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

FINAL STUDY REPORT

PM2734-B-001-08

PHASE II CLINICAL AND PHARMACOKINETIC TRIAL OF 30-MIN INFUSION OF PM02734 (IRVALEC®) EVERY THREE WEEKS IN PATIENTS WITH SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC) PREVIOUSLY TREATED WITH AT LEAST ONE LINE OF PLATINUM-BASED CHEMOTHERAPY

Investigational Medicinal Product:	Elisidepsin
Name of Test Drug:	Irvalec®
Study Design:	Non-randomized, open-label, single-arm, multicenter, phase II study
Protocol Number:	PM2734-B-001-08
Study Start Date:	12 December 2008 (First consent signed)
Study Completion Date:	15 June 2010 (Last follow-up)
Principal Investigator Name and Affiliation:	**Mariano Provencio Pulla, M.D.** Hospital Puerta de Hierro Majadahonda, Madrid, Spain
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Earlier Approved Reports:	None
Version:	Final version
Approval date:	29 April 2011

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

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2. SYNOPSIS

Name of Sponsor/ Company: PharmaMar, S.A. **Name of finished product:** Irvalec® **Name of active ingredient(s):** Elisidepsin	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	(*For National Authority Use only*)
Protocol number	PM2734-B-001-08	
Study title	Phase II Clinical and Pharmacokinetic Trial of 30-min Infusion of PM02734 (Irvalec®) Every Three Weeks in Patients with Squamous Non-small Cell Lung Cancer (NSCLC) Previously Treated with at least One Line of Platinum-based Chemotherapy.	
Coordinating investigator	**Mariano Provencio Pulla, M.D.** Hospital Puerta de Hierro, Majadahonda, Madrid, Spain.	
Co-investigators / Study centers	**Manuel Cobo Dols, M.D.**, Hospital Carlos Haya, Málaga, Spain. **Javier de Castro Carreño, M.D.**, Hospital La Paz, Madrid, Spain. **José Gómez Codina, M.D.**, Hospital La Fe, Valencia, Spain. **Manuel Constenla Figueiras, M.D.**, Complejo Hospitalario de Pontevedra, Pontevedra, Spain.	
Publications (references)	At the time of this report no articles have been published on the study described herein.	
Study period: **- First consent signed** **- Last consent signed** **- First infusion administered** **- Last infusion administered** **- Last follow-up**	 12 December 2008 19 January 2010 19 December 2008 11 February 2010 15 June 2010	**Phase of Development:** Phase II
Objectives	**Primary Objective:**	• To evaluate the antitumor activity of elisidepsin administered as a 30-minute (30-min) intravenous (i.v.) infusion every three weeks (q3wk) to patients with squamous NSCLC previously treated with at least one line of platinum-based chemotherapy.
	Secondary Objective:	• To determine the safety profile of this elisidepsin regimen in this population of patients. • To determine the pharmacokinetic (PK) profile of this elisidepsin regimen in these patients. • To determine the pharmacogenomic (PGx) profile of this elisidepsin regimen. Hypothesis-generating exploratory PGx analyses will be conducted to correlate the molecular parameters found in the tumor samples of the patients obtained at diagnosis with the clinical results achieved with elisidepsin.
Methodology	Non-randomized, open-label, single-arm, multicenter, phase II study.	
Number of subjects/patients	**Study design:** This study was designed as a phase II trial with single-agent elisidepsin in pretreated patients with squamous NSCLC progressing after at least one line of platinum-based chemotherapy. Elisidepsin was to be administered as a 30-min q3wk i.v. infusion at a flat dose of 2 mg. **Planned number of patients:** Twenty patients were planned to participate; if at least six of 20 evaluable patients reached the progression-free survival status at three months (PFS3), the treatment regimen was worthy of consideration for further development. **Patients analyzed:** A total of 19 patients were included and treated with elisidepsin. One patient was considered non-eligible because he was included with an undetected active infection (pneumonia) and died as a result of disease progression three days after receiving the	

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	first elisidepsin infusion. Of the other 18 patients, 1 patient was accepted as eligible by the sponsor having not a squamous NSCLC but a large cell carcinoma histology, since the investigator thought there could be a potential benefit for the patient. Only 1 out of this 18 eligible patients reached the main endpoint of the study (PFS3); as a result, the study was closed due to lack of efficacy.	
Diagnosis and main criteria for inclusion	**Inclusion Criteria:** 1. Voluntary written informed consent, obtained from the patient before the beginning of any specific study procedures. 2. Squamous NSCLC, histologically confirmed and with documented radiological disease progression at study entry. 3. Previous treatment with at least one line of platinum-based chemotherapy and no more than two chemotherapy lines (including biological therapies). 4. Complete recovery from the effects of radiotherapy, if there were any, and from any drug-related adverse events (AEs) derived from previous treatments, excluding alopecia and any grade 1 AE as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0). 5. At least one measurable lesion [according to Response Evaluation Criteria In Solid Tumors (RECIST)], located in a non-irradiated area, adequately measured by appropriate methods less than four weeks before entry into the study. 6. Age $\geq$ 18 years. 7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) $\leq$ 2. 8. Life expectancy $\geq$ 3 months. 9. Appropriate bone marrow reserve, renal and hepatic functions. a. Platelet count $\geq$ 75 x 10^9/l, hemoglobin $\geq$ 10 g/dl and absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/l. b. Alkaline phosphatase (AP) $\leq$ 2.5 x upper limit of normality (ULN) ($\leq$ 5 in case of bone or hepatic metastases). c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\leq$ 2.5 x ULN of the laboratory values of each site (or $\leq$ 5 x ULN in case of hepatic metastases). d. Total bilirubin $\leq$ 1.5 x ULN. e. Calculated creatinine clearance $\geq$ 30 ml/min. 10. Women of childbearing potential had to have a negative serum pregnancy test before study entry. Both men and women 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 (IUD), oral contraceptive, subdermal implant and double barrier (condom with a contraceptive sponge or contraceptive suppository). **Exclusion Criteria:** 1. Prior therapy with elisidepsin or Kahalalide F. 2. Pregnant or lactating women, or any person not using an appropriate contraceptive method. 3. Less than four weeks from radiation therapy, biological therapy or chemotherapy (six weeks in case of nitrosourea, mitomycin C, or high-dose chemotherapy). 4. More than two lines of prior therapy for metastatic disease. 5. History of other malignant neoplasms within five years of study enrollment (except for appropriately treated non-melanoma skin cancer or carcinoma *in situ*). 6. Evidence of progressive or symptomatic central nervous system (CNS) metastases or leptomeningeal metastases. 7. Other diseases or serious conditions: a. Increased cardiac risk: congestive heart failure, unstable angina pectoris, arrhythmia requiring treatment, uncontrolled arterial hypertension or myocardial infarction within 12 months before inclusion in the study. b. History of significant neurological or psychiatric disorders. c. Active infection. d. Significant non-neoplastic liver disease (e.g., cirrhosis, active chronic hepatitis).	

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	e. Immunocompromised patients, including those known to be infected with the human immunodeficiency virus (HIV). 8. Any other major illness that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in the study. 9. 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. 10. Treatment with any investigational product within 30 days prior to inclusion in the study. 11. Known hypersensitivity to any component of elisidepsin.	
Test product, dose and mode of administration, batch numbers	Elisidepsin was supplied by Pharma Mar, S.A. (Colmenar Viejo, Madrid, Spain) as powder for concentrate for solution for infusion in vials with one strength: 1 mg. The vials had to be reconstituted by adding 2 ml of sterile water for injection. Each ml of the reconstituted solution contained 0.5 mg of elisidepsin, 100 mg of trehalose dihydrate and 0.5 mg of citric acid. The resultant solution had to be colorless, clear and free of particulate matter by visual inspection. The reconstituted solution was to be further diluted with 0.9% saline solution for infusion and administered as a 30-min intravenous (i.v.) infusion. The **batch number** of elisidepsin used in this study was #P10106.	
Duration of treatment	Patients were to receive a treatment consisting of a flat dose of 2 mg of elisidepsin as a 30-min i.v. infusion every three weeks (q3wk). A treatment cycle consisted of the administration of elisidepsin infusion on Day 1, and all study evaluations done before the next cycle. Treatment was to be administered until disease progression, unacceptable toxicity, patient refusal, intercurrent illness, major protocol deviation, treatment delay for > 2 weeks (except in case of obvious clinical benefit), administrative reasons, or Sponsor's decision.	
Criteria for evaluation **Efficacy**	The primary efficacy endpoint was the PFS3, defined as the percentage of patients with no evidence of disease progression at three months after the first elisidepsin administration. Patients were to be evaluable for efficacy if they had received at least two complete treatment cycles and if they had at least one disease measurement recorded not less than six weeks after treatment onset. In addition, any eligible patients who received at least one treatment cycle and experienced disease progression or died due to progressive disease (PD) prior to response evaluation were to be considered evaluable for the primary endpoint and were to be categorized as an "early progression". Secondary efficacy endpoints were the overall response rate [ORR, defined as the percentage of patients with complete (CR) or partial response (PR) according to the RECIST, version 1.0], the duration of response (DR), the time to progression (TTP), the progression-free survival (PFS) and the overall survival (OS).	
Safety	Patients were evaluable for safety if they had received at least one complete elisidepsin infusion. Safety was to be evaluated using clinical examinations, which comprised vital signs analysis, clinical assessment of AEs, changes in laboratory parameters (hematological and biochemical, including liver function tests) and any other analyses that may have been considered necessary. All AEs were classified according to the NCI-CTCAE, version 3.0.	
Pharmacokinetics	The PK profile of elisidepsin in plasma was to be evaluated after the first and second cycles. A limited sampling schedule of eight samples per cycle was performed.	
Pharmacogenomics	The results of the PGx analyses conducted on tumor tissue samples obtained prior to treatment administration were planned to help to generate hypotheses for correlating the molecular parameters assessed in these samples with the clinical results of the treatment.	
Statistical methodology	A total of 20 evaluable patients were expected to participate in this clinical trial. A minimum PFS3 of 30% was required to declare the treatment worthy of consideration. This implied that at least six of 20 evaluable patients had to reach PFS3 (95% CI, 12-54%). This design ensured that, for a PFS3 of 30%, the lower limit of the 95% CI exceeded 10%.	

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	Binomial estimates with exact 95% confidence intervals were calculated for the analysis of the main endpoint (PFS3) and the ORR. Time-to-event endpoints (DR, TTP, PFS and OS) were analyzed according to the Kaplan-Meier method. If relevant, efficacy parameters *versus* baseline covariates were to be analyzed and appropriate tests were to 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 were analyzed. Continuous variables were tabulated and presented with summary statistics (i.e., median and range). Categorical variables were summarized in frequency tables by means of counts and percentages. Pharmacokinetic parameters were calculated using population methods, after pooling data from this study with data obtained during phase I studies.	
Results (1): Patient characteristics	All 18 eligible patients were male Caucasians, with a median age of 64.7 years (range, 52.5-77.3 years), and had been diagnosed with squamous NSCLC (but 1 with large cell histology). All had metastatic disease at baseline, mostly involving lung (n=17, 94.4%) and pleura (n=5, 27.8%). The most common clinical stage at diagnosis was stage IV (n=9, 50.0%). All patients had been treated with at least one line of platinum-based chemotherapy and no more than two therapy lines (including biological therapies), with a median of one line (range, 1-2) and two therapeutic agents (range, 2-4). Beside platinum compounds, vinca alkaloids (n=9, 50.0%) and taxanes (n=8, 44.4%) were the most common prior antineoplastic agents. Four patients (22.2%) had radical surgery as prior treatment. Radiotherapy had been given to eight patients (44.4%), mostly as a palliative therapy (n=5, 27.8%). Only two laboratory abnormalities (lymphopenia and hyperglycemia) reached grade 3 at baseline (one patient each).	
Results (2): Extent of exposure to investigational product	**Drug exposure:** Overall, 46 treatment cycles were administered during the study, with a median of 3 cycles per patient (range, 1-4 cycles). The median relative dose intensity was 100.0% (range, 67.7%-103.7%). **Dose delays and reductions:** Three (10.7%) of 28 cycles susceptible of delay (i.e., after excluding the first cycle) were delayed for reasons unrelated to elisidepsin. No dose reductions occurred. **Treatment discontinuation:** Sixteen (88.9%) patients discontinued the study because of disease progression. Two patients discontinued due to other causes: one patient died after four cycles due to massive hemoptysis unrelated to elisidepsin, and another patient had an elisidepsin-related grade 4 hepatic enzyme increase in Cycle 1.	
Results (3): Efficacy	All 18 eligible patients were evaluable for the analysis of efficacy endpoints. Only one (5.6%) achieved PFS3. No objective responses were found. Disease stabilizations (range, 2.76-3.12 months) were observed in four patients (22.2%). The median TTP was 1.3 months (95% CI, 1.2-1.8 months), the median PFS was 1.4 months (95% CI, 1.2-2.1 months) and the median OS was 4.4 months (95% CI, 2.9-8.2 months), respectively. The rate of patients alive at three and six months was 66.7% (95% CI, 44.9%-88.4%) and 37.5% (95% CI, 14.6%-60.4%), respectively.	
Results (4): Safety	All 18 patients were evaluated for safety. Most elisidepsin-related AEs that occurred during the study were grade 1/2 and allowed the patients to remain on treatment. The most common elisidepsin-related AEs were fatigue (50.0% of patients/34.8% of cycles), constipation (16.7% of patients/8.7% of cycles) and pruritus (16.7% of patients/6.5% of cycles). Four (22.2%) patients had grade 3/4 elisidepsin-related events: two had grade 3 fatigue and grade 3 anorexia, one had grade 3 fatigue alone, and one had grade 4 hepatic enzyme increase, which was considered a SAE and resulted in patient withdrawal. Fourteen deaths occurred during follow-up; all were due to progression of the underlying disease, except one that was due to massive hemoptysis unrelated to elisidepsin. Anemia (83.3% of patients/69.5% of cycles), lymphopenia (72.2%/47.8% of cycles) and increases in the levels of blood transaminases (ALT: 44.4% of patients/35.1% of cycles; AST: 22.2% of patients/10.0% of cycles) and AP (23.5% of patients/15.6% of cycles) were the	

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	laboratory abnormalities most frequently found after elisidepsin administration. Lymphopenia was the only hematological abnormality that reached grade 3 and occurred in four patients (three of theses patients already had grade ≥2 lymphopenia at baseline). Only two patients had grade 3/4 biochemical toxicities during the study: one had grade 3 ALT increase and the other one had concomitant grade 4 ALT increase and grade 4 AST increase (this event was classified as a grade 4 hepatic enzyme increase related to elisidepsin; see above). Grade 3 metabolic abnormalities comprised hyperglycemia (in three patients, two of whom already had grade ≥1 hyperglycemia at baseline), hyperkalemia, hypercalcemia, hypermagnesemia and hyponatremia (one patient each).	
Results (5): Pharmacokinetics	Eighteen patients treated with elisidepsin as a flat dose of 2 mg using the 0.5-hour i.v infusion q3wk schedule were evaluable after the first elisidepsin infusion and 13 patients after the second infusion. The mean (standard deviation) clearance, volume of distribution and terminal half-life of elisidepsin in plasma were: 11.1 (3.6) l/h, 63.4 (46) l and 19.6 (11) h, respectively. These results were in accordance with those found in patients with solid tumors treated at a similar dose and with the same schedule in a previous phase I trial.	
Results (6): Pharmagenomics	No analyses were performed due to the low number of samples obtained (tumor tissue from seven patients) and the lack of response to the study treatment.	
Conclusions	In conclusion, elisidepsin 2 mg flat dose given as a 30-min i.v. infusion on Day 1, q3wk, to pretreated patients with squamous NSCLC progressing after at least one line of platinum-based chemotherapy had predictable and manageable toxicity. Elisidepsin treatment showed poor antitumor activity at this dose and schedule, which resulted in a low accrual rate and in the premature closure of this exploratory clinical trial before the figure of 20 patients, established by the protocol, had been reached. No recommendation for further evaluation of single-agent elisidepsin given at a flat dose of 2 mg flat as a 30 i.v. infusion q3wk is considered in the treatment of patients with metastatic squamous NSCLC. Other schedules (different infusion time) are being explored in order to optimize the dose.	
Date of report (Final version)	29 April 2011.	