two patients with progressing advanced cervix carcinoma had disease stabilization lasting for more than 6 months (see Table 7 in next section).

1.3.5.4. Evidence for Antitumor Activity against Endometrial Cancer and Cervical Cancer in the Phase I Clinical Development of PM00104

Preliminary evidence of antitumor activity was found during the phase I program of PM00104 in one patient with endometrial cancer and in three patients with cervical cancer (Table 7). All four patients had disease stabilization of their previously progressive disease, and treatment was well tolerated, with the exception of injection site reactions that nevertheless allowed treatment continuation. Central venous catheter was not a requisite for infusion in phase I trials, but it is mandatory in the current study protocol (see Section 7.2.1).

Table 7. Characteristics of patients with endometrial and cervical cancer showing clinically meaningful disease stabilization with PM00104 in phase I trials.

PM00104 dose (mg/m²)/schedule	Age	ECOG PS	Tumor type	No. of prior regimens (including CTRT)	TTP/PFS last prior treatment (months)	Agent (last treatment)	Best response (last treatment)	% tumor shrinkage	No. of cycles received	TTP** (months) / best response with PM00104
0.318 / 1-hour Day 1-5 q3wk	68	1	Endocervix adenocarcinoma	3	6.9	Cisplatin/topotecan	SD	12.5%	24	10.9 / SD
0.212 / 1-hour Day 1-5 q3wk	54	1	Endocervix adenocarcinoma	2***	6.7	Cisplatin/topotecan	SD	1.4%	11	7.9 / SD
0.15 / 1-hour Day 1, 8 and 15 q4wk	51	1	Squamous carcinoma of cervix	1	30.4	Cisplatin (as chemosensitizing)	Not known	-	4	3.4 / SD
3.2 / 24-hour Day 1 q3wk	61	0	Endometrium adenocarcinoma	3	1.2	Investigational drugs	PD	12.5%	4	2.8 / SD

*Not clearly stated if primary tumor was endocervix or endometrium with extension to the endocervix. **Patients ordered by TTP.

***Cetuximab monotherapy (only one cycle) was also administered with non-evaluable response.

ECOG, Eastern Cooperative Oncology group; PD, progressive disease; PFS, progression-free survival; PS, performance status; CTRT, chemoradiotherapy; SD, stable disease; TTP, time to progression.

1.3.5.4.1. Endometrial Cancer

- Study PM104-A-003-05: In this phase I study, the patients were treated with PM00104 administered i.v. over 24-hour every three weeks.
    - A 61-year-old patient with endometrium adenocarcinoma had two target lesions of 45 mm in the peritoneum at study entry. The patient had been previously treated with surgery (abdominal hysterectomy plus double anexectomy and lymphadenectomy) and systemic therapy with tamoxifen,

epirubicin and two investigational drugs. Time to progression (TTP) with last prior treatment was 1.2 months and best response was disease progression. This patient received four cycles of PM00104 3.2 mg/m^2 every three weeks (1.07 mg/m^2/week) and had disease stabilization (tumor shrinkage of 12.5%), with TTP of 2.8 months.

1.3.5.4.2. Cervical Cancer

Three patients with advanced cervix carcinoma had disease stabilization during the phase I program of PM00104: two patients in study PM104-A-002-05 and one patient in study PM104-A-004-05.

- Study PM104-A-002-05: In this phase I study, the patients were treated with PM00104 administered i.v. over 1 hour daily for 5 days, every three weeks.
  - A 54-year-old patient with adenosquamous carcinoma of the endocervix had multiple lymph nodes (10-20 mm each) as site of the disease at study entry. This patient had had prior treatment with adjuvant cisplatin concomitant with radiotherapy of pelvis, para-aortic and cervical region previous to surgery (fine needle aspiration of the right retroperitoneum and left supraclavicular lymph node). The patient had complete response as best response, with disease progression after 24 months. Later, two lines of systemic therapy for advanced disease (cisplatin with cetuximab, with non-evaluable response; cisplatin with topotecan, with stable disease as best response lasting 6.7 months) were administered. This patient received 11 cycles of PM00104 0.212 mg/m^2/day and had disease stabilization (non-significant tumor shrinkage), with TTP of 7.9 months. She discontinued the study due to disease progression in a left supraclavicular lymph node, which required palliative radiotherapy.
  - A 68-year-old patient with adenosquamous carcinoma of the endocervix had multiple lung nodes (10-30 mm each) as site of the disease at study entry, and prior treatment with surgery and two systemic lines for advanced disease: cisplatin plus radiotherapy of pelvis inguinal region (complete response, with disease progression after 28 months), and cisplatin plus topotecan, with stable disease lasting 6.9 months. This patient received 24 cycles of PM00104 0.318 mg/m^2/day and had disease stabilization as best response (tumor shrinkage of 12.5%), with TTP of 10.9 months.

  In these two cases, clear disease progression was documented before treatment with PM00104. According to the investigator, it was difficult to determine (at least, in the second case) whether the tumor origin was the endocervix or the endometrium (with later extension to the endocervix).

- Study PM104-A-004-05: In this phase I study, the patients were treated with PM00104 administered i.v. over 1 hour on Day 1, 8 and 15 every four weeks (the same schedule planned for the current phase II study protocol).
  - A 51-year-old patient with cervical cancer had a left latero-pelvic lesion of 55 mm at study entry. This patient had had previous treatment with surgery (large hysterectomy) followed by adjuvant cisplatin and concomitant pelvic radiotherapy (best response was unknown). The patient received four cycles of PM00104 0.150 mg/m^2/week. This patient had disease stabilization as best

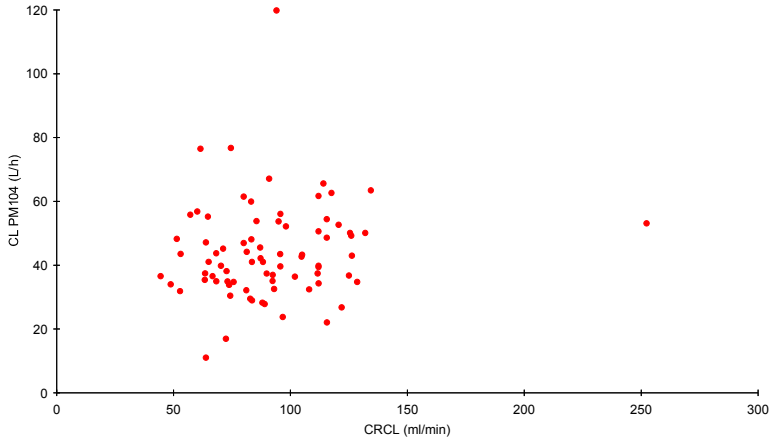
response, with a TTP of 3.4 months. She discontinued the study due to disease progression in non-target lesions (uretheral dilatation).

1.3.5.5. Pharmacokinetic Data

1.3.5.5.1. Renal Function and PM00104 Clearance

In vitro studies indicated that PM00104 underwent extensive hepatic microsomal-mediated metabolism (see Section 1.3.4). The analysis of pharmacokinetic (PK) data obtained during phase I studies has shown no relationship between the renal function of the patient (as measured by clearance of baseline creatinine) and PM00104 clearance (Figure 3).

Figure 3. Relationship between creatinine clearance and PM00104 clearance from patients trated in phase I studies.



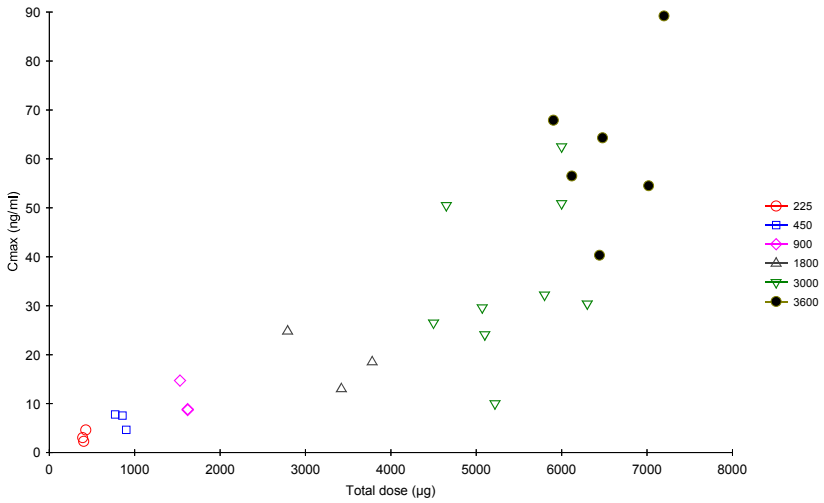
CLPM104, clearance of PM00104; CRCL, creatinine clearance.

All these data suggest an unlikely role of the kidney in PM00104 clearance. According with this preliminary evidence, calculated creatinine clearance for inclusion criteria (see Section 4.1) and for retreatment (see Section 7.2.2, Table 11) was established as ≥ 30 ml/min (using the Cockcroft and Gault formula, see Appendix 3. Cockcroft and Gault Formula).

1.3.5.5.2. PK/PD Analysis of Neutropenia Associated to Treatment with PM00104

Preliminary PK data from the aforementioned phase I clinical trials showed a lack of linearity between total dose and maximum PM00104 plasma concentration (C_{max}) at the higher tested doses (Figure 4). In particular, non-linear PK affecting both C_{max} and area under the curve (AUC) was found when infused using the 1-hour q3wk schedule at doses higher than 3,000 µg/m^2 (i.e., 3 mg/m^2). Such disproportional, higher C_{max} or AUC at the highest total doses might result in an increase in the incidence and/or severity of toxic events associated to PM00104 treatment, like neutropenia or thrombocytopenia.

Figure 4. Total dose *vs.* maximal plasma concentration (grouped by dose level after first cycle of treatment in patients with 1-hour, day 1, q3wk PM00104 infusion).



Source: Investigator's Brochure.

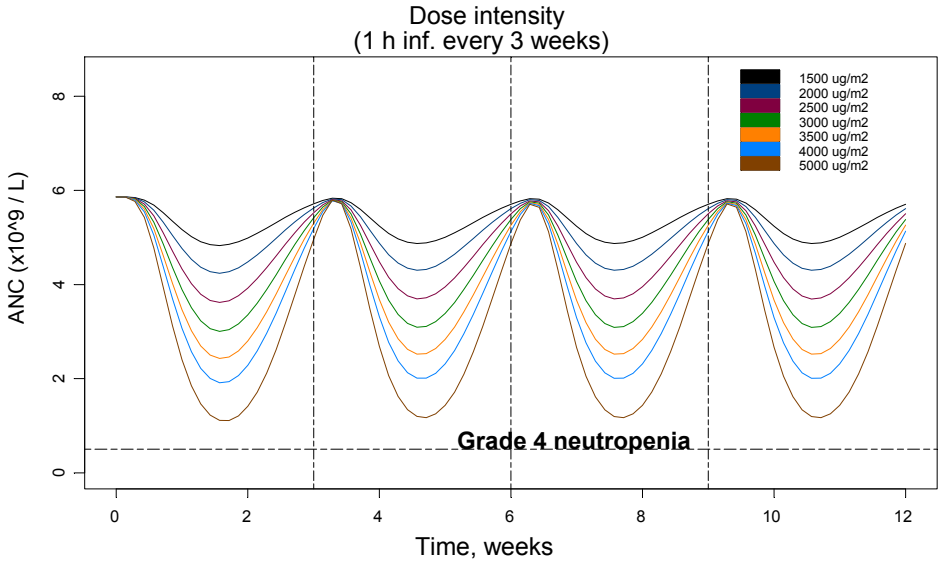
To check the effect of PM00104 dose intensity, density and duration on toxic events, a preliminary, longitudinal population pharmacokinetic/pharmacodynamic (PK/PD) analysis of the relationship between PM00104 exposure and absolute neutrophil count (ANC) was conducted with data from 78 patients from four phase I clinical trials with PM00104 administered as a single agent. A total of 1,332 plasma samples and 1,058 ANC measurements were included in this analysis.

The pharmacokinetic part of the population model was defined by a 3-compartment model with linear elimination from the central compartment and linear transfer constants between compartments. The PK/PD model comprised a trabectedin-sensitive progenitor cell compartment, linked to the peripheral blood compartment, through three transition compartments representing the maturation chain in the bone marrow. To capture the rebound effect due to endogenous growth factors, the model included a feedback mechanism. The model estimated three system-related parameters: ANC at baseline, mean transit time in bone marrow, and a feedback parameter. PM00104 plasma concentrations (Cp) were assumed to reduce the proliferation rate and/or to increase the killing rate of the progenitor cells according to the function αCp^{β}. The model was qualified and simulations were undertaken to evaluate the neutropenia schedule dependency. NONMEM software was used to perform the modelling and simulation analyses.

The extent and time-course of neutropenia following the five different dosing regimens of PM00104 tested in phase I studies were well predicted by this semi-physiological PK/PD model. The simulations indicated that PM00104 dose and dosing interval, but not infusion duration, are the main determinants of the neutropenia severity and duration. The model predicted the time-course of the ANC and confirmed that neutropenia is reversible, short-lasting, and non-cumulative.

The unpublished results of this PK/PD analysis showed a non-linear relationship between PM00104 dose intensity and the ANC time-course. Therefore, increases in the PM00104 dose for a determined, fixed infusion time could result in decreases in the neutrophil nadir higher than those expected for a proportional relationship with exposure (Figure 5).

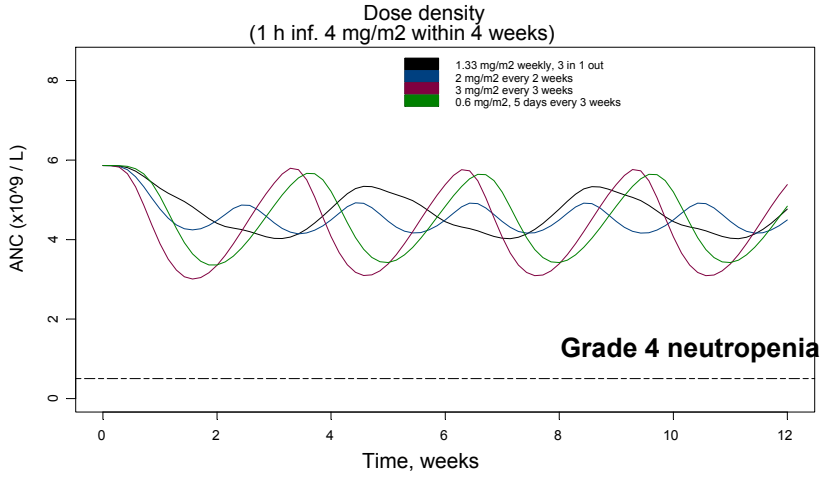
Figure 5. Effect of PM00104 dose intensity on neutropenia.



ANC, absolute neutrophil count; data shown for the PK/PD model with the 1-hour infusion every 3 weeks schedule. Dose intensity increased from 1500 to 5000 µg/m^2/week (i.e., 1.5 to 5.0 mg/m^2/week).

This PK/PD analysis also showed that the severity of neutropenia associated with PM00104 treatment might be reduced by using treatment regimens with a more frequent dosing for a given total, cumulative dose (i.e., more dense regimens, such as weekly). Thus, large-dose and less frequent dosing regimens (e.g., one single dose administered every three weeks) might lead to a more severe neutropenia (Figure 6).

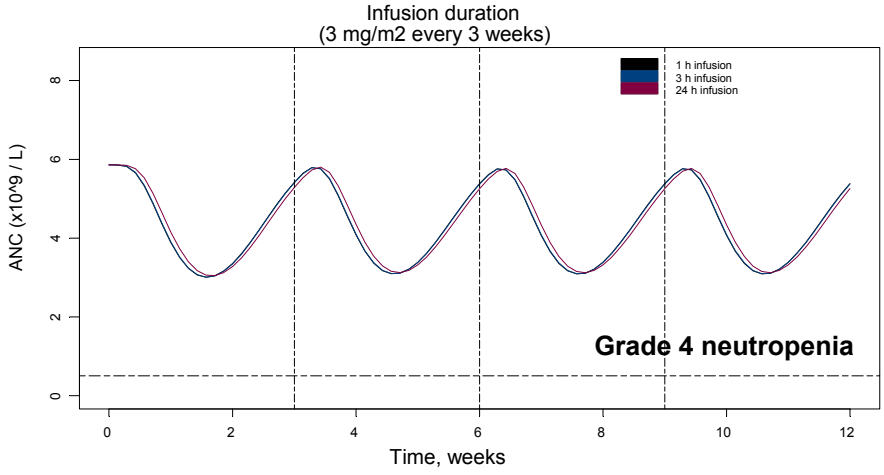
Figure 6. Effect of PM00104 dose density on neutropenia.



ANC, absolute neutrophil count; data shown for the PK/PD model with the 1-hour infusion every 4 weeks schedule at a fixed dose of 4 mg/m^2. Dose intensity increased from 1500 to 5000 µg/m^2/week (i.e., 1.5 to 5.0 mg/m^2/week).

This PK/PD analysis also showed that duration of the PM00014 infusion had a negligible effect on the severity of neutropenia (Figure 7).

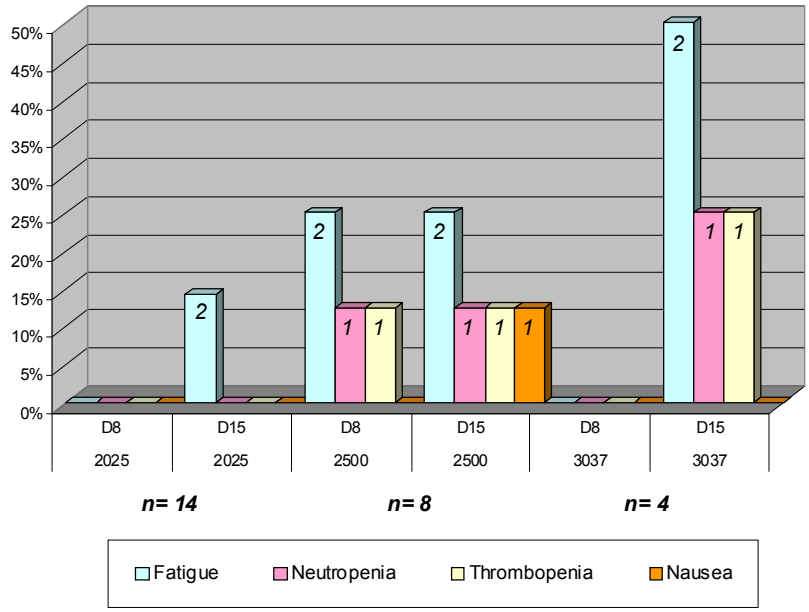
Figure 7. Effect of PM00104 infusion duration on neutropenia.



ANC, absolute neutrophil count; data shown for the PK/PD model with the every three weeks schedule at a fixed dose of 3 mg/m^2 and varying the infusion time from 1 hour to 24 hour.

In accordance with the PK/PD modeling discussed above, preliminary analysis of data from the phase I study PMA104-004-05 shows that the recommended dose (2 mg/m^2) had a low rate of grade 3/4 neutropenia and a low rate of skipped doses due to toxic events and, of note, no skipped doses due to neutropenia (Figure 8).

Figure 8. Skipped doses due to toxicity in the phase I study PMA104-004-05 evaluating the same schedule planned for the current phase II study protocol: PM00104 over 1 hour on Day 1, 8 and 15 every four weeks.



1.3.6. Pharmacogenomic Data

During the past 30 years medical oncologists have focused on optimizing the outcome of cancer patients, developing new antitumoral agents and defining new prognostic factors as well as integrating more effective supportive care measures. However, clinical anticancer strategies indicate that conceptually active therapies benefit just a small proportion of patients; thus, there is a need to expose a large cohort of patients to antitumor treatments to obtain benefit in just a fraction of them.

Molecular targeted therapies and personalized cancer therapies are concepts that are raising expectations in anticancer drug development as a consequence of the genomics technology developed and our improved understanding of cancer at the molecular level.

Pharmacogenomic studies are aimed at identifying prognostic biomarkers that can help to define subpopulations of patients who will, or will not, benefit from a particular therapy. These molecular markers of response to the drugs are not exclusive of the so-called “targeted therapies”, but have also been identified in widely used cytotoxic agents. Representative examples include the relation between thymilydate synthase mRNA expression and response and survival with antifolates (66), beta tubulin III mRNA levels and response to tubulin interacting agents (67), PTEN methylation and resistance to irinotecan (68), and STAT3 overexpression and resistance to epidermal growth factor receptor (EGFR) interacting agents (69).

During the last five years, PharmaMar has implemented a translational research program oriented to the identification of molecular markers correlated with the

response to the anticancer agents that PharmaMar is currently developing. Based on the experimental studies that indicate that there is an increased sensitivity to trabectedin in tumors with efficient Nucleotide Excision Repair and deficient Homologous Recombination Repair DNA repair machinery, the expression of a set of DNA repair genes was analyzed in a retrospective cohort of sarcoma patient tumor samples (70). The main result obtained was the identification of the levels of expression of the gene BRCA1 as a marker that correlates with longer progression-free survival and overall survival after the treatment with trabectedin. This fact, which nowadays has been validated in greater patient samples cohort, opens the possibility of identifying before to treatment those patients that would benefit from the treatment of trabectedin in a prospective fashion.

These very promising results are the founding for a more exhaustive research for molecular markers of tumor response to treatment that will in the future allow a real personalized antitumoral medicine.

1.3.6.1. Rationale for the Pharmacogenomic Substudy Associated to PM104-B-001-09

PM00104 is a novel synthetic antineoplastic agent currently in phase I clinical development. This agent has strong antitumor activity in a wide variety of tumor lines *in vitro* and *in vivo*. Preliminary data suggest that PM00104 has DNA binding properties, induces cell cycle arrest and inhibits transcription. Although the precise mechanism of action of this agent remains mostly unknown, there are increasing experimental data describing PM00104 antitumoral activity. Three main molecular characteristics describe the antitumoral activity of PM00104:

- PM00104 is a DNA binder: PM00104 binds to the minor groove of DNA. This binding occurs in preferred GC-rich trinucleotide sequences, preferably to GCG trinucleotide (C. Bailey, unpublished PharmaMar internal report). The binding of PM00104 to the DNA produces a stabilization of the DNA duplex, with notable increase (13-18^{o} C) in the melting temperatures of DNA oligos containing either single or tandemly arranged binding sites (71). This stabilization could account for the need of the same DNA repair machinery that usually deals with inter-strand cross-links and involves proteins from both homologous recombination (HR) and nucleotide excision repair (NER) machineries.
- PM00104 produces DNA double strand breaks: treatment of cells with PM00104 led to cell cycle delay in S phase, activation of the DNA damage checkpoint, and cell death. Additionally, *Schizosaccharomyces pombe* containing a RAD51 mutation was found to be extremely sensitive to PM00104, thus suggesting that the compound induces double-strand breaks. Since these effects are suggestive of stalled transcription and replication forks, the dependency of the killing mechanism on an intact NER system was tested by studying the cytotoxic effects of the drug on cells deficient in RAD13, which is the *S. pombe* counterpart of human XPG, a protein that has been shown to mediate, at least in part, the mechanism of action of other agents in this class in human cells. RAD13, haploid deletion mutants were found to be as sensitive to

PM00104 as wild-type cells, thus indicating the independence of the cytotoxic effect of this compound to the lack of a functional nucleotide excision repair system. This evidence is in contrast with the pattern noted with other antitumoral agents with DNA-binding activity as trabectedin and cisplatin, which are highly dependent on the activity of this repair pathway.

- PM00104 interferes with DNA repair: experimental data reveal that the DNA damage repair machinery is essential to overcome PM00104-induced DNA damage and suggest that this damage is mainly due to double strand breaks. The sensitivity to PM00104 has been determined in the collection of 5,000 haploid deletion mutants of the yeast *Saccharomyces cerevisiae* as a model. Approximately 40 hypersensitive mutants and about 90 mutants resistant to PM00104 activity have been identified (72). A set of genes involved in sensing/repairing double strand breaks were found among the genes whose deletion produced sensitivity to PM00104. These are components of the MRX complex; several members of the homologous recombination proteins of the Rad52 epistasis group (which are recruited to the sites of DNA damage specifically during S-phase and G2); the Swi/Snf complex, a chromatin remodeling complex conserved in humans, whose inactivation results in inefficient DSB repair and increased DNA damage sensitivity as well as a large defect in γ-H2AX phosphorylation strain with a deletion in SUMO ligase Siz1 was one of the most resistant mutants to PM00104. A role for this protein in the inhibition of homologous recombination at replication forks has been described recently, indicating again that the main lesions induced by PM00104 are double strand breaks.

This evidence of the lack of effect of NER pathways in PM00104 *in vitro* cytotoxicity is in contrast with the resistance to treatment with platinum-based therapies both *in vivo* and *in vitro*. The evidence generated at the preclinical and clinical level demonstrates that the efficiency of the NER mechanism is associated to a poor outcome in patients bearing different tumor types and exposed to a platinum-based chemotherapy. Similarly, an increased sensitivity to trabectedin is found in patients having increased expression of genes in the NER pathway.

1.4. RATIONALE FOR THIS PHASE II EXPLORATORY TRIAL OF PM00104 IN ENDOMETRIAL AND CERVICAL CANCER

- In patients with advanced/metastatic endometrial cancer, despite the use of combinations or novel agents and therapies for first-line, responses are of short duration, with PFS of 6-9 months and OS of 12-15 months. Results of second-line chemotherapy are generally poor, with only taxanes showing response rates greater than 20%. Short PFS (2 months) and OS (6-8 months) have been found with second-line regimens. Therefore, treatment of advanced/metastatic endometrial cancer is a clearly unmet medical need and investigation of new agents is warranted.
- In patients with cervical cancer, despite the therapeutic benefit obtained with first-line cisplatin/topotecan or cisplatin/paclitaxel combinations, most patients do not

respond to treatment, responses are short and median survival is still less than one year. Results with second-line chemotherapy are poor, with median PFS of 2 months and median survival of 6 months.

- Therefore, clinical trials are necessary to incorporate new agents to the existing available options in order to improve the treatment outcome in advanced, persistent or recurrent endometrial and/or cervical cancer.
- Close to the completion of the phase I development program of PM00104 as a single-agent, the safety profile of PM00104 indicates a positive risk/benefit ratio, which supports the continuation of the program with the beginning of phase II studies.
- Minor tumor shrinkage not qualifying as response per RECIST was observed as well as clinically meaningful disease stabilization of previously progressive disease during the phase I program of PM00104 in one patient with endometrial cancer and in three patients with cervical cancer. Therefore, possible indications for PM00104 in exploratory phase II studies include endometrium and cervix carcinoma.
- PK/PD simulation have indicated that PM00104 dose and dosing interval, but not infusion duration, are the main determinants of the neutropenia severity and duration. PK/PD model have shown that increasing the PM00104 dose might result in a more than proportional decrease in the neutrophil nadir, and that the severity and/or incidence of severe neutropenia associated to PM00104 treatment might be reduced by using treatment regimens with a more frequent dosing for a given total, cumulative dose. Then, dose fractioning increasing dose density could result in a safety advantage, while preserving dose intensity. In agreement with PK/PD modeling, no skipped doses due to neutropenia occurred in the phase I trial at the recommended dose (2 mg/m^2) with the schedule to be used in the current phase II trial.
- The recommended dose for phase II studies found in the phase I study PM104-A-004-05 for the schedule to be used in the current phase II clinical trial (d1, d8 and d15; q4wk) was 2 mg/m^2.
- The current exploratory phase II trial will use the PM00104 schedule (d1, d8 and d15; q4wk) with the highest dose intensity (1.5 mg/m^2/week) of all five schedules tested in phase I trials.

2. STUDY OBJECTIVES

2.1. PRIMARY

- To evaluate the antitumor activity of PM00104 administered as a 1-hour i.v. infusion on Day 1, 8 and 15 every four weeks (d1, d8 and d15; q4wk) to patients with advanced and/or metastatic endometrial or cervical cancer previously treated with one line of systemic chemotherapy.

2.2. SECONDARY

- To determine the safety profile of this PM00104 regimen in these patients.

- To determine the pharmacokinetic (PK) profile of this PM00104 regimen in these patients.
- To determine the pharmacogenomic (PGx) profile of this PM00104 regimen in these patients. Hypothesis-generating exploratory PGx analyses will be conducted to correlate the molecular parameters found in the tumor and blood samples of the patients with the clinical results achieved with PM00104.

3. OVERALL STUDY DESIGN

Multicenter, open label, phase II clinical trial with single-agent PM00104 given as a 1-h i.v. infusion on d1, d8 and d15 q4wk to patients with advanced and/or metastatic endometrial or cervical cancer in progression.

The primary endpoint of the study is the overall response rate (ORR), defined as the percentage of patients with objective response (OR; complete or partial response) as defined by the RECIST.

A comprehensive workup will be performed at baseline and every other cycle (± 1 week) until evidence of disease progression.

Treatment will be administered in the absence of disease progression and/or unacceptable toxicity. In case of obtaining a complete response, two additional cycles will be administered and then the treatment will be stopped.

Patients will be evaluated using clinical and laboratory assessments both after and before each treatment cycle. Any treatment-related AEs will be followed-up until the events or their sequelae resolve or stabilize at a level acceptable to the Investigator and the Sponsor. Patients no longer receiving study treatment will be followed up for survival (see Section 5.2).

4. SELECTION OF PATIENTS

4.1. INCLUSION CRITERIA

In order to be included into the trial, female patients had to fulfill all of the following criteria:

1. Voluntary written informed consent, obtained from the patient before the beginning of any specific study procedures.
2. Group 1 (endometrial cancer): histologically confirmed advanced and/or metastatic endometrial cancer (any grade, including endometroid, clear cell, serous and mixed types) with documented disease progression as per RECIST at study entry.

   Group 2 (cervical cancer): histologically confirmed advanced and/or metastatic cervical cancer with documented disease progression as per RECIST at study entry.
3. Group 1 (endometrial cancer): patients must have failed one prior systemic chemotherapy line for advanced/metastatic disease (excluding chemosensitizing chemotherapy); prior hormone therapy and biological therapy are allowed.

Group 2 (cervical cancer): patients must have failed one prior systemic chemotherapy line for advanced/metastatic disease (excluding chemosensitizing chemotherapy); prior hormone therapy and biological therapy are allowed.

4. Complete recovery from the effects of prior radiotherapy and from any drug-related AEs derived from previous treatments, excluding alopecia and grade 1 peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v. 3.0).
5. At least one measurable lesion ("target lesion" according to the RECIST), located in a non-irradiated area and adequately measured less than four weeks before study entry. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is clearly documented or biopsy proven.
6. Age ≥ 18 years.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 1.
8. Life expectancy ≥ 3 months.
9. Appropriate bone marrow reserve, renal and hepatic functions.
    a. Platelet count ≥ 100 x 10^9/l, hemoglobin ≥ 9 g/dl and absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l.
    b. Alkaline phosphatase (AP) ≤ 2.5 x upper limit of normality (ULN) (≤ 5 x ULN in case of extensive bone metastases).
    c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN in case of hepatic metastases).
    d. Total bilirubin ≤ 1.5 x ULN, unless due to Gilbert's syndrome.
    e. Renal function: patients with calculated creatinine clearance (using Cockcroft and Gault formula) ≥ 30 ml/min. [c]
    f. Albumin ≥ 2.5 g/dl.
10. Left ventricular ejection fraction (LVEF) within normal limits (LVEF of at least 50%).
11. Women of childbearing potential must have a negative serum pregnancy test before study entry. In case of childbearing potential, the patients and their partners must agree to use a medically acceptable method of contraception throughout the treatment period and for three months after discontinuation of treatment. Acceptable methods of contraception include complete abstinence, intrauterine contraceptive device (IUD), oral contraceptive, subdermal implant and double barrier (condom with a contraceptive sponge or contraceptive suppository).

[c] See details supporting the selection of this level of calculated creatinine clearance (≥ 30 ml/min) in Section 1.3.4 (metabolism of PM00104) and Section 1.3.5.5.1 (renal function and PM00104 clearance).

4.2. EXCLUSION CRITERIA

Female patients fulfilling any of the following criteria will not be included into the trial:

1. Prior therapy with PM00104.
2. Uterine sarcomas, adenosarcoma and malignant Mullerian tumors.
3. Cervical neuroendocrine or small cell carcinomas, non-epithelial cervical neoplasms such as sarcomas.
4. Patients who have isolated recurrences (vaginal, pelvic or para-aortic) potentially curative with radiation therapy or surgery.
5. Pregnant or lactating women, or in case of childbearing potential, women not using an appropriate contraceptive method.
6. Less than three weeks from prior radiation therapy, biological therapy or chemotherapy. Less than six weeks from prior nitrosourea, mitomycin C, high-dose chemotherapy or radiotherapy involving the whole pelvis or over 50% of the spine, provided that acute effects of radiation treatment have resolved. Hormonal therapy and palliative radiation therapy (i.e., for control of pain from bone metastases) must be discontinued before study entry.
7. Group 1 (endometrial cancer): more than one line of prior systemic chemotherapy for advanced/metastatic disease (excluding chemosensitizing chemotherapy).

   Group 2 (cervical cancer): more than one line of prior systemic chemotherapy for advanced/metastatic disease (excluding chemosensitizing chemotherapy).
8. Patients with a prior invasive malignancy (except non-melanoma skin cancer) who have had any evidence of disease within the last five years or whose prior malignancy treatment contraindicates the current protocol therapy.
9. Patients with serious non-healing wound, ulcer, or bone fracture. This includes history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess for which an interval of three to six months must pass before study entry. In addition, the patient must have undergone correction (or spontaneous healing) of the perforation/fistula and/or the underlying process causing the fistula/perforation. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations.
10. Evidence of progressive or symptomatic central nervous system (CNS) metastases or leptomeningeal metastases.
11. Other diseases or serious conditions:
    a. Increased cardiac risk as defined by:
       - Unstable angina or myocardial infarction within 12 months before inclusion in the study.
       - New York Heart Association (NYHA) grade II or greater congestive heart failure.
       - Symptomatic arrhythmia or any arrhythmia requiring ongoing treatment.

- Abnormal electrocardiogram (ECG), i.e., patients with the following are excluded: QT prolongation - QTc > 480 msec; signs of cardiac enlargement or hypertrophy; bundle branch block; partial blocks; signs of ischemia or necrosis, and Wolff Parkinson White patterns.
- History or presence of valvular heart disease.
- Uncontrolled arterial hypertension despite optimal medical therapy.
- Previous mediastinal radiotherapy.
- Previous treatment with doxorubicin at cumulative doses exceeding 400 mg/m^2.

b. History of significant neurological or psychiatric disorders.
c. Active infection requiring systemic treatment.
d. Significant non-neoplastic liver disease (e.g., cirrhosis, active chronic hepatitis).
e. Immunocompromised patients, including those known to be infected with the human immunodeficiency virus (HIV).

12. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in the study. The investigator should feel free to consult the Study Coordinator or the Sponsor for uncertainty in this regard.
13. Limitation of the patient's ability to comply with the treatment or to follow-up at a participating center. Patients enrolled into this trial must be treated and followed at a participating center.
14. Treatment with any investigational product within 30 days prior to inclusion in the study.
15. Known hypersensitivity to any component of PM00104.

4.3. PATIENTS FOR THE PHARMACOGENOMIC SUBSTUDY (ONLY FOR PATIENTS INCLUDED IN SITES LOCATED IN THE U.S.)

4.3.1. Inclusion Criteria

- All patients included in trial PM104-B-001-09 will be eligible.
- Only those patients with available tissue samples that voluntarily sign the Informed Consent Form for the PGx substudy will participate.

4.3.2. Exclusion Criteria

- Patients who do not consent to participate in this substudy. Refusal to participate in the PGx substudy will not affect the patients' participation in the main trial PM104-B-001-09.

5. PLAN OF THE STUDY

5.1. DURATION OF STUDY (WHOLE POPULATION)

The total duration of the study will be approximately 33 months, including about 24 months of active enrolment.

Planned start date (first patient on study): 3Q09.

Planned enrolment period: 24 months.

Planned study termination (clinical cutoff): six months after the last treatment visit of the last evaluable patient included in the study, or nine months after the last patient is included, whichever occurs first.

5.2. DURATION OF STUDY AND TREATMENT (PER PATIENT)

Patients will receive study treatment as long as it is considered to be in their own benefit (see Section 7.2.2). Patients will be evaluated at scheduled visits in up to three study periods:

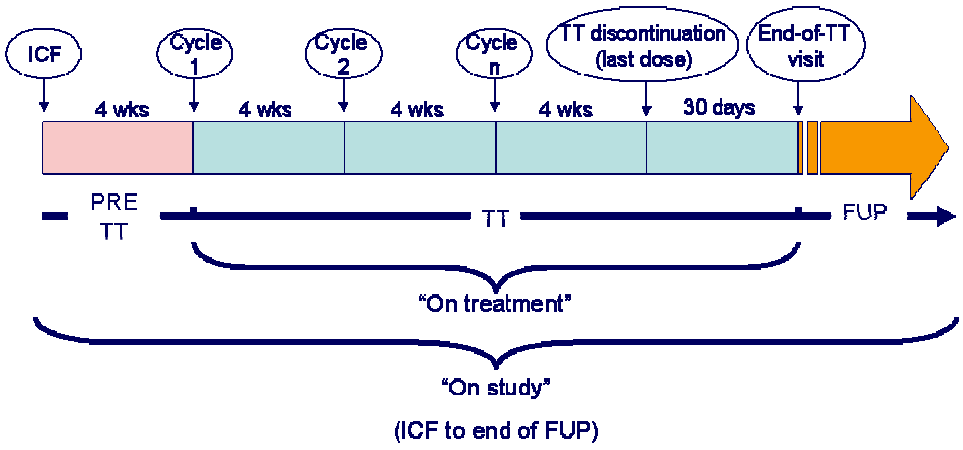
- **Pre-treatment (PRE TT):** from signature of informed consent to the first infusion of PM00104.
- **Treatment (TT):** from the first infusion of PM00104 to treatment discontinuation plus 30 days.
- **Follow-up (FUP):** after treatment discontinuation, patients will be followed until all toxicities or their sequelae resolve or stabilize at a level acceptable to the Investigator and the Sponsor. Patients who discontinue treatment without progression will be followed every three months until:
    1. Disease progression;
    2. Other antitumor therapy;
    3. Death, or
    4. The date of study termination, whichever occurs first.

  After disease progression or after other antitumor therapy, patients will be followed every three months until:
    1. Death, or
    2. The date of study termination, whichever occurs first.

Patients may withdraw their consent at any time; no further study activities will be conducted on them.

Patients will be considered to be **on-study** from the signature of the informed consent to the end of follow-up period. Patients will be considered to be **on-treatment** for the duration of their treatment and in the first 30 days following the last PM00104 administration. **Treatment discontinuation** is defined as the day of the last study drug dose administration (Figure 9).

Figure 9. Study periods.



FUP, follow-up; ICF, informed consent form; PRE TT, pre-treatment; TT, treatment.

5.2.1. Discontinuations

5.2.1.1. Treatment Discontinuation

Treatment discontinuation occurs when an enrolled patient ceases to receive the study medication, regardless of the circumstances. The primary reason for any discontinuation will be recorded on the patient's Case Report Form (CRF). By convention, the date of treatment discontinuation will be the day of the last PM00104 administration.

If a patient discontinues treatment, every effort should be made to complete the scheduled assessments.

5.2.1.2. Reasons for Treatment Discontinuation

Administration of the study treatment should be discontinued if this is considered to be in the best interest of the patient. More specifically, treatment will be discontinued due to any of the following reasons:

- Disease progression.
- Unacceptable toxicity (including any toxicity leading to the need for a third dose reduction or severe hypersensitivity reactions).
- Patient refusal.
- Intercurrent serious illness.
- Protocol deviation with an effect on the risk/benefit ratio of the clinical trial.
- Treatment delay > two weeks or impossibility to administer both Day 8 and Day 15 dose on a given cycle (except in case of clear clinical benefit, with the Sponsor's approval).
- Administrative reasons or Sponsor's decision.

Regardless of the reason, patients who discontinue the treatment must not be re-treated at any time.

In case of obtaining a complete response, two additional cycles will be administered and then the treatment will be discontinued.

Any subsequent therapies for the patients may be provided off-study according to the Investigator's criteria.

5.2.1.3. Study Discontinuation

Study discontinuation occurs when an enrolled patient ceases to participate in the study, regardless of the reason (as detailed under "Follow-up" in Section 5.2). Patients have the right to withdraw consent at any time; if this is the case, no further follow-up should be performed.

The date and reason for study discontinuation will be clearly documented on the patient's CRF.

5.2.2. Protocol Deviations

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and Competent Authorities. Therefore, this applies to deviations related to patient inclusion and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the investigator, etc.).

Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio, such as:

- Deviations that might affect the clinical trial objectives, such as those involving the inclusion/exclusion criteria (which could mean that the patient is not eligible for the trial) and those having an effect on patient evaluability.
- Deviations that might affect the patient's well-being and/or safety, such as an incorrect dosing of the investigational medicinal product (PM00104) due to not following dose adjustment specifications or an incorrect preparation of the medication.
- Deviations related to the following of GCP guidelines as described in the protocol and regulations in force, such as deviations when obtaining the Informed Consent or not following the terms established for reporting serious adverse events, etc.

The investigators may suggest to the Sponsor the authorization of certain protocol deviations, especially if they are related to the inclusion/exclusion criteria or if they may have an effect on the evaluability of the patients. As a general rule, NO deviations that may have an effect on the risk/benefit ratio of the clinical trial will be authorized.

All protocol deviations considered particularly relevant, which are related to ethical issues, fulfillment of GCP guidelines and trial procedures, will be notified to the pertinent IEC/IRB and, if pertinent, to the relevant authorities as established by local regulations.

5.3. REPLACEMENT OF PATIENTS

Patients must be replaced if they are considered not evaluable for efficacy, i.e., if they are withdrawn from the study due to significant clinical deterioration of unknown reason, hypersensitivity reactions, patient refusal or unrelated AEs without any tumor assessment after the start of study treatment.

Patients withdrawn from the study due to toxicity without any tumor assessments after the start of study treatment will be considered as "treatment failures" and will not be replaced.

The number of patients replaced will be reflected in the overall number of patients included into the trial.

5.4. STUDY TERMINATION (CLINICAL CUTOFF)

The planned study termination (clinical cutoff) will be six months after the last treatment visit of the last evaluable patient included in the study, or nine months after the last patient is included, whichever occurs first.

All patients on active treatment at the date of study termination will be offered to continue to receive PM00104 treatment off-study according to the Investigator criteria.

5.5. SCREENING EVALUATION

During the pre-treatment period, and once the patient has signed the Informed Consent Form, the Investigator will confirm the patient's eligibility for the study by conducting the following assessments (Table 8).

Additional information on the collection and processing of PGx samples may be found in Appendix 1. Samples, Methodology and Techniques of the Pharmacogenomic Substudy.

Table 8. Screening assessments.

	ASSESSMENT	TIME
1. History and clinical examination	◆ Written informed consent.	Prior to any specific study procedures (within four weeks prior to Day 1 of Cycle 1).
	◆ Medical history: o Date of diagnosis of the primary disease. o Demographic information (race/ethnicity, age). o Prior treatments (surgery, radiotherapy, chemotherapy, immunotherapy), specifying the best response and the date of PD. ◆ Concomitant diseases and treatments. ◆ Weight and height. ◆ Complete physical examination. ◆ Vital signs: heart rate, blood pressure and body temperature. ◆ Performance status (ECOG PS; see Appendix 2. ECOG Performance Status Assessment Scale).	Within four weeks prior to Day 1 of Cycle 1. Complete physical examination, ECOG PS and vital signs must be repeated on Day 1 of Cycle 1, prior to administration of the first PM00104 infusion. Weight and height: repeat on Day 1 of Cycle 1 whenever clinically indicated.
	◆ ECG. ◆ LVEF (ultrasound). All ECGs and LVEFs will be reviewed by an external cardiologist.	Within four weeks prior to Day 1 of Cycle. Repeat on Day 1 of Cycle 1 whenever clinically indicated.

	ASSESSMENT	TIME
2. Laboratory tests	◆ **Hematology:** differential WBC (neutrophils, lymphocytes), hemoglobin and platelets. ◆ **Biochemistry A:** liver function tests (ALT, AP, AST, LDH, total and direct bilirubin), creatinine, CPK, troponin I, glucose and serum electrolytes (Na^+, Cl^-, K^+, Ca^{++}, Mg^{++}). ◆ **Biochemistry B:** total protein, albumin, amylase and lipase. CPK-MB fraction to be analyzed if CPK and/or troponin I are abnormal. In the case of grade ≥ 3 increase in serum cardiac troponin I, an ECG and cardiac ultrasound will be performed as soon as possible.	Within one week prior to Day 1 of Cycle 1. Repeat on Day 1 of Cycle 1 prior to treatment with PM00104, if the treatment is administered more than one week after the screening test. Repeat Biochemistry B on Day 1 of Cycle 1 whenever clinically indicated.
3. Calculated creatinine clearance	Calculated using the Cockcroft and Gault formula (see Appendix 3. Cockcroft and Gault Formula).	Within one week prior to Day 1 of Cycle 1. Repeat on Day 1 of Cycle 1 prior to treatment with PM00104, if the treatment is administered more than one week after the screening test, or whenever clinically indicated.
4. Tumor assessment	CT-scan or MRI of all measurable/evaluable sites of disease, as per RECIST (see Appendix 4. Evaluation of Response. The RECIST).	Within four weeks prior to Day 1 of Cycle 1. Documentation of PD is mandatory.
5. Pregnancy test, if applicable		Within two weeks prior to Day 1 of Cycle 1. Repeat on Day 1 of Cycle 1 whenever clinically indicated.
6. PGx samples	See details in Appendix 1. Samples, Methodology and Techniques of the Pharmacogenomic Substudy.	Tumor tissue samples obtained at disease diagnosis. One blood sample taken prior to the first PM00104 infusion of Day1, Cycle 1.
7. Other tests	When indicated by the clinical and laboratory context.	Within four weeks prior to Day 1 of Cycle 1.

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase-fraction MB; CT, computed tomography, ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PD, progressive disease; PGx, pharmacogenomics, PS, performance status; RECIST, Response Evaluation Criteria In Solid Tumors; WBC, white blood cells.

5.6. PATIENT REGISTRATION

After ensuring that the patient meets all eligibility criteria and has given written informed consent, she will be entered into the trial by contacting the clinical trial monitor designated by the Sponsor and faxing the completed Patient Registration Form (Fast Fact Sheet). The Sponsor will then check and confirm this Registration Form. A patient number will be provided to the site of enrolment within one working day. This patient number should be used on all future documentation and correspondence referred to this patient.

5.7. EVALUATIONS DURING TREATMENT

The following assessments will be done while the patient is on treatment (Table 9).

A 2-day window is allowed for the different tests and procedures.

Table 9. Evaluations during treatment.

	ASSESSMENT	TIME
1. Clinical examination	◆ Complete physical examination. ◆ Performance status (ECOG PS; see Appendix 2. ECOG Performance Status Assessment Scale).	Day 1 of the first cycle prior to the PM00104 infusion, and then whenever clinically indicated.
	◆ Vital signs: heart rate, blood pressure and body temperature.	Before any PM00104 infusion.
	◆ Weight and height.	Repeat on Day 1 of each cycle prior to the PM00104 infusion, and then whenever clinically indicated.
	◆ Intercurrent events, concomitant disease and treatments.	Throughout the "on treatment" period (i.e., treatment plus 30 days following the last PM00104 administration).
2. Laboratory tests	◆ **Hematology:** differential WBC (neutrophils, lymphocytes), hemoglobin and platelets. ◆ **Biochemistry A:** liver function tests (AP, ALT, AST, LDH, total and direct bilirubin), creatinine, CPK, troponin I, glucose and serum electrolytes (Na^+, Cl^-, K^+, Ca^{++}, Mg^{++}).	Repeat on Day 1 of each cycle prior to the PM00104 infusion, and then weekly. If NCI-CTCAE grade ≥ 3 occurs, the appropriate test(s) should be repeated at least every 2-3 days until recovery.
	◆ **Biochemistry B:** total protein, albumin, amylase and lipase. CPK-MB fraction to be analyzed if CPK and/or troponin I are abnormal. In the case of grade ≥ 3 increase in serum cardiac troponin I, an ECG and cardiac ultrasound will be performed as soon as possible.	Repeat on Day 1 of each cycle prior to the PM00104 infusion, and then whenever clinically indicated. If NCI-CTCAE grade ≥ 3 occurs, the appropriate test(s) should be repeated at least every 2-3 days until recovery.
3. Calculated creatinine clearance	Calculated using the Cockcroft and Gault formula (see Appendix 3. Cockcroft and Gault Formula).	Repeat on Day 1 of each cycle prior to the PM00104 infusion, and then whenever clinically indicated.
4. ECG	All ECGs will be reviewed by an external cardiologist.	Repeat on Day 1 of each cycle prior to the PM00104 infusion, and then whenever clinically indicated. In the case of grade ≥ 3 increase in serum cardiac troponin I, ECG will be performed as soon as possible.
5. LVEF	Cardiac ultrasound. All LVEFs will be reviewed by an external cardiologist.	Every other cycle, and then whenever clinically indicated. In the case of grade ≥ 3 increase in serum cardiac troponin I, cardiac ultrasound will be performed as soon as possible.
6. Tumor assessment	CT-scan or MRI of all measurable/evaluable sites, as per RECIST (see Appendix 4. Evaluation of Response. The RECIST).	Every other cycle (± one week) until PD.
7. Pregnancy test, if applicable		Whenever clinically indicated.
8. AEs	As per NCI-CTCAE, version 3.0.	Throughout the "on treatment" period.
9. PK	See Section 6.	Only during the first two PM00104 infusions of the first cycle.
10. Other tests		When indicated, according to the clinical and laboratory context.

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase-fraction MB; CT, computed tomography, ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology

	ASSESSMENT	TIME

Criteria for Adverse Events; PD, progressive disease; PK, pharmacokinetics, PS, performance status; RECIST, Response Evaluation Criteria In Solid Tumors; WBC, white blood cells.

5.8. EVALUATION AT END OF TREATMENT

The end-of-treatment visit will be scheduled at 30 days after the last PM00104 infusion (a window of ± 2 days is allowed).

Regardless of the reason for discontinuation, the same complete workup conducted before study entry (except for medical history) will have to be done at this end-of-treatment visit. This will include the following assessments:

- Complete physical examination (including weight and height, if clinically indicated).
- Vital signs.
- ECOG PS.
- Hematology.
- Biochemistry A.
- Biochemistry B.
- Calculated creatinine clearance (if clinically indicated).
- Pregnancy test (if clinically indicated).
- ECG and cardiac ultrasound (for LVEF measurement).
- Intercurrent events, concomitant disease and treatments.
- Safety assessment (AEs).
- Tumor assessment.
- Other tests (when indicated, according to the clinical and laboratory context).

Adverse events must be reported for 30 days after the last study drug administration. All serious adverse events (SAEs) occurring within 30 days of the last study drug administration will be reported. Beyond this period of time, only those SAEs suspected to be treatment-related will be reported (see Section 9).

The Sponsor will evaluate all safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

5.9. FOLLOW-UP AFTER END-OF-TREATMENT VISIT

The date and reason of the study discontinuation will be recorded on the patient's CRF (see Section 5.2.1.1).

Patients who discontinue treatment without disease progression will be followed every three months until disease progression, other antitumor therapy or death or until the date of study termination, whichever occurs first. After disease progression or after other antitumor therapy, patients will be followed every three months until death or until the date of study termination, whichever occurs first.

Patients who withdraw consent will not be followed with any study procedures.

All AEs (including SAEs) suspected to be treatment-related will be followed-up until the events or their sequelae resolve or stabilize at a level acceptable to the Investigator and the Sponsor.

Additional parameters will be assessed and/or the frequency of observations will be increased at the Investigator's discretion and according to the nature of the observed AEs. When available, autopsy data should be provided.

6. PHARMACOKINETICS

All patients included in this study will be sampled for PK during the first and second infusion of PM00104 of the first cycle, following the sampling schedule detailed in Table 10.

6.1. SAMPLE COLLECTION, STORAGE, AND SHIPPING OF THE PHARMACOKINETIC SAMPLES

All sample collection dates and times will be recorded on the CRFs.

In the treatment infusions with plasma sampling for PK, the infusion rate will be established so as to ensure that the total dose is infused in 1 hour. The drug will be infused at a constant rate throughout the 1-hour period. In order to obtain reliable PK information, the infusion rate should not be modified once the infusion has begun. If a variation in the infusion time eventually occurs, it is very important to reflect it on the CRF, writing clearly the time of the beginning and the end of the infusion. The infusion rate should not be changed to maintain the scheduled duration of infusion. It would be enough with just recording the actual duration on the CRF and on the PK sampling sheet for those cycles in which PK sampling is performed.

Blood samples will be obtained through a peripheral vein located in the contralateral side to that of infusion. In any case, the sampling vein has to be different to that in which the study drug is infused. Even the last sample must never be collected from the infusion catheter. If the blood sample is obtained from a catheter, the first milliliter (ml) of blood will be discarded to avoid dilution of the sample with the solution used to keep it permeable.

Five-ml blood samples will be collected in sodium heparin tubes. Sample tubes will be gently inverted several times to ensure adequate mixing and immediately centrifuged at 2500 x g for 15 min at +4°C to separate the plasma. If immediate centrifugation is not possible, the tubes containing the blood samples must be placed in an ice bath at 0-4°C for a maximum of 30 minutes. After centrifugation, the plasma will be transferred to the provided polypropylene tubes (one per sample) and stored at -20ºC until shipped to the analysis laboratory. The cell pellet should be discarded. Blood and plasma tubes will be provided by PharmaMar.

Blood samples will be collected on Day 1 and Day 8 of Cycle 1, at the time points shown in Table 10.

Table 10. Plasma pharmacokinetic sampling schedule.

Sample number	Optimal time point	Adequate time frame
1	Pre SOI	Pre SOI
2	5 min before EOI	1-5 min before EOI
3	1.5 hour after EOI	1-2 h after EOI
4	3 hour after EOI	2-4 hour after EOI
5	7 hour after EOI	6-10 hour after EOI
6	24 hour after EOI	20-28 hour after EOI
7	48 hour after EOI	40-72 hour after EOI
8	168 hour after EOI	120-168 hour after EOI

EOI, end of infusion; SOI, start of infusion.

The accurate recording of actual dosing and sampling times is much more important than the strict adherence to the scheduled times.

Once all samples from a patient have been collected, they should be shipped to the central laboratory for PK analyses as soon as possible, ideally the next shipping day. The time span between the moment when the last PK sample for a patient has been collected and the shipment to the central laboratory of all samples from this patient should not exceed two months.

Samples will be sent for analysis in the boxes provided for this purpose, filled with dry ice, by the study courier service to the following address:

Mrs Sally Hannam

Icon Development Solutions

Manchester Bioanalytical Laboratory

Parkway One

Parkway Business Centre

300 Princess Road

Manchester

M14 7QU, United Kingdom

Samples will be identified with the following data: Study reference, Patient Number, sample number, date and time of collection. At all times, the confidentiality of patient's data will be maintained.

7. TREATMENT

PharmaMar will provide PM00104 (Zalypsis®) with identifying labels that will include all the information required by local regulations.

The PM00104 vials will have to be requested to PharmaMar using appropriate forms provided by the Sponsor.

The study sites will have to ensure drug traceability at all times.

7.1. DESCRIPTION OF TREATMENT

PM00104 Drug Product (2.5 mg/vial) is provided as a powder for concentrate for solution for infusion. There is only one strength: 2.5 mg PM00104.

For instructions regarding drug inventory, handling, reconstitution, dilution, storage, accountability and disposal, please refer to the Preparation Guide for Zalypsis® (PM00104) and the Zalypsis® Investigator's Brochure, both provided as separate documents.

7.2. ADMINISTRATION OF STUDY MEDICATION

7.2.1. Dose Schedule

A treatment cycle consists of the administration of three i.v. 1-hour infusions of PM00104 on Day 1, Day 8 and Day 15, and all study evaluations done before the next cycle. Treatment cycles will be repeated every four weeks.

The starting dose in each infusion is 2 mg/m^2. This is the recommended dose for phase II studies found in the phase I study PM104-A-004-05 (see Section 1.3.5).

The study treatment will be administered to the patients by a central catheter and by specialized on-site study personnel. Central catheter is mandatory as some cases of infusion site reactions were observed in the phase I trials (see Section 1.3.5.4).

7.2.2. Criteria for Treatment Continuation

In order to be re-treated on Day 1 of a new cycle, the patients will have to fulfill the same criteria as at study entry (Table 11).

If these criteria are not met on Day 1 of a new cycle, treatment administration should be delayed up to two weeks and reevaluated weekly. The new cycle will start upon recovery of these parameters, according to these same criteria.

A maximum delay of two weeks is allowed for recovery from drug-related AEs. If toxicities have not recovered after a maximum delay of two weeks, the patient should discontinue the treatment. In the event of obvious clinical benefit, the patient will remain on treatment only after having discussed and agreed upon the case with the Sponsor, and upon recovery of all parameters according to the aforementioned criteria.

In order to be re-treated on Day 8 and Day 15 of each cycle, the patients will have to fulfill the criteria also described in Table 11. If these criteria are not met on Day 8 or Day 15, the respective infusion will be skipped. If both Day 8 and Day 15 infusions cannot be administered for any reason, the patient should discontinue the treatment, except in the event of obvious clinical benefit, in which case the patient will be allowed to remain on treatment only after having discussed and agreed upon the case with the Sponsor, and upon subsequent recovery of all parameters according to the aforementioned criteria.

Table 11. Criteria for continuation of treatment.

Parameter	Value on Day 1	Value on Day 8/15
Platelet count	≥ 100 x 10^9/l	≥ 75 x 10^9/l
Hb	≥ 9 g/dl	≥ 9 g/dl
ANC	≥ 1.5 x 10^9/l	≥ 1.0 x 10^9/l
AP	≤ 2.5 x ULN (≤ 5 x ULN if bone metastases)	≤ 2.5 x ULN (≤ 5 x ULN if bone metastases)
ALT, AST	≤ 2.5 x ULN (≤ 5 x ULN if hepatic metastases)	≤ 2.5 x ULN (≤ 5 x ULN if hepatic metastases)
Total bilirubin	≤ 1.5 x ULN*	≤ 1.5 x ULN*
Calculated creatinine clearance (using Cockcroft and Gault formula)	≥ 30 ml/min**	≥ 30 ml/min**
Other non-hematological related events, including renal function (except alopecia and/or vomiting in patients not receiving optimal antiemetic prophylaxis).	NCI-CTCAE grade ≤ 1 (≤ grade 2 in case of asthenia).	NCI-CTCAE grade ≤ 1 (≤ grade 2 in case of asthenia).

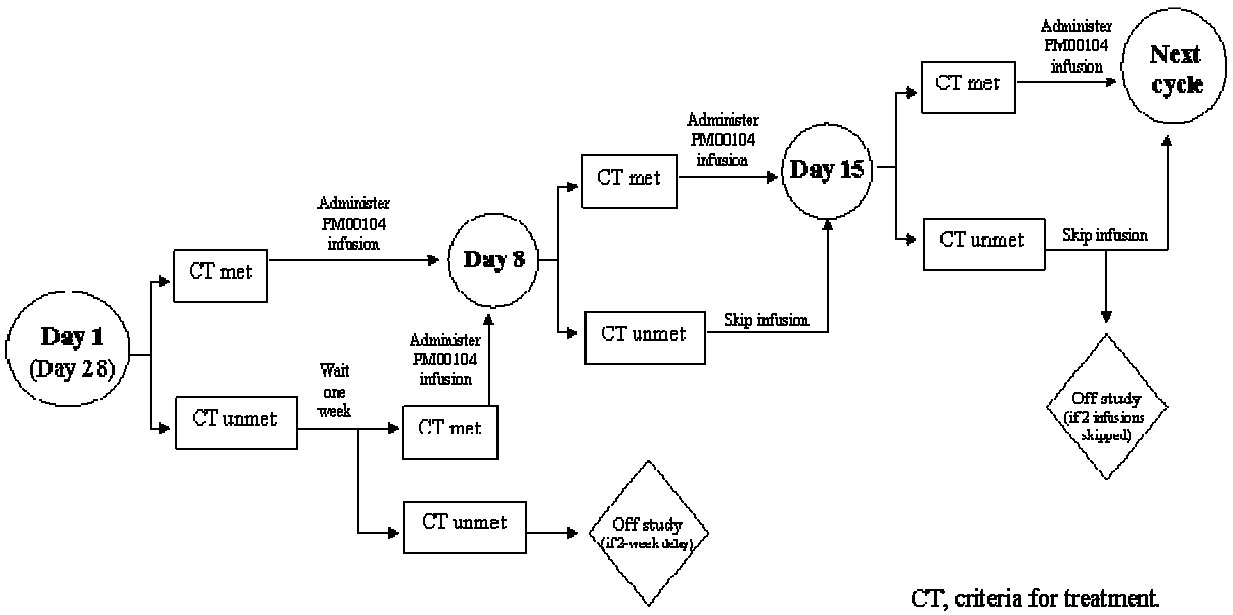
*Unless due to Gilbert's syndrome.

***In vitro* data (see Section 1.3.4) and data obtained in phase I trials (see Section 1.3.5.5.1) suggest an unlikely role of the kidney in PM00104 clearance. According with this preliminary evidence, calculated creatinine clearance for inclusion criteria (see Section 4.1) and for retreatment (see current table) was established as ≥ 30 ml/min (using the Cockcroft and Gault formula, see Appendix 3. Cockcroft and Gault Formula).

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST, aspartate aminotransferase; Hb, hemoglobin; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ULN, upper limit of normal.

Figure 10 summarizes the actions to be done in case of not meeting treatment criteria.

Figure 10. Time schedule of actions when treatment criteria are unmet.



7.2.3. Dose Reduction

Dose reductions will take place based on the worst drug-related toxicity found since the last dose administration. Table 12 shows the dose levels that will be used whenever a dose reduction is required.

Table 12. Dose reductions.

PM00104 dose level		% of dose reduction
Level 0	2 mg/m^2	-
Level -1	1.6 mg/m^2	20%
Level -2	1.3 mg/m^2	20%

No more than two dose reductions per patient will be allowed during the trial. Patients requiring more than two dose reductions should discontinue the treatment, except in the event of obvious clinical benefit, in which case the patient could be allowed to remain on treatment after having discussed and agreed upon the case with the Sponsor.

A patient who has undergone a dose reduction for whatever reason will not be allowed to escalate the dose level in later cycles.

Treatment will continue until disease progression or until discontinuation owing to any other reason (see Section 5.2.1).

7.2.3.1. Hematological Toxicity

The PM00104 dose administered to the patients will be reduced based on the nadir value of the platelet count and the ANC measured in the preceding cycle. In the event of a platelet count < 25 x 10^9/l or an ANC < 0.5 x 10^9/l lasting ≥ 5 days or associated with fever, sepsis or infection in the preceding cycle, the dose administered to the patient in following cycles will have to be reduced by one level (Table 13). In addition, re-treatment on the next infusion will only be allowed if the patient fulfils all pertinent criteria (see Section 7.2.2).

Table 13. Dose adjustments due to hematological toxicity.

Toxicity	PM00104 dose
Grade 4 neutropenia (ANC < 0.5 x 10^9/l) lasting ≥ 5 days. Grade 4 neutropenia with fever (≥38.5ºC). Grade 4 neutropenia with sepsis or severe infection.	Decrease one dose level
Thrombocytopenia. Platelets < 25 x 10^9/l	Decrease one dose level

Any dose reductions due to treatment-related hematological toxicities other than those listed in Table 13 will have to be discussed and agreed with the Sponsor.

7.2.3.2. Non-hematological Toxicity

In the event of non-hematological toxicity, the PM00104 dose administered to the patients will have to be reduced in case of:

- Any other grade 3/4 drug-related non-hematological AE, excluding alopecia, nausea/vomiting not treated with prophylactic medication or hypersensitivity reactions (patients with grade 3/4 hypersensitivity reactions should be discontinued from the study; see Section 5.2.1.2).

- Any increase in cardiac troponin I ≥ 0.1 ng/ml, together with evidence of cardiac damage by ECG or ECHO.
- Decrease in the LVEF >20% from the patient baseline value and <50%.

Any dose reductions due to treatment-related non-hematological toxicities other than those listed above will have to be discussed and agreed with the Sponsor.

Following the resolution of any of the aforementioned hematological or non-hematological toxicities, patients may continue treatment at one dose level below. If drug-related toxicities reappeared in the following drug administrations, a second dose reduction to a level below is allowed. If more than two dose reductions are required, the toxicity will be considered unacceptable and the patient must be withdrawn from the study. Exceptionally, patients recovering from the toxicity might continue treatment if there is objective evidence of antitumor response. This must always be discussed with the Sponsor.

7.2.4. Dose Escalation

No dose escalations will be allowed in this study.

7.3. CONCOMITANT MEDICATION

All tumor-specific prior chemotherapy, radiation therapy and all relevant information must be recorded on the patient's CRF.

In addition, reasonable efforts must be made to determine all treatments received by the patient during administration of the study treatment. This information must be documented in the concomitant therapy section of the CRF.

7.3.1. Prophylactic Antiemetic Treatment

According to the American Society of Clinical Oncology (ASCO) guidelines for drugs with moderate emetic risk (73), the patients will receive prophylactic treatment for emesis before the infusion of PM00104 consisting of dexamethasone 8 mg i.v. and 5-HT3 antagonists (ondansetron 8 mg i.v. or granisetron 1 mg i.v. or tropisetron 5 mg i.v.).

If necessary, in addition to the above, 10 mg of metoclopramide orally every 8 hours may be administered, or the duration of treatment with 5-HT3 antagonists and/or dexamethasone can be extended.

7.3.2. Concomitant Medication Permitted

- Therapies for preexisting and treatment-emergent medical conditions.
- Prophylactic antiemetic treatment (above described in Section 7.3.1).
- Erythropoietin therapy or derivatives (74).
- Bisphosphonates.
- In case of diarrhea (75) and pruritus, appropriate treatment will be permitted, including topical and systemic corticosteroids and antibiotics.
- Palliative local radiation may be applied. The irradiated lesion will then not be considered an area of measurable/evaluable disease.

7.3.3. Concomitant Medication Prohibited

- Concomitant administration of any other antineoplastic therapy.
- Investigational agents.
- Immunosuppressive therapies, including systemic corticosteroids, unless used as therapy for preexisting and treatment-emergent medical conditions (e.g., emesis, rash, anorexia).
- Primary prophylaxis (i.e., before the intended preventable events occurs) with colony-stimulating factors such as granulocyte (G-CSF) or granulocyte-macrophage (GM-CSF) colony-stimulating factors. Their use as secondary prophylaxis is permitted according to the ASCO guidelines (76). However, dose reduction will be applied if indicated, regardless of the use of secondary prophylaxis with colony-stimulating factors.

7.4. PACKAGING AND LABELING

PM00104 is provided as a sterile lyophilized powder for concentrate for solution for infusion. Each vial will contain 2.5 mg of PM00104.

The following information will appear on the labels:

- Name and address of the Sponsor.
- Study number/Patient number.
- Dosage and route of administration.
- Quantity or contents of container.
- Batch number/packaging number.
- Expiration date and storage conditions.
- Local legal information, as appropriate.

7.5. DRUG ACCOUNTABILITY

Proper drug accountability will be done by the clinical trial monitor. Each study site will keep records to allow a comparison of quantities of drug received and used at each site. The Investigator at each study site will be the person ultimately responsible for drug accountability at the site.

All unused drug supplied by the Sponsor will be properly destroyed at the study site. Documentation of this procedure must be provided to the clinical trial monitor. If PharmaMar agrees, unused drug supplies may be returned to the drug repository.

7.6. TREATMENT COMPLIANCE

The Investigator is responsible for supervising compliance with the instructions described in this study protocol.

8. STUDY EVALUATIONS

8.1. EFFICACY

To be evaluable for efficacy, patients must have:

- Received at least four of the six infusions in the first two cycles (i.e., two infusions in each cycle, or three infusions in Cycle 1 and one infusion in Cycle 2), and
- At least one disease measurement recorded not less than six weeks after treatment onset.

In addition, any eligible patient who receives at least two of the three infusions in one treatment cycle and experiences disease progression or dies due to progressive disease (PD) prior to response evaluation will be considered evaluable for the main endpoint (ORR) and will be categorized as an "early progression".

Patients withdrawn due to toxicity without any tumor assessment after the start of study treatment will be considered as "treatment failures" and will not be replaced.

Patients withdrawn due to significant clinical deterioration of unknown reason, hypersensitivity reactions, refusal to continue on study for any reason or unrelated AEs without any tumor assessment after the start of study treatment will be considered not evaluable for efficacy and will have to be replaced.

8.1.1. Primary Endpoint: Overall Response Rate per RECIST

The primary endpoint of this study is the overall response rate (ORR), defined as the percentage of patients with confirmed objective response (OR), either complete (CR) or partial (PR) response according to the Response Evaluation Criteria In Solid Tumors (RECIST).

Assessment of efficacy will be done using the RECIST and will be essentially based on a set of measurable lesions identified at baseline as target lesions and followed until disease progression. A comprehensive workup will be performed at baseline and every other cycle (± 1 week) until evidence of PD. The same procedure will be used to evaluate each identified lesion both at baseline and throughout the treatment period.

In case of detection of an objective response (complete or partial response), a confirmation assessment has to be performed four weeks after the first documentation of the response.

A quick reference to the RECIST may be found in Appendix 4. Evaluation of Response. The RECIST. The complete criteria may be found in the published RECIST document (77).

8.1.2. Secondary Endpoints of Efficacy

Secondary endpoints of efficacy in this study are:

- Progression-free survival rate at four months (PFS4), defined as the percentage of patients who are alive and with no evidence of disease progression at four months after the first study drug administration.
- Progression-free survival rate at six months (PFS6), defined as the percentage of patients who are alive and with no evidence of disease progression at six months after the first study drug administration.
- Duration of response (DR), defined as the time between the date when the response criteria (PR or CR, the first that is reached) are fulfilled and the first date when disease progression, recurrence or death is objectively documented (taking

the smallest measurements documented since the treatment started as reference for progressive disease).

- Progression-free survival (PFS), defined as the time from the first day of study treatment to the day of negative assessment (progression or death) or last tumor evaluation.
- Overall survival (OS), defined as the time from the first day of treatment to the date of death (or the last day when the patient is known to be alive). Survival will be followed for up to six months after the treatment discontinuation of the last patient.

8.2. SAFETY

Patients will be evaluable for safety (secondary study endpoint) if they have received at least one total or partial infusion of PM00104.

Safety will be evaluated using clinical examinations, which will comprise vital signs analysis, clinical assessment of adverse events (AEs), changes in laboratory parameters (hematological and biochemical, including liver function tests) and any other analyses that may be considered necessary.

All AEs will be classified according to the NCI-CTCAE, v. 3.0 (78), and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 10.0.

8.3. CENTRAL CARDIOLOGICAL REVIEW

Due to safety reasons, an independent cardiologist will review all the ECGs and ECHOs performed on the patients during the study, so as to improve consistency in the application of evaluation criteria.

Originals or copies of all ECGs and ECHOs will be provided by the Investigator to the independent reviewer on an ongoing basis. Other clinical or laboratory records from the patients may be provided by the Investigator, upon request from the independent reviewer.

In the event of disagreement between the Investigator's and the independent reviewer's assessments, discussion will take place between the two parties in order to reach a consensus. If no such consensus is reached, the independent reviewer's assessment will be retained in the report of the Expert Review, and in intermediate and final reports.

8.4. PHARMACOGENOMIC SUBSTUDY (ONLY ON SAMPLES COLLECTED IN THE U.S.)

The pharmacogenomic (PGx) profile of PM00104 is a secondary endpoint of this study to be evaluated in a PGx substudy. The aim of this PGx substudy is to identify and validate molecular markers whose expression may be associated with the clinical outcome of patients treated with PM00104. These molecular markers might allow the identification of those patients who will benefit from the treatment with PM00104, improving the health care by an individualized medicine.

The objectives of this PGx substudy are:

1. To determine the gene and protein expression profiles of selected genes in tumor tissue of the patients included in the clinical study PM104-B-001-09.

2. To determine the genotype of the SNP Asp1104His of XPG and other SNPs related to the mechanism of action of PM00104.

3. To correlate the gene and protein expression profiles and the SNP genotype with the clinical outcome of the patients and the evolution of the disease.

4. To validate in patient tumor samples selected putative markers of sensitivity to PM00104 found during *in vitro* studies

Appendix 1. Samples, Methodology and Techniques of the Pharmacogenomic Substudy includes a detailed protocol for sample collection and analysis. Briefly, the samples required for the molecular characterization analyses will be blood samples taken prior to the first PM00104 infusion and paraffin-embedded tumor tissue slices obtained at disease diagnosis from patients included in the trial who accepted to participate in the PGx substudy.

9. ADVERSE EVENTS REPORTING

9.1. DEFINITIONS

9.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or a clinical investigation patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), or a disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any event involving adverse drug reactions, illnesses with onset during the study or exacerbations of pre-existing illnesses should be recorded, including but not limited to clinically significant changes in physical examination findings and abnormal objective test findings (e.g., x-Ray, ECG). The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- the test result is associated with clinically significant symptoms, and/or
- the test result leads to a change in the study dosing or discontinuation from the clinical trial, significant additional concomitant drug treatment or other therapy, and/or
- the test result leads to any of the outcomes included in the definition of a SAE, and/or
- the test result is considered to be an AE by the Investigator.

9.1.2. Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any adverse experience occurring at any dose that:

- results in death (is fatal),
- is life-threatening,
- requires or prolongs inpatient hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,
- is medically significant, or
- is any suspected transmission of an infectious agent via a medicinal product.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such an important medical event that may not be immediately life-threatening or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the above definition.

9.1.2.1. Death

Death as such is the outcome of a SAE and should not be used as the SAE term itself. Instead, the cause of death should be recorded as the SAE term.

9.1.2.2. Life-Threatening Event

Any event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.1.2.3. Hospitalization or Prolongation of Hospitalization

Any AE requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during the course of a patient's participation in a clinical trial must be reported as a SAE unless exempted from SAE reporting (see Section 9.2.2). Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or by the treating physician.

Hospitalizations that do not meet criteria for SAE reporting are:

a. Reasons described in protocol [e.g., investigational medicinal product (IMP) administration, protocol-required intervention/investigations, etc.]. However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.
b. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in absence of an AE.
c. Pre-planned hospitalizations: any pre-planned surgery or procedure must be documented in the source documentation. Only if the pre-planned surgery needs to be performed earlier due to a worsening of the condition, should this event (worsened condition) be reported as a SAE.

Other situations that MUST NOT be considered as hospitalizations are the following:

d. An emergency visit due to an accident where the patient is treated and discharged.
e. When the patient is held 24 hours for observation and finally is not admitted.
f. Planned treatments at sites not associated to a hospital and generally considered as minor surgical procedures (i.e., laser eye surgery, arthroscopy, etc).

9.1.3. Unlisted/Unexpected Adverse Event

An AE, the nature or severity of which is not consistent with the applicable reference safety information.

The Sponsor will use as the reference safety information for the evaluation of listedness/expectedness the following documents:

- The current investigator brochure (IB) for any study drug/IMPs without a marketing authorization or used outside the conditions of its marketing authorization.
- The summary of product characteristics (SPC) or its national equivalent [i.e., U.S. package inserts (USPI)] defined in the protocol for non-Pharma Mar IMPs used within the conditions of its marketing authorization.

9.1.4. Adverse Events Related to Study Drug/s (IMP)

An AE is considered related to a study drug/IMP if the Investigator's assessment of causal relationship to the IMP is "1-Yes".

The Investigator will assess the causal relationship of each of the IMPs to the SAE.

The Sponsor may also consider related to the study drug/IMP those events for which the Investigator assesses the causal relationship with the IMP as "Unk" when it cannot rule out a role of the IMP in the event. See below (Section 9.1.6) for causality scale.

9.1.5. Expedited Reporting

The Sponsor is responsible for the appropriate expedited reporting of SAEs to the Regulatory Authorities. The Sponsor will also report all SAEs that are unlisted and related to the study drug/s (IMP/s), to the Investigators and to the Independent Ethics Committees/Institutional Review Board (IECs/IRBs) according to the current legislation unless otherwise required and documented by the IECs/IRB.

9.1.6. Assessment of Causal Relationship to the Study Drug/IMP

The Investigator must provide an assessment of causal relationship of each of the clinical trial IMPs (including combination and comparator products) to each SAE according to the following scale:

Y There is a reasonable possibility that the IMP/s caused the SAE.

N There is no reasonable possibility that the IMP/s caused the SAE and other causes are more probable.

Unk. Only to be used in special situations where the Investigator has insufficient information (i.e., the patient was not seen at his/her centre) if none of the above can be used.

9.2. PROCEDURES

9.2.1. Reporting Adverse Events

The Sponsor will collect AEs until 30 days after administration of the last dose of study drug/IMP. All AEs suspected to be related to the study drug/IMP must be followed after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at an acceptable level to the Investigator and the Sponsor.

All AEs must be recorded using medical terminology in the source document and the CRF. Whenever possible, the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

Investigators must assess severity (grade) of the event following the NCI-CTCAE v. 3.0 and assign relationship to each study drug/IMP; pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to PharmaMar or its designated representative. The Investigator must provide any relevant information as requested by the Sponsor in addition to that on the CRF.

Abnormal laboratory tests occurring during the study are AEs, but they should be collected only in the AE section of the CRF in some cases (please refer to the CRF guidelines for comprehensive information).

9.2.2. Reporting Serious Adverse Events

The Sponsor will collect SAEs from the signing of the Informed Consent Form. If the patient is definitively included in the study, this information will also be recorded in the AE section of the CRF.

SAEs will be collected until 30 days after administration of the last dose of study drug/IMP. Beyond this period of time, only those SAEs suspected to be related need to be reported. Nonetheless, the Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

All SAEs (as defined above) regardless of treatment group or relationship to the study drug/IMP must be reported within 24 hours to the Pharma Mar Pharmacovigilance function by fax (+34 91 846 6004) or telephone (+34 91 846 6054). Out of office hours (GMT), assistance on SAE reporting can be obtained by calling the Pharmacovigilance Service at +34 91 823 4749.

The preferred reporting method is by faxing the completed SAE form. An initial report by telephone must be followed by a completed “Serious Adverse Event Form” from the investigational staff within one working day.

All SAEs suspected to be related to the IMP/s must be followed until the event or its sequelae resolves or stabilizes at an acceptable level by the Investigator and the clinical monitor or his/her designated representative.

Death as such, is the outcome of a SAE and should not be used as the SAE term itself. Instead the cause of death should be recorded as the SAE term. When available, the autopsy report will be provided to the Sponsor.

9.2.3. Reporting Pregnancy Cases Occurred within the Clinical Trial

National regulations require that clinical trial Sponsors collect information on pregnancies occurring during clinical trials, in which exposure to the IMPs at any time during pregnancy, via either maternal or paternal exposure, is suspected.

Therefore, pregnancy and suspected pregnancy (including a positive pregnancy test regardless of age or disease state) of a female patient or the female partner of a male patient occurring while the patient is on study drug, or within 30 days of the patient's discontinuation visit, are considered immediately reportable events.

The Investigator will report the following events immediately and always within 24 hours from first knowledge:

- Any occurrence of a pregnancy where any kind of exposure to the IMP/s is suspected.
- Possible exposure of a pregnant woman (this could involve a partner of a male patient or a pregnant female who came in contact with the clinical trial IMP/s).
- All reports of elevated/ questionable or indeterminate beta human chorionic gonadotrophins (βhCGs).

Immediately after detecting a case of suspected pregnancy in a female clinical trial patient, the decision on her continued participation in the clinical trial will be jointly taken by the trial patient, the Investigator and the Sponsor, with the patient's best interest in mind. A decision to continue the pregnancy will require immediate withdrawal from the trial. If the trial is blinded, the Investigator will open the blind whenever the treatment information is needed for the management of the patient.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to PharmaMar Pharmacovigilance immediately by facsimile using the Pregnancy Report form. In the case of pregnancy of the female partner of a trial Patient the Investigator will obtain her informed consent to provide the information by using the applicable form provided by the Sponsor who will also advise the Investigator in these situations.

The Investigator will follow the pregnancy until its outcome, and must notify PharmaMar Pharmacovigilance the outcome of the pregnancy within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy, which meets a seriousness criterion (including fetal or neonatal death or congenital anomaly), the Investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to PharmaMar Pharmacovigilance by facsimile within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects is related to the exposure to the study drug/IMP should also

be reported to PharmaMar Pharmacovigilance by facsimile within 24 hours of the Investigators' knowledge of the event.

10. STATISTICAL METHODS

The statistical analysis will be done by the Sponsor or under the Sponsor's authority.

10.1. SAMPLE SIZE

In this phase II trial, efficacy of PM00104 will be evaluated in two different groups of patients with endometrial or cervical cancer. A total of 62 evaluable patients are expected to participate in this clinical trial:

- 30 patients in Group 1(endometrial cancer), and
- 32 patients in Group 2 (cervical cancer).

A different ORR is to be expected depending on the type of cancer. Thus, patients with endometrial cancer may achieve higher response rates with second-line single-agent therapies (around 25-30%) (6) than patients with cervical cancer (around 15-20%) (79, 80). Therefore, the sample size has been calculated in each group using a similar design (based on the Simon two-stage design for phase II trials) (81), but using different figures for null and alternative hypotheses.

Group 1 (endometrial cancer): patients with endometrial cancer who have received one previous systemic chemotherapy line for advanced/metastatic disease (excluding chemosensitizing chemotherapy); prior hormone therapy and biological therapy are allowed.

A Simon two-stage design will be adopted in this group to test the null hypothesis that the ORR by RECIST is ≤ 10% *versus* the alternative that ORR ≥ 30% (two-sided test; alpha=0.1 and beta=0.1). A maximum of 30 evaluable patients will be included in this group. In a first stage, 10 evaluable patients will be recruited. If one or more (≥ 1) patients achieve an objective response, the accrual in this group will be expanded with 20 additional evaluable patients. If the total number of patients with objective response is 6 or more (≥ 6) in 30 evaluable patients (i.e., an ORR in the whole study of at least 20%), the null hypothesis will be rejected and PM00104 will be considered for further clinical development in endometrial cancer.

Group 2 (cervical cancer): patients with cervical cancer who have received one previous systemic chemotherapy line for advanced/metastatic disease (excluding chemosensitizing chemotherapy); prior hormone therapy and biological therapy are allowed.

A Simon two-stage design will be adopted in this group to test the null hypothesis that the ORR by RECIST is ≤ 5% *versus* the alternative that ORR ≥ 20% (two-sided test; alpha=0.1 and beta=0.1). A maximum of 32 evaluable patients will be included in this group. In a first stage, 18 evaluable patients will be recruited. If one or more (≥ 1) patients achieve an objective response, the accrual in this group will be expanded with 14 additional evaluable patients. If the total number of patients with objective response is 4 or more (≥ 4) in 32 evaluable patients (i.e., an ORR in the whole study of at least 12.5%), the null hypothesis will be rejected and PM00104 will be considered for further clinical development in cervical cancer.

Early stopping rule

An early stopping rule for excessive toxicity will be evaluated when ten patients in each group will be recruited and followed for at least four weeks. A "serious toxicity" rate (STR) of 40% or more will be considered inadequate. The following are considered serious toxicities:

- Drug-related grade 4 neutropenia lasting for more than seven days.
- Grade 4 thrombocytopenia.
- Grade 3/4 nausea/vomiting despite adequate prophylaxis.
- Grade 3/4 transaminase increase lasting for more than seven days.
- Grade 3/4 fatigue.
- Any other grade 3/4 drug-related event leading to early study discontinuation.

If ≥ 4 patients of the first 10 patients had one of these serious toxicities, the trial will be stopped and the recommended dose and/or administration schedule for phase II will be re-evaluated.

With this stopping rule, the probability of ≥4/10 STR in the sample (if the true probability of STR is <1/6) is 0.0697. On the other hand, the probability of observing ≤3/10 STR in the sample (if the true probability of STR is >40%) would be 0.3822.

10.2. ENDPOINTS

10.2.1. Primary Endpoint

- Overall response rate (ORR) according to the RECIST.

10.2.2. Secondary Endpoints

Efficacy:

- Progression-free survival rate at four months (PFS4)
- Progression-free survival rate at six months (PFS6)
- Duration of response (DR).
- Progression-free survival (PFS).
- Overall survival (OS).

Safety profile:

- Clinical examinations.
- Vital signs analysis.
- Clinical assessment of AEs and SAEs.
- Changes in laboratory parameters (hematological and biochemical, including liver function tests).
- Reasons for study discontinuations.
- Any other analyses that may be considered necessary.

Others:

- Pharmacokinetic (PK) profile.
- Pharmacogenomic (PGx) profile.

10.3. STATISTICAL ANALYSIS

Continuous variables will be tabulated and presented with summary statistics (i.e., mean, standard deviation, median and range). Categorical variables will be summarized in frequency tables by means of counts and percentages.

10.3.1. Efficacy Analysis

All patients who have received at least four of the six infusions in the first two cycles (i.e., two infusions in each cycle, or three infusions in Cycle 1 and one infusion in Cycle 2), and who have at least one disease measurement recorded not less than six weeks after treatment onset, will be considered evaluable for efficacy. In addition, any eligible patient who receives at least two of three infusions in one treatment cycle and experiences disease progression or dies due to PD prior to response evaluation will be considered evaluable for the main endpoint (ORR) and will be categorized as an "early progression".

Patients withdrawn due to toxicity without any tumor assessment after the start of study treatment will be considered as "treatment failures" and will not be replaced.

Patients withdrawn due to significant clinical deterioration of unknown reason, hypersensitivity reactions, refusal to continue on study for any reason or unrelated AEs without any tumor assessment after the start of study treatment will be considered not evaluable for efficacy and will have to be replaced.

Binomial estimates with exact 95% CIs will be calculated for the analysis of the main endpoint (ORR) and the secondary endpoints PFS4 and PFS6 rates.

Time-to-event endpoints (DR, PFS and OS) will be analyzed according to the Kaplan-Meier method.

If relevant, efficacy parameters *versus* baseline covariates will be analyzed and appropriate test will be used (i.e., the Fisher exact test for categorical variables, the log-rank test or Cox regression for time-to-event variables, etc.).

10.3.2. Safety Analysis

All patients who have received at least one total or partial infusion of PM00104 will be included in the safety analysis.

The AEs, SAEs, laboratory evaluations, deaths and the reason for study discontinuations will be analyzed.

All AEs and SAEs will be classified according to the NCI-CTCAE, v. 3.0, and will be coded using the MedDRA, v.10.0.

10.3.3. Pharmacokinetic Analysis

Pharmacokinetic parameters will be calculated using population methods, after pooling data from this study with data obtained during phase I studies.

10.3.4. Pharmacogenomic Analysis

The results of the PGx analyses conducted on the tumor tissue obtained at disease diagnosis and blood samples obtained prior to the first treatment administration will help to generate hypotheses for correlating the molecular parameters assessed in these samples with the clinical results of the treatment.

11. ADMINISTRATIVE SECTION

11.1. ETHICS

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki (see Appendix 5. Declaration of Helsinki) and will be consistent with Good Clinical Practice (GCP) guidelines and pertinent regulatory requirements.

The study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective task(s).

The study will be conducted in compliance with the protocol. The protocol, any amendments and the patient informed consent will receive IEC/IRB approval/favorable opinion prior to initiation, according to pertinent regulations.

The decision of the IEC/IRB concerning the conduct of the study will be made in writing to the Investigator, and a copy of this decision will be provided to the Sponsor before the beginning of the study.

The Investigator and/or the Sponsor is/are responsible for keeping the IEC/IRB informed of any significant new information about the study drug.

All protocol amendments will be agreed upon by the Sponsor and the Investigator.

Administrative changes of the protocol are minor corrections and/or clarifications that have no impact on the way the study is to be conducted.

11.2. MONITORING, AUDITING AND INSPECTING

The study will be monitored by regular site visits and telephone calls to the Investigator by the PharmaMar clinical trial monitor.

During site visits, the trial monitor should revise original patient records, drug accountability records and document retention (study file). Additionally, the trial monitor should observe study procedures and will discuss any problems with the Investigator.

Adequate time for these visits should be allocated by the Investigator. The Investigator should also ensure that the monitor is given direct access [as per International Conference on Harmonization (ICH) Topic E6 (R1) Guideline for Good Clinical Practice, Sections 4.9.7 and 6.10] to source documents (i.e., hospital or private charts, original laboratory records, appointment books, etc.) of the patient which support data entered in the case report forms, as defined in the ICH Topic E6 (R1) Guideline for Good Clinical Practice, Sections 1.51 and 1.52.

Systems and procedures will be implemented to ensure the quality of every aspect of the trial.

During the course of the trial, the Clinical Quality Assurance Department of PharmaMar or external auditors contracted by the Sponsor may conduct an onsite audit visit (ICH Topic E6 (R1) Guideline for Good Clinical Practice, Section 1.6).

Participation in this trial implies acceptance of potential inspection by national or foreign health authorities.

11.3. PATIENT INFORMED CONSENT FORM

The rights, safety and well-being of the trial patients are the most important considerations and should prevail over interests of science and society.

The Informed Consent Forms will include all elements required by ICH, GCP and applicable regulatory requirements.

Prior to inclusion into the trial, the Investigator or a person designated by the Investigator must provide the patient with one copy of the Informed Consent Form for the clinical trial and one copy of the Informed Consent Form for the PGx substudy. Both copies must provide written fully information about the clinical trial and the PGx substudy in a language that is non-technical and easily understood. The Investigator should allow time necessary for the patient or his/her legally acceptable representative to inquire about the details of the clinical trial and the PGx substudy; then, both Informed Consent Forms must be freely signed and personally dated by the patient and by the person who conducted the informed consent discussion before the beginning of the study. The patient should receive a copy of both signed Informed Consent Forms and any other written information provided to study patients prior to participation in the trial.

During a patient's participation in the trial, any updates to the consent forms and any updates to the written information will be provided to him/her.

If there is a need to obtain new consent from the patients, the Investigator or a person designated by the Investigator should inform the patients of any new information relevant to the patients' willingness to continue participation in the study, before obtaining the written consent.

11.4. CONFIDENTIALITY / IDENTIFICATION OF PATIENTS

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the study drug used in this trial.

It is the Investigator's responsibility that sufficient information on the identity of the patients will be retained.

The trial monitor, the Sponsor's auditor, the IECs/IRBs and the regulatory authorities should have direct access to all requested trial-related records, and agree to keep the identity of study patients confidential.

The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Explicit consent for the processing of personal data will be obtained from the participating patient before data collection, and this consent should also address the transfer of the data to other entities and countries.

PharmaMar shall comply with the Directive 95/46/EEC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

11.5. CASE REPORT FORMS

Case report forms (CRFs) will be used to record all data for each patient. It is the responsibility of the Investigator to ensure that the CRFs are properly and completely filled in. CRFs must be completed for all patients who have given their informed consent and have been enrolled into the study.

A patient's source documentation is the physician's patient records, and as such they should be maintained at the study site.

The data collected in the CRF will be entered into PharmaMar databases, which comply with the Spanish Act implementing the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data.

11.6. INSURANCE

The Sponsor will provide insurance or indemnity in accordance with applicable regulatory requirements.

11.7. RETENTION OF RECORDS

The Investigator/Institution should maintain trial documents according to Section 8 of the ICH Topic E6 (R1) Guideline for Good Clinical Practice and as required by applicable regulatory requirements.

Essential documents should be retained as per the aforementioned ICH guideline or for a longer period of time, if required by the applicable regulations.

11.8. USE OF INFORMATION AND PUBLICATIONS

Before the investigators of this study submit a paper or abstract for publication or otherwise publicly disclose information concerning the study drug or products, PharmaMar must be provided with at least 60 days to revise and approve the proposed publication or disclosure to ensure that confidential and proprietary data are protected.

If PharmaMar determines that patentable patient matter is disclosed in the proposed publication or disclosure, the publication or disclosure will be withheld for a period of time considered convenient. If the study is part of a multicenter study, the first publication of the study shall be made in conjunction with the presentation of a joint, multicenter publication of the study results with the investigators and the institutions from all appropriate sites that are contributing data, analysis and comments. However, if such a multicenter publication is not submitted within 12 months after conclusion, abandonment or termination of the study at all sites, the present study may be published individually in accordance with the procedure established above.

The order of the coauthors will reflect the relative contribution of each one to study development and analysis. In general, the first author will be the investigator who recruits the highest number of patients with information finally available for data

analysis. Relevant PharmaMar personnel who have fully participated in the study must be considered for co-authorship of the publication.

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Appendix 1. Samples, Methodology and Techniques of the Pharmacogenomic Substudy (Only on Samples Collected in the U.S.)

1. PGx Study Design

For those patients who consent to participate in the pharmacogenomic study, response to therapy will be correlated with RNA/protein expression levels of selected genes. Tumor tissue blocks used for the initial diagnosis of the disease and blood samples taken prior to the first PM00104 infusion of Cycle 1, Day 1, will be collected. Provision of samples for such pharmacogenomics analyses will be optional.

These analyses will include the use of transcriptional profiling technologies and other molecular biology techniques to identify and validate pharmacogenomic markers from pre-treatment tumor samples. These basal expression levels of these markers will be correlated with the patient's response outcome data. In addition, the experimental data will be analyzed with respect to duration of response, time to disease progression and overall survival.

The gene expression of selected DNA repair related genes and the determination of the genotype for the selected SNPs will be determined by qRT-PCR at the laboratory of Molecular Oncology of Pangaea Biotech, Barcelona, Spain. The DNA repair related protein expression analysis will be determined at the Molecular Pathology laboratory of CNIO (Centro Nacional de Investigaciones Oncológicas Madrid, Spain) by IHC techniques using the correspondent antibodies. GEP and IHC analysis will be determined at basal conditions; that is using the tumor tissue obtained at the diagnosis of the disease. SNP analysis will be performed on blood samples obtained before the treatment with PM00104.

All patients included in the study PM104-B-001-09 are eligible for the PGx studies. However, only those patients that voluntarily sign the Informed Consent for the Pharmacogenomic study will participate. The refusal for participation in the Pharmacogenomic study will not affect the participation in the associated clinical study.

2. Blood and Tumor Tissue Samples

PharmaMar will provide a "Guide for identification, packaging and shipment of Pharmacogenomic samples" detailing the procedures to follow for sample collection, labeling and shipment.

The ideal sample for gene mRNA expression analysis is paraffin-embedded tumor tissue obtained at the diagnosis of the disease because it is frequently conserved in the pathology archives and allows the determination of the mRNA expression analysis of selected genes by Quantitative RT-PCR.

Depending on the availability of the tissue blocks to be shipped outside the site, the investigator can choose between two options:

Option #1 (for sites that will be sending the paraffin-embedded tissue blocks): ship only the paraffin block to PharmaMar, at ambient temperature using the labeled zip-lock bag and the air-bag envelope provided. Fill the biopsy specimen number in the PGx Sample Collection Form. PharmaMar will take responsibility for processing the

tissue block and preparing the slides. The tissue block will be shipped back in 3-4 weeks after reception.

Option #2 (for sites that will not be sending paraffin blocks): mount the sample slices into the appropriate microscope slides. A detailed description of the procedure of cutting sections is provided in the "Guide for identification, packaging and shipment of Pharmacogenomic samples". Number and characteristics of the paraffin embedded tissue samples required.

1.- RNA slices: five tissue slices 5 µm thick mounted in PEN Membrane Slides for microdissection of tumoral tissue to extract RNA.

2.- IHC slices: ten tissue slices 3 µm thick mounted in SuperFrost Slides for immunohistochemistry analysis.

Blood samples: 10 ml of patient's peripheral blood in a 10 ml purple top tube containing EDTA as anticoagulant. Blood samples have to be stored frozen at least at –20ºC until shipment.

3. Patient Samples Labeling and Shipment

The blocks or the slides and the tubes containing the samples are labelled with coded numbers (PGx code) to ensure the blindness of the study. Samples will be sent to PharmaMar stripped of all patient identifiers with the Investigator team holding the key that correlates the tumor sample with the response to PM00104 and all patient's clinical data.

Sample shipments to PharmaMar will be performed every 6 months or 5 patients, whatever come first. PharmaMar will contact the investigator requesting the preparation of the shipment and will obtain the legal authorizations required for shipping biological samples (legal authorizations vary between countries of origin of the samples). The contact person in PharmaMar is Dr. Juan Carlos Tercero, jctercero@pharmamar.com, phone +34 91 846 60 23.

PharmaMar will cover all the expenses of the shipment and will provide all the shipment materials in advance.

PharmaMar is responsible for long-term storage of the samples and for the shipment to the genomics laboratories where the PGx analysis will be performed. Once tissue slices have been obtained, the tissue blocks will be returned to the pathology departments of origin 3-4 weeks after reception

The labeling and shipment of patient samples is described in more detail in the "Guide for identification, packaging and shipment of Pharmacogenomic samples".

4. Methodology for Analysis

a. Tumoral tissue microdisection: Those samples having large proportion of non-tumoral tissue need to be laser microdissected for isolation of the tumoral cells. Paraffin-embedded tissue slices need to be mounted on Pen Membrane microscope slides provided by PharmaMar. The tumoral tissue is laser captured under the microscope and separated for DNA/RNA extraction. If necessary, several tissue slices will be microdissected to obtain a minimum of 1 mm^2 of microdissected tumoral tissue that is required for the analysis.

b. DNA/RNA isolation: DNA is isolated using a commercial kit (QIAmp® DNA blood Mini kit; Qiagen). Total RNA was recovered from formalin-fixed, paraffin-embedded surgical specimens using proteinase K digestion and phenol-chloroform extraction.

c. Quantitation of mRNA expression will be analyzed by real-time quantitative reverse transcriptase PCR using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA) in a two-step process. In the reverse-transcription (RT) step, cDNA synthesized by reverse transcription from 1-100 ng of total RNA extracted from the samples using random primers. In the PCR step, PCR products are synthesized from cDNA samples using the TaqMan Universal PCR Master Mix. The PCR step employs the 5′ nuclease assay, which produces a fluorescent signal proportional to the amount of amplified DNA produced in each PCR cycle. Finally, the initial relative amount of mRNA is determined by the Cycle Threshold method, using as control the control gene and the control samples. The mRNA expression levels are normalized to the B-actin expression in the same samples.

d. Genotyping: genotyping of the single nucleotide polymorphisms is performed using the 5' nuclease allelic discrimination assay. The PrimerExpress program (Applied Biosystems) was used to design probes and primers for the analysis of each single nucleotide polymorphism. To avoid amplification of non-specific DNA all oligonucleotide sequences were checked in the BLAST Search program (available at http://www.ncbi.nlm.nih.gov/LocusLink/BLAST/). Each reaction mixture (25 μL) of polymerase chain reaction contained 50 ng of DNA, 900 nM of each forward and reverse primer, 300 nM of each allele specific probe and 12.5 μL of Taqman Universal PCR Master Mix (Applied Biosystems). Fluorescence in each sample well is measured each cycle before and after polymerase chain reaction using ABI Prism 7000 Sequence Detection System (Applied Biosystems). Data are analyzed using Allelic Discrimination Program (Applied Biosystems). To assure the accuracy of genotyping with the use of this method, 10 DNA samples will be randomly selected and subjected them to polymerase chain reaction and direct DNA sequencing in an ABI Prism 310 Sequence Detection System (Applied Biosystems).

e. Generation of tissue-arrays (TMA): for characterization of IHC protein expression, we will construct a tissue-array containing the patient samples assembled as previously described (1). Briefly, two 1.5-mm-diameter cylinders of tissue are taken from representative areas of each archival paraffin block and arrayed into a new recipient paraffin block with a custom-built precision instrument (Beecher Instruments, Silver Spring, MD) according to the previously described method (2). Areas chosen for the cylinder core have high tumor cellularity. In order to evaluate the most active part of each primary tumor, the invasive border of the tumor in large lesions and all tumor cells in smaller samples are selected. In addition, normal tissues and three different cell lines with known cell-cycle alterations are placed adjacent to tumoral tissues to serve as internal controls and to ensure the quality of staining slides. Initial

sections are stained for hematoxylin and eosin to verify the histopathological findings.

f. Immunohistochemistry: three-micrometer tissue sections from the TMA blocks are sectioned and applied to special immunohistochemistry coated slides (Dako). These slides are baked overnight in a 56ºC oven. Sections are deparaffinized in xylene for 20 minutes, rehydrated through a graded ethanol series and washed with phosphate-buffered saline. Antigen retrieval is achieved by a 2-minute heat treatment in a pressure cooker, containing 1 l of 10 mM sodium citrate buffer, pH 6.5, that has been previously brought to the boil. Before staining, endogenous peroxidase activity is quenched with 1.5 % hydrogen peroxide in methanol for 10 min. Immunohistochemical staining is performed on these sections using adequate antibodies for detection of the selected proteins. After incubation, in the case of nuclear markers, immunodetection is performed with the LSAB Visualization System (Dako, Glostrup, Denmark) using 3,3'-diaminobenzidine chromogen as substrate, according to the manufacturer's instructions. In addition, whenever possible, cytoplasmic markers are visualized with the APAAP system (alkaline phosphatase anti-alkaline phosphatase, Dako, Glostrup, Denmark), using neo-fuchsine chromogen as substrate to rule out the possibility of a role of endogenous melanin in the observed reactivity. All sections are counterstained with hematoxylin. Negative controls are obtained by omitting the primary antibody.

g. Scoring systems: immunostaining intensity is evaluated by two different pathologists and scored using uniform and clear cut-off criteria, in order to maintain the reproducibility of the method. Discrepancies are resolved by simultaneous re-evaluation. Briefly, the result of immunostaining is recorded as negative or positive, and low versus high expression, taking into account the expression in tumoral cells and the specific cut-off for each marker. As a general criterion, the cut-offs are selected in order to facilitate reproducibility, and when possible, to translate biological events.

h. Statistics: clinical data and immunohistochemistry scoring are performed blind, and data are compiled only after all analyses are completed. Fisher's exact test is used to test whether a specific protein-expression profile is associated with the clinical outcome after Zalypsis® treatment. Significance is concluded for values of $p < 0.05$. The prognosis value of markers will be explored for objective clinical response, progression free survival and survival. In each case, a multivariate model is developed by backwards elimination, starting with all markers with a p-value lower than 0.10 in the univariate analysis. Hazard ratios will be calculated with the univariate Cox model, and comparison between Kaplan-Meier survival and progression free survival curves will be performed with the log-rank test. All tests of statistical significance are two-sided, and significance is set at 0.05 except in multiple comparisons, where it is set at 0.017 in accordance with the Bonferroni correction.

References:

1. Kononen, J., Bubendorf, L., Kallioniemi, A., Barlund, M., Schraml, P., Leighton, S., Torhorst, J., Mihatsch, M. J., Sauter, G., and Kallioniemi, O. P. (1998). Tissue microarrays for high-throughput molecular profiling of tumor specimens. Nat Med 4, 844-847

2. Schöffski P, Casali PG, Taron M, Van Oosterom AT, Judson IR, Grosso F, et al. DNA repair functionality modulates the clinical outcome of patients with advanced sarcoma treated with trabectedin (ET-743). Proc Am Soc Clin Oncol. 2006; 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement): 9522.

Appendix 2. ECOG Performance Status Assessment Scale

Grade	Activity
0	Able to carry on all normal activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix 3. Cockcroft and Gault Formula

$$\text{Creatinine clearance (ml/min)} = \frac{[(140\text{-age (years)}) \times \text{weight (Kg)}]}{72 \times \text{serum creatinine (mg/dl)}} \times G^{1}$$

[1]G (Gender) = 0.85 if female; 1 if male.

Reference: Cockcroft, DW, Gault, H. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Appendix 4. Evaluation of Response. The RECIST

Measurability of tumor lesions at baseline

Definitions

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be pathologically confirmed.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm. With spiral CT scan, lesions must be ≥ 10 mm in at least one dimension.

Non-measurable lesions - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and other non-measurable lesions. These include: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, cutaneous or pulmonary lymphangitis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

All measurements should be recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before the beginning of the treatment.

For the present study, lesions in irradiated area are considered as measurable provided radiotherapy has ended three months prior to entry, and they have progressed or appeared since then. They must satisfy the previous criteria.

Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography -including a ruler to estimate the size of the lesion- is recommended.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen and pelvis, while head and neck tumors and those of the extremities usually require specific protocols.

Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It may be used as a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Tumor response evaluation

Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

*** Complete Response (CR):**	Disappearance of all target lesions.
*** Partial Response (PR):**	At least a 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum LD.
*** Progression (PD):**	At least a 20% increase in the sum of LD of target lesions, taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
*** Stable Disease (SD):**	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest sum LD since the treatment started.

Evaluation of non target lesions

*** Complete Response (CR):**	Disappearance of all non-target lesions and normalization of tumor marker level.
*** Incomplete Response / Stable Disease**	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
*** Progression (PD):**	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of best overall morphological response

The best overall morphological response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than four weeks after the criteria for response were first met. If PR or CR is found at Week 6, it is recommended that response is confirmed using the evaluation scheduled at Week 12.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry, at a minimum 6-week interval.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Every effort should be made to document objective progression, even after discontinuation of treatment.

Appendix 5. Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations

of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the

researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    a. The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    b. Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.