Pharma Mar, S.A.
Colmenar Viejo, Madrid, Spain

**FINAL STUDY REPORT**

# APL-B-005-02

## PHASE II MULTICENTER,OPEN-LABEL, CLINICAL AND PHARMACOKINETIC STUDY OF APLIDIN® AS A 3-HOUR INFUSION EVERY 2 WEEKS, IN PATIENTS WITH ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM, RELAPSING OR PROGRESSING AFTER FIRST LINE CHEMOTHERAPY

| | |
|---|---|
| **Compound name (INN):** | Plitidepsin |
| **Investigational Medicinal Product:** | Aplidin® |
| **Study design:** | Non-randomized, open-label, single-arm, multicenter, exploratory, phase II study |
| **Protocol number:** | APL-B-005-02 |
| **Study start date:** | 1 October 2004 (First consent signed) |
| **Study completion date:** | 16 February 2007 (Last follow-up) |
| **Principal investigator name and affiliation:** | **Prof. Patrick Schöffski, M.D., M.P.H.**<br>Department of Clinical Oncology<br>U. Z. Gasthuisberg; Catholic University Leuven<br>Herestraat 49, 3000 Leuven, Belgium<br>Phone: +32 16 34 69 00/16; Fax: +32 16 34 69 01/24<br>E-mail: patrick.schoffski@uz.kuleuven.ac.be |
| **Responsible medical officer:** | **Alejandro Yovine, M.D.**<br>Clinical Research and Development Director<br>Pharma Mar S.A.<br>(mentioned as Pharma Mar in this report)<br>Avenida de los Reyes, 1<br>Polígono Industrial La Mina-Norte<br>28770 Colmenar Viejo, Madrid, Spain<br>Phone: +34 918 466 014; Fax: +34 918 234 504<br>E-mail: ayovine@pharmamar.com |
| **Earlier approved reports:** | None |
| **Version:** | Final version |
| **Approval date:** | 18 March 2008 |

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

# 2. SYNOPSIS

| | | |
|---|---|---|
| **Name of Sponsor/Company: Pharma Mar, S.A.**<br>**Name of finished product:** Aplidin®<br>**Name of active ingredient(s):** Plitidepsin | **Individual Study Table Referring to Part of the Dossier**<br>**Volume:**<br>**Page:** | (*For National Authority Use only*) |
| **Protocol number** | APL-B-005-02 | |
| **Study title** | Phase II Multicenter, Open-label, Clinical and Pharmacokinetic Study of Aplidin® as a 3-Hour Infusion Every 2 Weeks, in Patients with Advanced or Metastatic Transitional Cell Carcinoma of the Urothelium, Relapsing or Progressing after First Line Chemotherapy. | |
| **Principal investigator** | **Prof. Patrick Schöffski, M.D., M.P.H.**, Catholic University Leuven, Belgium. | |
| **Co-investigators** | **Jean P. Droz, M.D., Ph.D.** (Centre Leon Berard, Lyon, France)<br>**Luis Paz-Ares, M.D., Ph.D.** (Hospital Universitario 12 de Octubre, Madrid, Spain)<br>**Stephane Culine, M.D.** (Parc Euromedicine, Montpellier, France)<br>**Enrique Gallardo, M.D.** (Corporació Parc Taulí, Sabadell, Spain)<br>**Joan Carles Galceran, M.D.** (Hospital Universitari del Mar, Barcelona, Spain)<br>**Miguel Angel Climent Duran, M.D.** (Instituto Valenciano de Oncología, Valencia, Spain) | |
| **Study centers** | **Catholic University Leuven**<br>U. Z. Gasthuisberg<br>Department of Clinical Oncology<br>Herestraat 49, 3000 Leuven, Belgium<br>**Hospital Universitario 12 de Octubre**<br>Servicio de Oncología Médica<br>Edificio Maternidad. 2ª Planta<br>Ctra. de Andalucía, Km 5,5.<br>28041 Madrid, Spain<br>**Corporació Parc Taulí**<br>Hospital de Sabadell<br>Servicio de Oncología<br>C/ Parc Taulí, s/n.<br>08027 Sabadell (Barcelona), Spain<br>**Instituto Valenciano de Oncología**<br>C. Profesor Beltrán Báguena 19<br>46009 Valencia, Spain | **Centre Léon Bérard**<br>Dept of Medical Oncology<br>28 Rue Laennec<br>Lyon F-69008, France<br>**Parc Euromedicine**<br>C.R.L.C. Vall d'Aurelle<br>323 Rue des Apothicaires<br>34298 Montpellier, France<br>**Hospital Universitari del Mar**<br>Servicio de Oncología<br>Passeig Marítim, 25-29<br>08003 Ciutat Vella, Barcelona, Spain |
| **Publications (references)** | At the time of this report no articles have been published on the study described herein. | |
| **Study period:**<br>**- First consent signed**<br>**- Last consent signed**<br>**- Last infusion administered**<br>**- Last follow-up** | 1 October 2004<br>25 October 2006<br>28 December 2006<br>16 February 2007 | **Phase of Development:**<br>Phase II |
| **Objectives** | **Primary Objective:** | • To assess the antitumor activity of plitidepsin given as a 3-hour intravenous (i.v.) infusion every two weeks in patients with advanced or metastatic transitional cell carcinoma of the urothelium, relapsing or progressing after first-line chemotherapy. |
| | **Secondary Objective:** | • To further investigate the safety profile of plitidepsin given as a 3-hour i.v. infusion every two weeks in this patient population.<br>• To evaluate the pharmacokinetics (PK) of this schedule of plitidepsin in this patient population. |
| **Methodology** | Non-randomized, open-label, single-arm, multicenter, exploratory, phase II study. | |
| **Number of subjects/patients** | **Study design:**<br>A Simon's two-stage minimax design was applied to test the null hypothesis that the probability of objective response (confirmed partial or complete response) was ≤5% *vs.* the alternative hypothesis that it was p ≥20%. With this study design, the probability of early termination was 0.397. If plitidepsin was not effective, there was a 0.072 probability of concluding that it was. Otherwise, if plitidepsin was actually effective, there was a 0.099 probability of concluding that it was not. | |

| | | |
|---|---|---|
| **Name of Sponsor/Company: Pharma Mar, S.A.**<br>**Name of finished product:** Aplidin®<br>**Name of active ingredient(s):** Plitidepsin | **Individual Study Table Referring to Part of the Dossier**<br>**Volume:**<br>**Page:** | (*For National Authority Use only*) |
| | **Planned number of patients:**<br>Plitidepsin was to be tested on 18 evaluable patients in the first stage, and the trial was to be discontinued if no responses were observed. Otherwise, the trial had to go onto the second stage, and a total of 32 patients were to be evaluated. The Simons's design stated that if the total number of patients with an objective tumor response was ≤3, this schedule was not to be considered for further evaluation.<br><br>**Patients analyzed:**<br>Finally, the study was closed early after the first phase with 21 included and treated patients, as the efficacy reported in the 18 evaluable patients (two patients had SD according to RECIST that lasted less than six months) was considered too low to merit further interest for plitidepsin in transitional cell carcinoma of the urothelium of the bladder, ureter or renal pelvis. | |
| **Diagnosis and main criteria for inclusion** | **Inclusion Criteria**<br>1. Signed informed consent by the patient before starting any specific study procedures. If any patient was unable to give consent, it was to be obtained from the patient's legal representative if in accordance with local laws and regulations.<br>2. Transitional cell carcinoma (TCC) of the urothelium of the bladder, ureter or renal pelvis, with the following characteristics:<br>• Confirmed pathological diagnosis.<br>• Advanced (locally advanced or metastatic) and/or non-resectable disease (surgical exeresis did not eradicate all the macroscopic disease).<br>• Documented objective progression according to Response Evaluation Criteria In Solid Tumors (RECIST) within six months prior to registration.<br>• Presence of at least one measurable lesion (RECIST). In case of a single measurable lesion, pathological proof of malignancy was mandatory.<br>3. One previous line of systemic chemotherapy, which had to be discontinued at least three weeks before patient registration.<br>4. Prior radiotherapy was allowed. A minimum of four weeks (eight weeks in case of extensive prior radiotherapy) had to elapse between the end of the prior radiotherapy and patient registration. Previously irradiated lesions could not be used as indicator lesions unless a new lesion had occurred in a previously irradiated area.<br>5. Recovery from any toxicity derived from previous treatments. The presence of alopecia and National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade <2 symptomatic peripheral neuropathy was allowed.<br>6. Age ≥18 years.<br>7. Performance status (Eastern Cooperative Oncology Group, ECOG) ≤2.<br>8. Life expectancy > 3 months.<br>9. Adequate renal, hepatic, and bone marrow function (to be documented ≤14 days before inclusion in the study):<br>• Neutrophil count ≥1.5 x $10^9$/l;<br>• Platelet count ≥100 x $10^9$/l;<br>• Hemoglobin ≥9 g/dl;<br>• Creatinine clearance ≥40 ml/min (calculated according to the Cockcroft and Gault formula);<br>• Serum bilirubin ≤1.5 mg/dl and alkaline phosphatase (AP) ≤2.5 x upper limit of normal (ULN) (≤5 x ULN in case of extensive bone metastases);<br>• Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 x ULN (≤5 x ULN in case of liver metastases);<br>• Albumin ≥25 g/l.<br>10. Left ventricular ejection fraction (LVEF) within normal limits.<br><br>**Exclusion Criteria**<br>1. Prior therapy with plitidepsin.<br>2. More than one line of prior systemic chemotherapy.<br>3. Pregnant or lactating women; men and women of reproductive potential who were not using | |

| **Name of Sponsor/Company: Pharma Mar, S.A.** | **Individual Study Table Referring to Part of the Dossier** | (*For National Authority Use only*) |
|---|---|---|
| **Name of finished product:** Aplidin® | **Volume:** **Page:** | |
| **Name of active ingredient(s):** Plitidepsin | | |

| | |
|---|---|
| | effective contraceptive methods.<br>Females were eligible to enter and participate in this study if they were of:<br>• Non-child-bearing potential (i.e., physiologically incapable of becoming pregnant); or,<br>• Child-bearing potential, had a negative pregnancy test (urine or serum) at screening, and agreed to one of the following contraceptive methods:<br>  • Complete abstinence from intercourse from two weeks prior to administration of plitidepsin, throughout the study, and for a time interval after completion or premature discontinuation from the study until complete elimination of plitidepsin (proportional to a minimum of five plasma half-lives); or,<br>  • Female sterilization; or,<br>  • Sterilization of male partner; or,<br>  • Implants of levonorgestrel; or,<br>  • Injectable progestogen; or,<br>  • Oral contraceptive (combined or progestogen only); or,<br>  • Any intrauterine device (IUD) with published data showing that the lowest expected failure rate is less than 1% per year; or,<br>  • Double barrier method (two physical barriers or one physical barrier plus spermicide); or,<br>  • Any other method with published data showing that the lowest expected failure rate for that method is less than 1% per year.<br>Subject taking oral contraceptives should have been on a stable regimen for at least two months prior to screening.<br>4. History of another neoplastic disease (except for non-melanoma skin cancer, carcinoma *in situ* of any site or any other cancer curatively treated with no evidence of disease for at least 10 years).<br>5. Known symptomatic cerebral or leptomeningeal involvement.<br>6. Other relevant diseases or adverse clinical situations:<br>• Congestive heart failure or angina pectoris, myocardial infarction within 12 months before inclusion in the study;<br>• Uncontrolled arterial hypertension (i.e., current arterial diastolic blood pressure over 100 mmHg);<br>• Uncontrolled cardiac supraventricular arrhythmias (i.e., requiring a change in medication within the last three months or a hospital admission within the past six months);<br>• Cardiac ventricular arrhythmia;<br>• History of significant neurological or psychiatric disorders;<br>• Active infection;<br>• Myopathy or any clinical situation that causes significant and persistent elevation of creatine phosphokinase (CPK) >2.5 x ULN in two different assessments one week apart;<br>• Significant non-neoplastic liver disease (e.g., cirrhosis, active chronic hepatitis);<br>• Limitation of the patient's capacity to comply with the protocol treatment or follow-up protocol;<br>• Uncontrolled endocrine diseases (e.g., diabetes mellitus, hypothyroidism or hyperthyroidism) (i.e., requiring a change in medication within the last month or a hospital admission within the last three months).<br>7. Treatment with any investigational product in the 30-day period prior to inclusion in the study.<br>8. Known hypersensitivity to plitidepsin, mannitol, Cremophor EL, or ethanol. |
| **Test product, dose and mode of administration, batch numbers** | Plitidepsin was supplied by Pharma Mar S.A. (Colmenar Viejo, Madrid, Spain) as a lyophilized powder for concentrate for solution for infusion. Two different sizes of vials containing 0.5 mg and 2 mg of the active ingredient plitidepsin, respectively, and mannitol as the inactive ingredient were provided. The reconstitution solution was supplied in ampoules containing 1 ml and 4 ml of Cremophor/ethanol/Water for Injection (WFI) (15%/15%/70% v/v/v). Both vials and reconstituted solution had to be stored in a locked area with limited access at 5 ± 3ºC, and protected from light. Under these storage conditions, plitidepsin vials and reconstitution solvents were stable for 18 months and 12 months, respectively. Upon reconstitution of the 0.5-mg and 2-mg plitidepsin vials |

| **Name of Sponsor/Company: Pharma Mar, S.A.**<br>**Name of finished product:** Aplidin®<br>**Name of active ingredient(s):** Plitidepsin | **Individual Study Table Referring to Part of the Dossier**<br>**Volume:**<br>**Page:** | (*For National Authority Use only*) |
|---|---|---|
| | with 1-ml and 4-ml ampoules of reconstitution solvent, respectively, the reconstituted solution was clear, colorless, free from visible particles, and contained 0.5 mg/ml of plitidepsin. If not immediately used, this solution was chemically and physically stable for 24 hours (more if reconstitution was performed at controlled and validated aseptic conditions) at 2-8ºC. To prepare the drug for i.v. infusion, the reconstituted solution had to be immediately diluted with 0.9% w/v sodium chloride solution for infusion. The allowed dilution range was 1:10 to 1:400 (v:v). The solution of plitidepsin for infusion was stable in 0.9% sodium chloride for 48 hours at temperatures not exceeding 25±2ºC and did not need to be protected from light.<br>The total volume of infusion was to be 250 ml for administration through the central venous catheter (recommended way). In cases where administration occurred through a peripheral line, the reconstituted drug was to be diluted to 1000-1500 ml of total volume. An in-line filter of 0.2 µm had to be used for infusion. The infusion rate was to be established in a manner that ensured that the total dose of infusion was infused within three hours, either through a peripheral or a central i.v. line.<br>The batch numbers of plitidepsin used in this study were as follows:<br>• **0.5-mg vials:** #04K25 and #01G02.<br>• **2-mg vials:** #05C10, #04H27, #03I25, and #05E25. | |
| **Duration of treatment** | Plitidepsin was to be administered at a starting dose of 5 mg/m$^2$, as a 3-hour continuous i.v. infusion repeated every two weeks. Each administration of plitidepsin was considered a cycle (one cycle = two weeks). Treatment cycles were repeated every two weeks for a maximum of six months except in case of disease progression, unacceptable toxicity, patient refusal or treatment delay >2 weeks (except in case of obvious patient's benefit). | |
| **Criteria for evaluation** | **Primary Endpoint:**<br>• Objective tumor response defined as the sum of complete (CR) and partial (PR) responses, according to RECIST.<br>**Secondary Endpoints:**<br>• Stable disease (according to RECIST) lasting for at least six months.<br>• Tumor response duration and time to progression (TTP).<br>• Progression-free survival (PFS) and overall survival (OS).<br>• Description of pharmacokinetic (PK) parameters.<br>• Characterization of toxicity, serious adverse events (SAEs) and treatment withdrawals. | |
| **Statistical methodology** | Objective response rates were analyzed in all evaluable patients (i.e., patients having received a minimum of two treatment cycles of plitidepsin and with at least one disease assessment performed at least six weeks after start of treatment). Additionally, eligible patients who experienced early disease progression, died of progressive disease prior to response evaluation or stopped treatment because of unmanageable toxicity were also considered evaluable for response and categorized as "non-responders". Safety parameters had to be evaluated in all subjects who received at least one infusion (or part of it) of plitidepsin according to NCI-CTC (version 3.0).<br>Descriptive statistics (mean, median, standard deviation and 95% confidence interval, range of value) were used in the analysis of demographic factors, response rate, safety profile and laboratory observations. TTP, PFS and OS were analyzed according to the Kaplan-Meier method. PFS and OS rates at fixed time points (three and six months and one year, respectively) were estimated using Kaplan-Meier analysis.<br>Whole blood samples (5 ml) for PK analysis had to be collected during the first and third infusions at different time intervals from the arm contralateral to the one used for infusion. PK results were to be obtained using Bayesian and/or single stage population methods. | |
| **Results (1):**<br><u>Patient characteristics</u> | A total of 21 patients with confirmed TCC of the urothelium were enrolled at five medical institutions. Patients had a median age of 64.0 years (range, 41-72 years), 16 patients (76.2%) were male and all save one were Caucasians. Most patients had ECOG PS scores of 0 or 1, save one who had a PS score of 2. All patients had documented sites of disease at baseline (median of 1 site; range, 1-3). Lymph nodes (52.4%), liver (28.6%) and lung (14.3%) were the most common sites observed at baseline. All patients had received one prior line of chemotherapy, mostly in the advanced setting (76.2%), with a median of 2 agents per patient (range, 1-4 agents). Additionally, three patients (14.3%) had also received biological therapy. All patients had previously received surgical treatments, while radiotherapy had been given to five patients (23.8%). Twenty patients | |

| **Name of Sponsor/Company: Pharma Mar, S.A.**<br>**Name of finished product:** Aplidin®<br>**Name of active ingredient(s):** Plitidepsin | **Individual Study Table Referring to Part of the Dossier**<br>**Volume:**<br>**Page:** | (*For National Authority Use only*) |
|---|---|---|
| | (95.2%) entered the study showing signs and symptoms of disease at baseline, with a median of 5 symptoms per patient (range 0-8). Fatigue, hematuria, and arthralgia were the most frequent symptoms. All patients had grade 1/2 symptoms, save two patients who had grade 3 groin pain and hypertension NOS at study entry. Grade 1/2 anemia (n=15; 71.4%) and lymphopenia (n=11; 52.4%) were the only hematological abnormalities at baseline, save one patient who had grade 3 lymphopenia. Grade 1/2 increase of creatinine (n=10; 47.6%) and AP (n=8; 38.1%) were the most frequent biochemical abnormalities at baseline. Additionally, two patients had grade 3 hyponatremia. | |
| **Results (2):**<br>Extent of exposure to investigational product | **Drug exposure:**<br>Overall, 57 treatment cycles were administered to 21 patients during the study, with a median of 2 cycles per patient (range, 1-8). Most patients received two cycles (nine patients, 42.9%). The median relative calculated dose intensity was 99.4% (range, 52.1-101.0%).<br><br>**Dose delays and reductions:**<br>Five of the 36 cycles (13.9%) susceptible of delay were delayed in four patients (19.0%). All cycles were delayed due to non-treatment-related reasons and ranged from 3-7 days. Only one patient (4.8%) had one dose reduction during the study, which was due to an allergic reaction.<br><br>**Treatment discontinuation:**<br>Most patients discontinued plitidepsin treatment because of disease progression (n=13, 61.9%), early death (n=3; 14.3%), patient refusal (n=2; 9.5%), other reasons (n=2; 9.5%) and toxicity (n=1; 4.8%). | |
| **Results (3):**<br>Efficacy | Eighteen of 21 patients were evaluable for the analysis of efficacy endpoints. The primary efficacy endpoint was unmet, as no objective responses per RECIST were found in these 18 evaluable patients during the first stage of the study. Two patients (9.5%) had SD according to RECIST that lasted less than six months, while other patients showed progression of the disease. With a median follow-up of 4.6 months (95% confidence interval [CI], 3.3- upper limit not reached), the median TTP/PFS was 1.4 months (95% CI, 0.9-1.6 months) and the median OS was 2.3 months (95% CI, 1.4-4.6 months).<br>The results of this PK analysis will be pooled with those of other plitidepsin studies in a population PK analysis (independent of the present abbreviated final study report). | |
| **Results (4):**<br>Safety | All 21 patients were evaluated for extent of drug exposure and safety. Most plitidepsin-related AEs that occurred during the study were mild or moderate (grade 1/2) in severity and allowed the patients to remain on treatment. No plitidepsin-related grade 4 AEs were observed. Four patients (19.0%) had six grade 3 plitidepsin-related AEs: fatigue in two patients, and CPK increase, anorexia, musculoskeletal cramps and aggravation of Parkinson's disease in one patient each (all during one cycle). Two plitidepsin-related SAEs (6.5%) were observed in one patient each: grade 2 hypersensitivity and grade 3 worsening of Parkinson's disease. No toxic deaths occurred up to the date of last follow-up, all of them due to progression of the underlying disease. The laboratory toxicities most frequently found after plitidepsin administration were anemia (100% of patients/94.5% of cycles), lymphopenia (55.0% of patients/35.8% of cycles), and increases in the levels of AP (76.2% of patients/56.4% of cycles), blood transaminases (ALT: 61.9% of patients/58.2% of cycles; AST: 52.4% of patients/39.3% of cycles), creatinine (61.9% of patients/61.1% of cycles) and LDH (57.1% of patients and 32.7% of cycles). Lymphopenia was the only hematological toxicity that reached grade 4 in one patient and one cycle, while grade 3 lymphopenia and anemia were found in one patient and one cycle each. Only one case of grade 4 biochemical toxicity (LDH increase) occurred in one patient (4.8%) and one cycle (1.9%). Grade 3 AP occurred in four patients (19.0%) and five cycles (9.1%), grade 3 ALT was found in one patient (4.8%) and two cycles (3.6%), and grade 3 LDH was found in one patient (4.8%) and three cycles (5.8%). Other laboratory toxicities occurred at lower frequencies or were mild or moderate. | |
| **Results (5):**<br>Pharmacokinetics | The PK evaluation was based on a limited sampling approach (seven samples per patient). The results of this PK analysis will be pooled with those of other plitidepsin studies in a population PK analysis (independent of the present abbreviated final study report). | |

| | | |
|---|---|---|
| **Name of Sponsor/Company: Pharma Mar, S.A.** | **Individual Study Table Referring to Part of the Dossier**<br>**Volume:**<br>**Page:** | (*For National Authority Use only*) |
| **Name of finished product:** Aplidin® | | |
| **Name of active ingredient(s):** Plitidepsin | | |
| **Conclusions** | Plitidepsin 5 mg/m$^2$ 1-hour i.v. weekly infusion was a safe chemotherapy regimen with predictable and manageable toxicity. This phase II trial was early closed after the first stage, in accordance with the Simon's minimax design, because of the lack of objective tumor response as per RECIST (primary efficacy endpoint). No recommendation for further plitidepsin single-agent evaluation is considered in the treatment of patients with relapsed or refractory TCC of the urothelium. | |
| **Date of report (final version)** | 18 March 2008 | |