Pharma Mar, S.A. Sociedad Unipersonal
Colmenar Viejo
28770 Madrid, Spain

# CLINICAL STUDY REPORT

## PM104-B-004-10

### PHASE II CLINICAL AND PHARMACOKINETIC TRIAL OF PM00104 (ZALYPSIS®) IN UROTHELIAL CARCINOMA PATIENTS PROGRESSING AFTER FIRST-LINE PLATINUM-BASED REGIMEN

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| **Compound Number:** | PM00104 |
| **Investigational Medicinal Product:** | Zalypsis® |
| **Study Design:** | Multicenter, open-label, exploratory phase II clinical and pharmacokinetic trial |
| **Protocol Number:** | PM104-B-004-10 |
| **Eudra CT:** | 2010-020994-18 |
| **Study Start Date:** | 24 November 2010 (First consent signed) |
| **Study Completion Date:** | 23 February 2012 (Date of the end of the study according to the study protocol)<br>3 April 2012 (Date of last follow-up) |
| **Principal/Coordinating Investigator Name and Affiliation:** | **Daniel Castellano, M.D.**<br>Hospital Universitario Doce de Octubre<br>Avda. Córdoba s/n<br>28041 Madrid, Spain<br>Phone: + 34 913 908 349<br>Fax: + 34 914 603 310<br>E-mail: cdanicas@hotmail.com |
| **Responsible Medical Officer:** | **Arturo Soto Matos-Pita, M.D.**<br>Clinical Research and Development Director<br>PharmaMar S.A., Sociedad Unipersonal<br>(abbreviated as PharmaMar in this report)<br>Avenida de los Reyes, 1<br>Polígono Industrial La Mina-Norte<br>28770 Colmenar Viejo, Madrid, Spain<br>Phone: +34 918 466 053<br>Fax: +34 918 234 504<br>E-mail: asoto@pharmamar.com |
| **Earlier Approved Reports:** | None |
| **Version:** | Final version |
| **Approval Date:** | 12 April 2013 |

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

# 2. SYNOPSIS

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| **Name of Sponsor/Company:** PharmaMar S.A., Sociedad Unipersonal<br>**Name of finished product:** Zalypsis®<br>**Name of active ingredient(s):** PM00104 | **Individual Study Table Referring to Part of the Dossier**<br><br>**Volume:**<br><br>**Page:** | **(*For National Authority Use only*)** |
| **Protocol number** | PM104-B-004-10 | |
| **Eudra CT** | 2010-020994-18 | |
| **Title of the study** | Phase II clinical and pharmacokinetic trial of PM00104 (Zalypsis®) in urothelial carcinoma patients progressing after first-line platinum-based regimen. | |
| **Coordinating investigator** | **Daniel Castellano, M.D.**<br>Hospital Universitario Doce de Octubre, Madrid, Spain. | |
| **Study centers** | Hospital Universitario Doce de Octubre, Madrid, Spain.<br>Hospital Vall d'Hebrón, Barcelona, Spain.<br>Hospital Universitario del Mar, Barcelona, Spain.<br>Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.<br>Hospital Universitario Germans Trias i Pujol, Badalona, Spain. | |
| **Publication (references)** | At the time of this report no articles have been published on the study described herein.<br>Preliminary results of this study were presented at:<br>• *American Society of Clinical Oncology (ASCO) 2012 Meeting.* Ghanem I, Carles J, Bellmunt Molins J, Coronado C, Maroto JP, Font Pous A, Morales R. Suarez C, Etxaniz O, Capdevila, L, Martin Lorente C, Rodriguez C, Kahatt CM, Luque M, Castellano DE. Phase II clinical and pharmacokinetic (PK) trial of zalypsis (Z) in patients with urothelial carcinoma (UC) progressing after a first-line platinum-based regimen. J Clin Oncol 30(suppl; abstr e15001)(2012).<br>• *37th ESMO Congress, 2012.* Carles J, Bellmunt J, Maroto JP, Font A, Morales-Barrera R, Gahanem I, Suarez C, Martin Lorente C, Etxaniz O, Capdevila L, Coronado C, Castellano DE, Rodriguez C, Kahatt C, Luque M. Phase II clinical and pharmacokinetic (PK) trial of Zalypsis (Z) in patients with urothelial carcinoma (UC) progressing after a first-line platinum-based regimen. Ann Oncol 23(Supl 9), page 266 (abstract no.806P)(2012). | |
| **Study period:**<br>**. First consent signed**<br>**. Last consent signed**<br>**. First dose first cycle**<br>**. First dose last cycle**<br>**. Last follow-up** | <br>24 November 2010<br>2 June 2011<br>15 December 2010<br>27 October 2011<br>3 April 2012 | **Phase of Development:**<br><br>Phase II |
| **Study objectives** | **Primary:**<br>• To evaluate the antitumor activity of PM00104 administered as a 1-hour intravenous (i.v.) infusion on Day 1 every three weeks (D1 q3wk) to advanced and/or metastatic urothelial carcinoma patients progressing after first-line platinum-based chemotherapy.<br>**Secondary:**<br>• To determine the safety profile.<br>• To determine the pharmacokinetic (PK) profile.<br>• To determine the pharmacogenomic (PGx) profile. Hypothesis-generating exploratory PGx analyses were to be conducted to correlate the molecular parameters found in the tumor and blood samples of the patients with the clinical results achieved with PM00104 (finally, PGx analyses were not performed due to the lack of clinical benefit reported in this phase II clinical trial). | |
| **Methodology** | Exploratory, two-stage, phase II clinical trial evaluating PM00104 in patients with advanced and/or metastatic urothelial carcinoma progressing after first-line platinum-based chemotherapy. The schedule (1-hour i.v. infusion D1 q3wk) and dose (3 mg/m$^2$) evaluated in this phase II clinical trial were those recommended in a previous phase I study conducted in patients with advanced solid tumors (PM104-A-001-04), in which some patients with urothelial carcinoma were treated. | |

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| **Number of patients (planned and analyzed)** | **Planned number of patients:**<br>The study protocol established that, in the first stage, at least 17 evaluable patients had to be recruited. If ≥ 4 patients achieved an objective response of any duration or were alive and progression-free at three months [i.e., achieved tumor control rate (TCR), the primary efficacy endpoint], the accrual had to be expanded with 20 additional evaluable patients in a second stage.<br>**Patients analyzed:**<br>No objective responses were observed, and only two of 20 patients included in the first study stage had progression-free survival (PFS) ≥ 3 months. However, one of these two patients was considered not evaluable for efficacy as he has pure squamous histological type and therefore he met exclusion criteria No. 2. Then, TCR (primary efficacy endpoint) was 5.3% (one in 19 evaluable patients). In accordance to the study protocol, a "no go decision" was taken and recruitment was closed without proceeding to the second stage. | |
| **Diagnosis and main selection criteria** | **Inclusion Criteria**<br>Patients who met all following criteria participated in the study:<br>**1.** Voluntary written informed consent, obtained from the patient before the beginning of any specific study procedure.<br>**2.** Histological confirmed advanced and/or metastatic urothelial carcinoma, including transitional cell carcinoma (TCC) and mixed histologies with TCC component, from renal pelvis, ureter, bladder or urethra.<br>**3.** Patients had to have failed to one prior line of platinum-based chemotherapy for urothelial cancer and demonstrated progression or relapse before study entry.<br>**4.** Recovery to grade 1 or less from the effects of drug-related adverse events (AEs) derived from previous treatments, excluding grade 2 alopecia according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v.4.0).<br>**5.** At least one measurable lesion ("target lesion" according to the Response Evaluation Criteria in Solid Tumors, RECIST v.1.1), located in a non-irradiated area and adequately measured less than four weeks before study entry. Tumors within a previously irradiated field were designated as "non-target" lesions unless progression was clearly documented or biopsy proven.<br>**6.** Age ≥ 18 years.<br>**7.** Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 2.<br>**8.** Life expectancy ≥ 3 months.<br>**9.** Appropriate bone marrow reserve, and renal and hepatic functions:<br>a) Platelet count ≥ 100 x $10^9$/l, hemoglobin ≥ 9 g/dl and absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/l.<br>b) Alkaline phosphatase (AP) ≤ 2.5 x upper limit of normal (ULN) (≤ 5 x ULN in case of extensive bone metastases).<br>c) Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤ 3 x ULN (≤ 5 x ULN in case of hepatic metastases).<br>d) Total bilirubin ≤ 1.5 x ULN, unless due to Gilbert's syndrome.<br>e) Renal function: patients with calculated creatinine clearance (using Cockcroft and Gault´s formula) ≥ 30 ml/min.<br>f) Albumin ≥ 2.5 g/dl.<br>g) Troponin I within normal ranges.<br>**10.** Left ventricular ejection fraction (LVEF) within normal limits (LVEF ≥ 50%).<br>**11.** Women of childbearing potential had to have a negative serum pregnancy test before study entry. In case of childbearing potential, the patients and their partners had to 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 included complete abstinence, intrauterine contraceptive device, oral contraceptive, subdermal implant and | |

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| **Name of finished product:** Zalypsis® | **Volume:** | |
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double barrier (condom with a contraceptive sponge or contraceptive suppository).

**Exclusion Criteria**

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

1. Prior therapy with PM00104.
2. Patients with any of the following histologies: neuroendocrine, pure squamous, pure adenocarcinoma, small cell carcinomas, or non-epithelial neoplasms such as sarcomas.
3. Patients who had isolated recurrences potentially curable with radiation therapy or surgery.
4. Pregnant or lactating women, or in case of childbearing potential, women not using an appropriate contraceptive method.
5. Less than three weeks from prior biological therapy or chemotherapy.
6. Patients who received more than two lines of any prior anticancer therapy.
7. Less than 12 weeks from prior radiation therapy involving the whole pelvis or over 50% of the spine, provided that acute effects of radiation treatment had resolved. Palliative radiation therapy (i.e., for control of pain from bone metastases) had to be discontinued before study entry for at least one week.
8. Patients with a prior invasive malignancy (except non-melanoma skin cancer or *in situ* cervical cancer) who have had any evidence of disease within the last five years or whose prior malignancy treatment contraindicated the current protocol therapy.
9. Evidence of progressive or symptomatic central nervous system metastases or leptomeningeal metastases.
10. 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 or left ventricular systolic dysfunction.
        - Symptomatic arrhythmia or any arrhythmia requiring ongoing treatment.
        - Abnormal electrocardiogram (ECG), i.e., patients with the following were 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 ≥ grade 1 aortic valve disease, mitral valve disease or severe pulmonary valve 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).
    e) Hepatitis B or C virus infection.
    f) Immunocompromised patients, including those known to be infected with the human immunodeficiency virus.
    g) 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).
11. Any other major illness that, in the Investigator's judgment, could substantially increase the risk associated with the patient's participation in the study. The

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| | investigator should feel free to consult the Sponsor for uncertainty in this regard.<br>**12.** Limitation of the patient's ability to comply with the treatment or to follow-up at a participating center. Patients enrolled into this trial had to be treated and followed at a participating center.<br>**13.** Treatment with any investigational product within 30 days prior to inclusion in the study.<br>**14.** Known hypersensitivity to any component of Zalypsis®. | |
| **Test product, dose and mode of administration** | PM00104 was administered at a dose of 3 mg/m$^2$ as a 1-hour i.v. infusion on D1 q3wk. Before PM00104 infusion, the patients received prophylactic treatment for emesis consisting of dexamethasone 8 mg i.v. and 5-HT3 antagonists (ondansetron 8 mg or equivalent), according to the American Society of 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 could be administered, or the duration of treatment with 5-HT3 antagonists and/or dexamethasone could be extended.<br>PM00104 was provided as a powder for concentrate for solution for infusion in only one strength (2.5 mg/vial). The numbers of PM00104 batches were as follows:<br>• **2.5-mg vial batches:** 00203 and 81103. | |
| **Duration of treatment** | Patients remained on treatment in the absence of confirmed or unacceptable toxicity that was not resolved after applying the appropriate dose delays or reductions. | |
| **Criteria for evaluation**<br>**Efficacy**<br><br><br><br><br><br>**Pharmacogenomics**<br><br><br><br><br>**Safety** | <br>The primary efficacy endpoint was tumor control rate (TCR), defined as the percentage of patients with confirmed objective response (OR), either complete response (CR) or partial response (PR) of any duration, or patients alive and progression-free at three months (PFS3) according to the RECIST v.1.1.<br>Secondary endpoints of efficacy included overall response rate (ORR), duration of response (DR), progression-free survival (PFS), progression-free survival rate at six months (PFS6) and overall survival (OS).<br>The study included hypothesis-generating exploratory PGx analyses to be conducted to correlate the molecular parameters found in the tumor and blood samples of the patients with the clinical results achieved with PM00104. Finally, these PGx analyses were not performed due to the lack of clinical benefit reported in this phase II clinical trial.<br>All patients who received at least one total or partial infusion of PM00104 were evaluable for safety. | |
| **Statistical methodology** | Continuous variables were tabulated and presented with summary statistics (i.e., mean, standard deviation, median and range). Categorical variables were summarized in frequency tables by means of counts and percentages.<br>**Efficacy:** Binomial estimates with exact 95% confidence intervals were calculated for the analysis of the main endpoint (TCR), overall response and PFS3 rate. Time-to-event endpoints (DR, PFS and OS) were analyzed according to the Kaplan-Meier method.<br>**Pharmacokinetics:** All individual PK parameters were tabulated and summarized for the evaluable PK population using count (n), arithmetic mean, median, maximum, minimum, standard deviation (SDev) and coefficient of variation (CV%). Linear regression of natural log-transformed plasma PK parameters predicted by natural log-transformed demographic and other log-transformed covariates (liver enzymes, creatine phosphokinase, bilirubin, creatinine and creatinine clearance, total proteins and hematological parameters) was carried out. Ninety-five percent confidence intervals (CIs) for the slope, and p-test with a level of significance of 0.05 were calculated.<br>**Safety:** Safety was evaluated using clinical examinations, which comprised vital signs analysis, clinical assessment of AEs, changes in laboratory parameters (hematological and biochemical, including liver function tests), deaths, reason for study discontinuations, dose delays and reductions, and any other analyses that could be | |

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| | considered necessary to characterize the safety profile of PM00104 in advanced and/or metastatic urothelial carcinoma. Cardiac tests as troponin I, ECG and LVEF measurements were analyzed descriptively. All AEs were classified according to the NCI-CTCAE, v.4.0, and were coded using MedDRA, v.11.0. | |
| **Results (1):** Patient characteristics | Most patients (n=17; 85.0%) were males, their median age was 71 years (range, 54-83 years), and the majority (75.0%) had ECOG PS=1. The most common primary tumor was bladder carcinoma (n=16; 80.0%) and the most reported histological type was TCC (n=17; 85.0%). Disease at study entry was metastatic in 19 patients (95.0%) and locally advanced in one patient (5.0%). The median number of sites involved per patient was 3 (range, 1-4 sites). The most common disease locations were liver, lung and lymph nodes (n=9; 45.0% each).<br>Six patients (30.0%) had previously received radiotherapy. Twelve patients (60.0%) had undergone previous curative surgery. All 20 patients had previously received systemic anticancer therapy. The median number of lines of systemic anticancer therapy was one (range, 1-2 lines). As defined per protocol, all 20 patients had received prior platinum-based chemotherapy. | |
| **Results (2):** Efficacy | The primary analysis of efficacy was based on the *efficacy population* (i.e., the 19 evaluable patients). Only one evaluable patient (a male with pure TCC of the ureter) achieved TCR (stable disease as best response and PFS of 3.1 months) during the first study stage. Hence, the TCR was 5.3% (one of 19 evaluable patients). The number of patients with TCR was lower than that expected (≥4 patients) and, therefore, a "no go decision" was taken and the study was closed without proceeding to the second stage.<br>No objective responses per RECIST were achieved. Six evaluable patients (31.6%) had SD. Median PFS was 1.2 months (95% CI, 1.1-1.5 months) and median OS was 4.6 months (95% CI, 1.8-9.5 months). | |
| **Results (3):** Pharmacokinetics | PK profiles were available in 19 patients in the first cycle and in 14 patients in the second cycle. Mean PK results for PM00104 in the first cycle at the dose of 3 mg/m² [maximum plasma concentration ($C_{max}$)=48.57 µg/l and area under the curve from time zero to infinity (AUC)=154.97 h·µg/l] were similar than those observed in the phase I clinical trial PM104-A-001-04 at 3 mg/m² in the first cycle ($C_{max}$=35.17 µg/l and AUC=155.50 h·µg/l). Additionally, the mean clearance (CL) found in the current phase II trial (first cycle 38.77 l/h, second cycle 35.58 l/h) is in accordance with the CL (43.7 l/h) reported in the PM00104 population PK publication. Therefore, the PK behavior found here is similar to that reported in previous studies evaluating PM00104.<br>No PK differences were reported between the first and second cycle. The inter- and intra- patient variability was close to 20% for $C_{max}$, AUC and CL in patients treated at 3 mg/m² in both cycles. There were no trends in $C_{max}$ or AUC between cycles; therefore, PM00104 accumulation was not reported between the first two cycles.<br>The effect of PM00104 exposure on hematological parameters was assessed in Cycle 1, while serial assessment of troponin I was done in both Cycle 1 and Cycle 2. The results showed only a relationship between AUC and decreases in platelets. With respect to troponin I assessment, only few troponin I concentrations (higher than 0.1 ng/ml) were detected and none of them were related to AUC or $C_{max}$. | |
| **Results (4):** Safety | All 20 patients included in this study received at least one infusion of PM00104 and therefore were evaluable for safety. The median number of cycles administered per patient was 2 (range, 1-9 cycles).<br>The most common PM00104-related AE was fatigue (n=10 patients, 50.0%). Other common PM00104-related AEs included anorexia, nausea and troponin I increase (n=5; 25.0% each). Overall, most PM00104-related AEs were grade 1/2. The following AEs reached grade 3: troponin I increase (n=5; 25.0%), fatigue, hypotension, *Pseudomonas* infection and troponin T increase (n=1 each; 5.0%). Four of the five patients with grade 3 troponin I increases required reduction of PM00104 dose, but none of these troponin I increases was associated with clinical symptoms or ECG and ECHO findings. None of PM00104-related AEs resulted in treatment | |

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| | discontinuation and no deaths were reported as outcome of PM00104-related AEs.<br>Three patients had serious adverse events (SAEs) related to PM00104 treatment, which consisted of grade 3 anemia (this patient also had grade 3 acute renal failure related to the disease under study), grade 3 *Pseudomonas* infection (declared a suspected unexpected serious adverse reaction, SUSAR) and grade 3 hypotension (requiring interruption of PM00104 infusion for 10 min); all three SAEs were resolved.<br>The most common hematological abnormality was anemia, which occurred in all 20 patients, three of them with grade 3 (grade 1/2 anemia was already present at baseline in 14 of these 20 patients). One case of grade 3 neutropenia and one case of grade 3 thrombocytopenia were observed. None of these laboratory abnormalities caused changes in the study treatment.<br>Biochemical abnormalities were mostly grade 1/2. As expected from the disease under study, creatinine increase was the most frequent biochemical abnormality (n=19 patients; 95.0%), but only two cases reached grade 3 (both of them with grade 1 creatinine at baseline). Indeed, 12 of 20 patients (60%) had grade 1/2 creatinine increase at baseline. Two patients had grade 3 transaminases increases, concomitant in one case with grade 3 AP increase. Usually, these biochemical abnormalities had no effects on PM00104 treatment. Only one case of PM00104-unrelated grade 3 lipase increase led to a 3-day dose delay in one cycle. | |
| **Conclusions** | The primary endpoint of the study was unmet and, therefore, no further evaluation of PM00104 3 mg/m$^2$ 1-hour D1 q3wk i.v. infusion as treatment of patients with advanced and/or metastatic urothelial carcinoma progressing after first-line platinum-based chemotherapy is planned. Pharmacokinetic results were very similar to those obtained in previous studies and in accordance with the population PK analysis previously published. The toxicities found related to PM00104 exposure were those already known, and there were only some isolated troponin I increases unrelated to PM00104 exposure (AUC or $C_{max}$). This PM00104 schedule has an acceptable tolerability, with mostly mild to moderate, reversible and predictable adverse reactions. | |
| **Date of report (final version)** | 12 April 2013 | |