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

CLINICAL STUDY REPORT

PM2734-B-002-09

(IMAGE: IRVALEC® IN METASTATIC OR ADVANCED GASTRIC/ESOPHAGEAL CANCER)

PHASE IB-II, MULTICENTER, OPEN-LABEL, RANDOMIZED, CLINICAL STUDY WITH DOSE OPTIMIZATION OF TWO DIFFERENT SCHEDULES OF ELISIDEPSIN TRIFLUOROACETATE (IRVALEC®) AS A SINGLE AGENT IN PATIENTS WITH UNRESECTABLE, LOCALLY ADVANCED OR METASTATIC ESOPHAGEAL, ESOPHAGOGASTRIC JUNCTION OR GASTRIC CANCER AFTER FAILURE OF ONE BUT NOT MORE THAN TWO PRIOR LINES OF SYSTEMIC THERAPY

Investigational Medicinal Product:	Elisidepsin trifluoroacetate (PM02734)
Name of Test Drug:	Irvalec®
Study Design:	Multicenter, open-label, randomized phase Ib-II clinical trial
Protocol Number:	PM2734-B-002-09
Study Start Date:	5 October 2010 (First consent signed)
Study Completion Date:	4 May 2012 (Date reported to the Competent Authorities) 1 December 2012 (Last follow-up)
Principal Investigator Name and Affiliation:	**Ramón Salazar, M.D.** Instituto Catalán de Oncología L'Hospitalet de Llobregat, Spain
Responsible Medical Officer:	**Arturo Soto Matos-Pita, M.D.** Clinical Research and Development Director Pharma Mar, S.A., Sociedad Unipersonal (abbreviated as PharmaMar S.A. in this report) Avenida de los Reyes, 1; Polígono Industrial La Mina-Norte 28770 Colmenar Viejo, Madrid, Spain Phone: +34 91 846 6053 Fax: +34 91 823 4504 E-mail: asoto@pharmamar.com
Earlier Approved Reports:	None
Version:	Final version
Approval Date:	10 July 2013

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

NOTE:

This report has been written according to the International Conference of Harmonization (ICH) HARMONISED TRIPARTITE GUIDELINE E3: "STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS":

- EU: adopted by CPMP, December 1995, issued as CPMP/ICH/137/95.
- MHLW: adopted May 1996, PAB/PCD Notification No.335.
- FDA: published in the Federal Register, Vol. 61, July 17, 1996, page 37320.

The primary objective of the first (phase Ib) stage of this study was to determine the safety and to identify the optimal dose of two single-agent elisidepsin schedules in patients with esophageal, esophagogastric junction or gastric cancer. This optimal dose was part of the safety results. Therefore, in order to show first safety parameters, the content of Sections 11 (Efficacy evaluation) and 12 (Safety evaluation) has been exchanged.

Additionally, a summary of results regarding dose-limiting toxicities (DLTs) and the optimal dose for each schedule is described in Section 11.2.

2. SYNOPSIS

Name of Sponsor(s)/Company(ies): PharmaMar, S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(*For National Authority Use only*)**
Name of finished product: Irvalec®		
Name of active ingredient(s): Elisidepsin		
Protocol number	PM2734-B-002-09	
Title of the study	Phase Ib-II, Multicenter, Open-Label, Randomized, Clinical Study with Dose Optimization of Two Different Schedules of Elisidepsin Trifluoroacetate (Irvalec®) as a Single Agent in Patients with Unresectable, Locally Advanced or Metastatic Esophageal, Esophagogastric Junction or Gastric Cancer After Failure of One but not More than Two Prior Lines of Systemic Therapy.	
Investigators / Study centers	**Maria Alsina, M.D**. Hospital General de la Vall d'Hebrón, Barcelona, Spain. **Alan Anthoney, M.D.** St James University Hospital, Leeds, United Kingdom. **Jeff Evans, M.D.** The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom. **Anthony Gonçalves, M.D.** Institut Paoli Calmettes, Marseille, France. **Katharina Gunzer, M.D.** Centre François Baclesse, Caen, France. **Jean-Philippe Metges, M.D.** Centre Hospitalier Universitaire Morvan, Brest, France. **Clara Montagut, M.D.** Hospital del Mar, Barcelona, Spain. **Russell Petty, M.D.** Aberdeen Royal Infirmary, Aberdeen, United Kingdom. **Ramón Salazar, M.D.** Instituto Catalán de Oncología, L'Hospitalet de Llobregat, Spain.	
Publication (references)	At the time of this report no articles have been published on the study described herein. Preliminary results of this study were presented at: • American Society of Clinical Oncology (ASCO) 2011 Meeting. "Szyldergemajn S, Goncalves A, Metges J-P, Gunzer K, Montagut C, Salazar R, Alsina Maqueda M, Evans J, Swinson D, Petty R, Singer H, Kahatt C. IMAGE, a randomized phase Ib-II study of elisidepsin in pre-treated advanced gastroesophageal cancer. J Clin Oncol 2011, 29(Suppl): Abstract TPS169". • 2013 Gastrointestinal Cancers Symposium. "Salazar R, Metges JP, Anthoney DA, Laus G, Maqueda MA, Goncalves A, Montagut C, Brown J, Gunzer K, Szyldergemajn S, Petty RD. IMAGE, a randomized phase Ib-II study of elisidepsin (E) as a single agent in pretreated advanced gastroesophageal (GE) cancer. J Clin Oncol 2013, 31(4 Suppl): Abstract 92".	
Study period: **. First consent signed** **. Last consent signed** **. First infusion administered** **. Last infusion administered** **. Last follow-up** **. Date of completion reported to authorities**	 5 October 2010 2 September 2011 13 October 2010 13 March 2012 1 December 2012 4 May 2012	**Phase of Development:** Phase Ib-II
Study objectives	**Primary:** <u>Phase Ib stage.</u> • To determine the optimal dose of elisidepsin trifluoroacetate (PM02734, Irvalec®; abbreviated as elisidepsin, the base and active ingredient) as a single agent administered as a 24-hour intravenous (i.v.) infusion fortnightly or as a 3-hour i.v. infusion weekly to patients with unresectable, locally advanced or metastatic esophageal, esophagogastric junction or gastric cancer who failed one but not more than two prior lines of systemic anticancer therapy. In both study regimens, each cycle lasted four weeks. <u>Phase II stage.</u> • To determine the antitumor activity of elisidepsin as a single agent administered as a 24-hour i.v. infusion fortnightly or as a 3-hour i.v. infusion weekly in the study patient population.	

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	Secondary: Phase Ib stage. • To determine the antitumor activity of elisidepsin as a single agent administered as a 24-hour i.v. infusion fortnightly or as a 3-hour i.v. infusion weekly. Both stages. • To characterize the safety profile and feasibility of elisidepsin in patients with unresectable, locally advanced or metastatic esophageal, esophagogastric junction or gastric cancer. • To determine the time-to-event outcomes and response rate. • To characterize the pharmacokinetics (PK) and pharmacodynamics (PDy) of elisidepsin when administered as a single agent in patients with esophageal, esophagogastric junction or gastric cancer. • To pe**r**form a preliminary pharmacogenomic (PGx) study to explore potential biological markers of tumor sensitivity/resistance to elisidepsin in patients with esophagogastric cancer. • Each of these secondary endpoints was characterized separately for each study regimen.	
Methodology	This was a multicenter, open-label, randomized, two-arm, uncontrolled phase Ib-II clinical trial conducted in adult men and women with unresectable, locally advanced or metastatic esophageal, esophagogastric junction or gastric cancer who failed one or two prior lines of systemic therapy. • The **phase Ib (dose optimization) stage** was conducted to determine the appropriate dose of elisidepsin for each schedule. Dose optimization occurred separately in each treatment arm; the starting doses were 8.0 mg flat dose (FD) in Arm 1 and 3.0 mg FD in Arm 2. This stage used a standard phase I design that included three patients per dose level, which was expanded up to six patients if one of the first three patients had experienced a dose-limiting toxicity (DLT) during Cycle 1. • The **phase II (expansion) stage** was started once an optimal dose had been defined for each treatment arm during the phase Ib stage. This stage was designed to assess the antitumor activity of the optimized schedules (i.e. 24-hour infusion fortnightly in Arm 1, and 3-hour infusion weekly in Arm 2).	
Number of patients (planned and analyzed)	**Planned number of patients:** • Phase Ib Stage. Between 6 and 18 patients evaluable for DLTs were to be included in each treatment arm for dose optimization. • Phase II Stage. A maximum of 40 patients were to be included at the optimal dose in each arm. A Simon two-stage design was adopted in each arm to test the null hypothesis that the rate of tumor control was $\leq$ 10% *vs.* the alternative that it was $\geq$ 30% (two-sided test; alpha $\leq$ 0.1 and beta $\leq$ 0.1). According to this design, 15 patients were first recruited into each arm during the phase II stage. If $\geq$ 2 patients at an arm met the primary endpoint (i.e., tumor control) and $\leq$ 4 experienced a DLT during their first cycle, then accrual in the corresponding arm was to be expanded with 25 additional patients. If the total number of patients with tumor control was $\geq$ 7 in 40 patients (i.e., a rate of tumor control in the phase II stage of at least 17.5%) in an arm, the null hypothesis would be rejected and elisidepsin would be considered active in this setting. **Patients analyzed:** • Phase Ib Stage. Twelve patients were enrolled during the phase Ib stage: six in each treatment arm. All were distributed among two dose levels per arm and were treated with elisidepsin as a 24-hour infusion fortnightly (Arm 1) or as a 3-hour infusion weekly (Arm 2):	

<table>
<tr><td>Name of Sponsor(s)/Company(ies):
PharmaMar, S.A.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of finished product:
Irvalec®</td></tr>
<tr><td>Name of active ingredient(s):
Elisidepsin</td></tr>
<tr><td></td><td colspan="2">
<table>
<tr><th>Dose level</th><th>Elisidepsin (mg FD)</th><th>No. of patients</th></tr>
<tr><td colspan="3">Arm 1 (24-hour infusion fortnightly)</td></tr>
<tr><td>I</td><td>8.0</td><td>3</td></tr>
<tr><td>II</td><td>10.0</td><td>3</td></tr>
<tr><td colspan="3">Arm 2 (3-hour infusion weekly)</td></tr>
<tr><td>I</td><td>3.0</td><td>3</td></tr>
<tr><td>II</td><td>3.75</td><td>3</td></tr>
</table>
q4wk, every four weeks.

• <u>Phase II Stage.</u>
An interim analysis conducted after 15 patients had been enrolled into each treatment arm found tumor control in one patient in Arm 1, and in none in Arm 2. As a result, patient accrual into both arms was discontinued.
Overall, 33 patients were enrolled during the phase II stage: 15 in Arm 1 and 18 in Arm 2. The elisidepsin dose administered in each arm during the phase II stage was the optimal dose established for each schedule during the previous phase Ib stage. Thus, 14 patients in Arm 1 were given elisidepsin 10.0 mg FD as a 24-hour infusion fortnightly and 18 patients in Arm 2 were treated with elisidepsin 3.75 mg FD as a 3-hour infusion weekly.</td></tr>
<tr><td>Diagnosis and main selection criteria</td><td colspan="2"><u>Inclusion Criteria</u>
1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 1.
3. Life expectancy ≥ 3 months.
4. Patients with histologically/cytologically confirmed diagnosis of locally advanced (unresectable) or metastatic esophageal, esophagogastric junction or gastric cancer. Patients had to have received one but not more than two prior lines of systemic therapy and had to be progressing after last prior therapy before study entry.
5. Adequate bone marrow, renal, hepatic, and metabolic function (assessed ≤ 7 days before first study drug administration:
a) Platelet count ≥ 100 x 10^9/l, hemoglobin ≥ 8.5 g/dl and absolute neutrophil count (ANC) ≥ 1.0 x 10^9/l.
b) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x upper limit of normal (ULN), independently of the presence of liver metastases.
c) Direct bilirubin ≤ ULN and total bilirubin ≤ 1.5 x ULN.
d) International Normalized Ratio (INR) ≤ 1.5 (except if ongoing oral anticoagulation therapy).
e) Renal function: patients with calculated creatinine clearance (using Cockcroft and Gault's formula) ≥ 30 ml/min.
f) Albumin ≥ 2.5 g/dl.
6. Recovery to grade ≤ 1 from any adverse event (AE) derived from any previous anticancer treatment (excluding alopecia and grade 2 non-painful peripheral neuropathy).
7. Women of childbearing potential had to have a negative serum pregnancy test before study entry. Both women and men had to agree to use a medically acceptable method of contraception throughout the treatment period and for six months after discontinuation of treatment. Acceptable methods of contraception included complete abstinence, intrauterine device (IUD), oral contraceptive, subdermal implant and double barrier (condom with a contraceptive sponge or contraceptive suppository).
8. Voluntarily signed and dated written informed consent, obtained from the patient prior to any specific study procedure.</td></tr>
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	<u>Exclusion Criteria</u> 1. Concomitant diseases/conditions: a) Clinically relevant non-neoplastic liver disease (i.e., cirrhosis; active chronic hepatitis, hepatitis C virus (HCV)/hepatitis B virus (HBV) infection). b) History or presence of unstable angina, myocardial infarction, clinically relevant valvular heart disease, treatment-requiring and/or symptomatic arrhythmia or congestive heart failure within the last six months prior to enrollment. c) Active uncontrolled infection. d) Known human immunodeficiency virus infection (HIV1/2). e) Limitation of the patient's ability to comply with the treatment or follow-up protocol. f) Parenteral nutritional support ≥ 25% of total daily caloric requirements. g) Any other major illness that, in the Investigator's or the Sponsor's judgment, substantially increased the risk associated with the patient's participation in this study. h) Painful peripheral neuropathy ≥ grade 2. i) Any ongoing cancer-related coagulopathy disorder [other than medically treated deep venous thrombosis (DVT) during at least one month]. 2. Known central nervous system (CNS) metastatic involvement. 3. Malignant or non-malignant ascitis ≥ grade 3. 4. Primary histology other than squamous-cell carcinoma or adenocarcinoma. 5. Prior treatment with elisidepsin or Kahalalide F (KF). 6. Less than 50 kg of body weight (only for patients included in the dose optimization phase). 7. Men or women of childbearing potential who were not using an effective method of contraception as previously described; women who were pregnant or breast feeding. 8. High transfusional requirements (> 4 packages of red blood cells and/or one platelet transfusion) in the last four weeks prior to study entry. 9. Participation in another clinical trial or concomitant treatment with any investigational product in the 4-week period prior to study entry. 10. Patients with a prior invasive malignancy (except non-melanoma skin cancer) who had any evidence of disease within the last three years. 11. Major surgery performed or planned within four weeks of the start of study treatment (line placement is not considered major surgery). 12. Patients with serious non-healing wound or ulcer. This included history of abdominal fistula, gastrointestinal perforation, active uncontrolled bleeding or intra-abdominal abscess during the last three months before study entry.	
Test product, dose and mode of administration	Elisidepsin was supplied by Pharma Mar (Colmenar Viejo, Madrid, Spain) as powder for concentrate for solution for infusion. It was administered **as a 24-hour i.v. infusion fortnightly** or **as a 3-hour i.v. infusion weekly.** The following **1-mg vial batches** were used: #P08209, #P03910 and #P06410.	
Duration of treatment	Treatment was administered until disease progression; persisting unacceptable toxicity; intercurrent illness of sufficient magnitude to preclude safety continuation of the trial; patient refusal and/or non compliance with study requirements; protocol deviation with an effect on the risk/benefit ratio; treatment delay for > 2 weeks due to drug-related AEs (except in case of clear clinical benefit); or administrative reasons or Sponsor's decision. Adverse events were documented during the 30 days following the last elisidepsin administration. Serious adverse events (SAEs) that occurred within 30 days after the last study drug administration were reported. After that date, only SAEs suspected to be related to the investigational drug were reported.	

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Criteria for evaluation

Efficacy

The primary efficacy endpoint was the rate of tumor control, defined as confirmed objective response of any duration according to the Response Evaluation Criteria In Solid Tumors (RECIST, v.1.1) or PFS-4 (absence of disease progression or death at Week 16 ± 1). Secondary efficacy endpoints were: progression-free survival rate at six months and one year (PFS-6 and 1-yr PFS), rate of response (RR), duration of response (DR), progression-free survival (PFS), overall survival (OS) and survival rate at one year (1-yr OS).

The primary efficacy analysis was done during the phase II stage on the intention-to-treat (ITT) population of patients. Analyses as per protocol (PP) were performed, if appropriate. Efficacy data collected from patients treated during the phase Ib stage were listed but were not used in the primary efficacy analysis; however, they were used in the secondary efficacy analyses whenever applicable.

Safety

In both stages, patients were evaluable for safety if they had received at least one complete elisidepsin infusion or if they had discontinued due to any elisidepsin-related AE before infusion was completed. Safety was evaluated using clinical examinations, which comprised vital signs analysis, clinical assessment of AEs, and changes in laboratory parameters (hematological and biochemical, including liver function tests). Baseline characteristics, deaths and the reason for study discontinuation were also analyzed. All AEs and SAEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v.4.03), and were coded using the Medical Dictionary for Regulatory Activities (MedDRA, v.11.0).

DLTs, MTD and RD

During the Phase Ib stage, patients were evaluable for DLTs if they had received at least one complete elisidepsin infusion during Cycle 1 and had been followed for four weeks after Day 1 (i.e., until completion of Cycle 1), or if they had previously discontinued due to an elisidepsin-related DLT.

DLTs were defined as follows:

- Grade 4 neutropenia (ANC < 0.5 x 10^9/l) lasting > 7 days.
- Grade 3/4 febrile neutropenia or neutropenic infection.
- Any grade 4 thrombocytopenia (platelet count < 25 x 10^9/l).
- Elisidepsin-related grade 3 ALT or AST increase lasting >14 days, or any duration grade 4 ALT and/or AST increase.
- Elisidepsin-related grade ≥ 2 ALT or AST increase concomitantly with ≥ 2 times ULN total bilirubin increase and normal alkaline phosphatase (AP).
- Any other grade 3/4 non-hematological adverse event suspected to be related to the study drug, except nausea/vomiting (unless the patient is receiving an optimal anti-emetic regimen), hypersensitivity reactions, grade 3 diarrhea lasting less than 24 hours with adequate anti-diarrheal treatment, grade 3 fatigue/asthenia lasting less than 72 hours, and non-clinically relevant biochemical abnormalities [e.g., isolated gamma-glutamyltransferase (GGT) and/or AP increase]. In any case, the clinical relevance had to be discussed between the investigators and Sponsor's representatives.
- Two subsequent treatment-related dose omissions during the first cycle (including omissions on Day 15 of Cycle 1 and Day 1 of Cycle 2 for patients treated with elisidepsin as a 24-hour i.v. infusion fortnightly in Arm 1).
- The following circumstances were discussed between the Principal Investigator and the Sponsor, and the final consensus was documented:
  - DLTs with delayed onset (i.e., occurred after Week 4).
  - Non-compliance with the intended dose intensity or frequent dose delays or omissions not conforming a formal DLT definition.

The **optimal dose** of elisidepsin for each treatment arm was defined as the maximum dose at which less than one third of the patients experienced a DLT during Cycle 1.

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Pharmacokinetics **Pharmacogenomics**	All patients included in this study were to be sampled for PK. Blood samples were to be taken at specific times before, during and after administration of the first and third elisidepsin infusions. Paraffin-embedded or fresh frozen tumor tissue samples were obtained from patients consenting for the pharmacogenomic (PGx) testing.	
Statistical methodology	**Patient Disposition and Protocol Deviations** Accrual and study discontinuation details were presented descriptively. The reasons for treatment discontinuation were described by counts and percentages, overall and by number of cycles received. Reasons of treatment discontinuation other than disease progression were detailed. Protocol deviations were listed by type of deviation. **Demographics and Baseline Characteristics** Demographics and baseline characteristics were summarized for all patients recruited. Continuous variables were summarized and presented with summary statistics, i.e., mean, standard deviation, median and range. Categorical variables were summarized in frequency tables. Age, baseline weight, height, and body surface area (BSA) were summarized descriptively. For the cancer history, histologic type, primary site and grade, time from diagnosis, metastatic or locally advanced, the number of metastatic organs involved, initial surgery with oncological intention, number of prior lines of therapy (excluding neoadjuvant and/or adjuvant therapies) and best response, if available, were summarized. Time from initial diagnosis and time from the last documentation of disease progression to the date of start of study treatment were calculated in months and summarized descriptively. A frequency tabulation of the number of patients with and the different types of previous cancer surgery, radiotherapy, or chemotherapy (number of lines and number of agents) was given. Hematology and serum biochemistry abnormalities at baseline were displayed by tabulation of frequencies according to NCI-CTCAE toxicity grades. Means and standard deviation, or medians and intervals were used for continuous variables. Absolute frequencies and percentages were calculated for qualitative variables. Whenever indicated, these summarized measurements were accompanied by their corresponding confidence interval. **Efficacy** Data from each group were analyzed separately. In addition, exploratory analysis by tumor type was performed within each group. Binomial estimates with exact 95% confidence intervals were calculated for the analysis of the main endpoint (rate of tumor control) and other rates (RR, PFS4, PFS-6, 1-yr PFS and 1-yr OS) in all treated patients. Time-to-event parameters were described with an exploratory intention: median time to onset and duration of response, PFS and OS were calculated by Kaplan-Meier estimates with 95% confidence intervals. The characteristics of patients with PFS-4, CR or PR were described. **Safety** Descriptive statistics were used for the evaluation of safety. The incidence and grade of AEs and laboratory abnormalities were calculated considering the most severe grade per patient and infusion, and were displayed in frequency tables using counts and percentages. All AEs were coded using the MedDRA v.11.0 dictionary. Toxicities were graded using the NCI-CTCAE v.4.03. Deaths, SAEs and events resulting in study discontinuation were tabulated. Performance status and weight gain-loss during the study were summarized by frequency tabulation. Hematological toxicities classified according to the NCI-CTCAE were calculated in all cycles; the worst grade reached by each patient during treatment was also calculated. Grades of serum biochemistry toxicities during a cycle were calculated as explained for hematological toxicities. Exposure to treatment was described for all patients who received at least one of the study treatments. The distribution of delays according to the infusion administered,	

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	and the dose level whenever applicable (dose optimization) was studied by means of counts and percentages. The reasons for infusion delay were detailed. All dose reductions were considered and described, specifying the reason for reduction. **Pharmacokinetics** The PK profile was elucidated using standard non-compartmental methods. If considered appropriate, compartmental analysis on the study results was also performed, and a population kinetic analysis was done on the pooled results of the different studies with elisidepsin. The PK parameters were tabulated and graphically displayed using descriptive methods (counts, percentages, median, range, mean, standard deviations).	
Results (1): Patient characteristics	Phase Ib Stage *Arm 1 (24-hour Infusion Fortnightly)* All six patients in this arm were male. Median age was 63.0 years (range, 53-72 years) for patients treated at 8.0 mg FD and 66.0 years (range, 45-74 years) for those treated at 10 mg FD (the optimal dose). All patients had ECOG PS scores of 0-1. Three patients had gastric cancer, two had esophageal cancer and one had esophagogastric junction cancer. Most (n=4) had adenocarcinoma. Disease at baseline was metastatic in five patients and locally advanced in one. The median number of sites of disease per patient at baseline was 4 (range, 2-4 sites) at 8.0 mg FD and 3 (range, 1-3 sites) at the optimal dose. The most common sites were the lymph nodes and the liver. Two patients underwent prior surgery and one received prior radiotherapy. Furthermore, all six patients in this arm received prior chemotherapy. The patients treated at 8.0 mg FD received one line and a median of 3 agents (range, 2-3 agents) each, while those at the optimal dose were given a median of 2 lines (range, 1-2 lines) and 4 agents (range, 3-4 agents) each. The most frequent prior anticancer agents were pyrimidine analogues and platinum compounds. *Arm 2 (3-hour Infusion Weekly)* Four of six patients in this arm were male. Median age was 62.0 years (range, 61-70 years) at 3.0 mg FD and 55.0 years (range, 34-75 years) at 3.75 mg FD (the optimal dose). Most patients had scores of 0-1. Three patients had esophageal cancer, two had esophagogastric junction cancer and one had gastric cancer. Disease at baseline was metastatic in all six patients. The median number of sites of disease per patient at baseline was 8 (range, 2-9 sites) at 3.0 mg FD and 3 (range, 2-4 sites) at the optimal dose. The most common sites were the lymph nodes and the lungs. Two patients underwent prior surgery and three received prior radiotherapy. All six patients were given prior chemotherapy. The median number of lines and agents of prior chemotherapy per patient was 2 (range, 1-2 lines at both dose levels) and 4 agents (range, 3-6 agents at 3.0 mg FD, and 2-6 agents at the optimal dose, respectively). The most frequent prior anticancer agents were pyrimidine analogues and platinum compounds. Phase II Stage *Arm 1 (24-hour Infusion Fortnightly)* Twelve (85.7%) of 14 treated patients were male. The median age was 60.0 years (range, 33-79 years). All had ECOG PS scores of 0-1. The most common primary tumors were esophageal cancer (n=6, 42.9%) and gastric cancer (n=6, 42.9%). At baseline, disease was metastatic in 12 patients (85.7%) and locally advanced in two (14.3%). The median number of sites of disease per patient at baseline was 4 (range, 1-7 sites). The most common sites were the lymph nodes (n=8, 57.1%) and the lungs, the esophagus and the peritoneum (n=5 each, 35.7%). Six patients (42.9%) underwent prior surgery and five (35.7%) received prior radiotherapy. In addition, all patients received prior chemotherapy; the median number of lines and agents per patient were 2 (range, 1-2 lines) and 4 (range, 2-5 agents), respectively. The most frequently administered anticancer agents were pyrimidine analogues (all patients) and platinum compounds (n=13, 92.9%).	

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	Arm 2 (3-hour Infusion Weekly) Seventeen (94.4%) of 18 treated patients were male. The median age was 58.5 years (range, 37-81 years). All had ECOG PS scores of 0-1. Most patients had esophagogastric junction cancer (n=8, 44.4%) or esophageal cancer (n=6, 33.3%). At baseline, 17 patients (94.4%) had metastatic disease and one (5.6%) had locally advanced disease. The median number of sites of disease per patient at baseline was 3 (range, 1-6 sites). The most common sites were the lymph nodes (n=11, 61.1%), and the liver (n=9, 50.0%). Two patients (11.1%) underwent prior surgery and seven (38.9%) received prior radiotherapy. Prior chemotherapy was administered to all 18 patients; the median number of lines and agents were 2 (range, 1-2 lines) and 3 (range, 2-7 agents), respectively. The most frequent prior anticancer agents were pyrimidine analogues and platinum compounds (all patients).	
Results (2): Extent of exposure to investigational product	**Drug Exposure:** Phase Ib Stage *Arm 1 (24-hour Infusion Fortnightly)* Twenty-five cycles were given in this arm: five at 8.0 mg FD and 20 at the optimal dose. The median number of cycles per patient was two (range, 1-2 cycles) at 8.0 mg FD and six (range, 2-12 cycles) at the optimal dose. Overall, 47 infusions were administered. At the optimal dose, the median cumulative dose per patient was 110.0 mg (range, 40.0-230.0 mg), the median dose intensity was 4.8 mg/week (range, 4.3-4.8 mg/week) and the median relative dose intensity was 95.3% (range, 85.6-96.6%). *Arm 2 (3-hour Infusion Weekly)* Fifteen cycles were administered in Arm 2: six at 3.0 mg FD and nine at the optimal dose. All patients at 3.0 mg FD received two cycles each, whereas the median number of cycles per patient at the optimal dose was three (range, 2-4). A total of 53 elisidepsin infusions were given. At the optimal dose, the median elisidepsin cumulative dose per patient was 33.8 mg (range, 24.0-60.0 mg), the median dose intensity was 3.8 mg/week (range, 3.0-3.8 mg/ week) and the median relative dose intensity was 100.0% Phase II stage *Arm 1 (24-hour Infusion Fortnightly)* Thirty-six cycles were given, for a median of two (range, 1-12 cycles) cycles per patient. A total of 63 infusions were administered. The median cumulative dose per patient was 40.0 mg (range, 10.0-220.0 mg), the median dose intensity was 4.7 mg/week (range, 2.3-4.8 mg/week) and the median relative dose intensity was 94.1% (range, 46.7-96.6%). *Arm 2 (3-hour Infusion Weekly)* Forty-three cycles were administered, for a median of two (range, 1-6 cycles) cycles per patient. Overall, 146 infusions were given. The median cumulative dose per patient was 27.0 mg (range, 3.8-86.3 mg), the median dose intensity was 3.5 mg/week (range, 1.3-3.8 mg/week) and the median relative dose intensity was 92.1% (range, 33.3-100.0%). **Dose Delays, Omissions and Reductions:** Phase Ib Stage *Arm 1 (24-hour Infusion Fortnightly)* One infusion was delayed due to hematological toxicity (grade 3 anemia). Three infusions were skipped in three patients, all due to reasons unrelated to elisidepsin. No dose reductions occurred.	

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	Arm 2 (3-hour Infusion Weekly) One infusion was delayed and two infusions in one patient were skipped due to reasons unrelated to elisidepsin. No dose reductions occurred. Phase II Stage *Arm 1 (24-hour Infusion Fortnightly)* No dosing delays or reductions occurred. Seven infusions were skipped in five patients due to reasons unrelated to elisidepsin. *Arm 2 (3-hour Infusion Weekly)* Three infusions were delayed in three patients. One delay was due to non-hematological toxicity (grade 2 AST increase, grade 1 bilirubin conjugated increase, and grade1 blood bilirubin increase), and the other two were unrelated to elisidepsin. A total of 16 infusions were omitted in 11 patients. Seven were related to elisidepsin: six were due to non-hematological toxicity [grade 2/3 ALT increase alone (n=3) or concomitant with grade 3 GGT increase (n=1); grade 3 bilirubin increase (n=1); and grade 2 conjugated bilirubin increase (n=1)] and one was due to hematological toxicity (grade 3 anemia). The other nine omissions were unrelated to elisidepsin. Two patients had one dose reduction each: one was due to non-hematological toxicity (grade 2 ALT increase), and the other one was unrelated to elisidepsin. **Study Discontinuation:** Phase Ib Stage *Arm 1 (24-hour Infusion Fortnightly)* All six patients discontinued due to disease progression. *Arm 2 (3-hour Infusion Weekly)* Five patients discontinued due to disease progression, and one refused further treatment after Cycle 4. Phase II Stage *Arm 1 (24-hour Infusion Fortnightly)* Most patients discontinued due to disease progression (n=11, 78.6%). Two patients (14.3%) died due to reasons unrelated to elisidepsin, and one (7.1%) discontinued following a decision by the Investigator. *Arm 2 (3-hour Infusion Weekly)* Sixteen patients (88.9%) discontinued due to disease progression, and two (11.1%) discontinued due to other reasons [ischemic cerebrovascular accident; and hematemesis (n=1 each)].	
Results (3): Dose-limiting toxicities and optimal dose (phase Ib stage only)	**Dose-limiting Toxicities (DLTs):** All patients treated with elisidepsin during the phase Ib stage were evaluable for DLTs. No DLTs were found at either treatment arm. **Optimal Dose:** *Arm 1 (24-hour Infusion Fortnightly)* The optimal dose for elisidepsin given as a 24-hour infusion fortnightly was 10.0 mg FD. *Arm 2 (3-hour Infusion Weekly)* The optimal dose for elisidepsin given as a 3-hour infusion weekly was 3.75 mg FD.	
Results (4): Safety	Phase Ib Stage *Arm 1 (24-hour Infusion Fortnightly)* All six treated patients were evaluable for safety. All elisidepsin-related AEs at all dose levels were grade 1 or 2. At the optimal dose, elisidepsin-related AEs comprised	

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grade 1/2 fatigue (two patients and 17 cycles), grade 2 constipation, and grade 1 aphagia, injection site pain and pruritus (one patient and one cycle each).
Regardless of their relationship to elisidepsin, most hematological abnormalities were grade 1 or 2 and none reached grade 4. At the optimal dose, grade 3 anemia occurred in two patients and five cycles, and grade 3 neutropenia in one patient and one cycle. The episode of grade 3 neutropenia resolved within one week without the need for concomitant colony-stimulating factors. No cases of febrile neutropenia were found.
Most biochemical abnormalities were grade 1 or 2 regardless of their relationship to elisidepsin. No severe biochemical abnormalities occurred at the optimal dose.
No elisidepsin-related SAEs were reported in Arm 1 during this stage. Four patients died while on study, all due to disease progression.

Arm 2 (3-hour Infusion Weekly)
All six treated patients were evaluable for safety. All elisidepsin-related AEs at all dose levels were grade 1/2. At the optimal dose, they comprised grade 1 pruritus (two patients and four cycles), grade 2 fatigue (one patient and two cycles), and grade 1 nausea, erythema and hypotension (one patient and one cycle each).
Regardless of relationship, most hematological and biochemical abnormalities were grade 1 or 2. No severe abnormalities were found at the optimal dose. No cases of febrile neutropenia occurred.
One elisidepsin-related SAE consisting of grade 2 pruritus was reported; the event resulted in prolongation of hospitalization and resolved without sequelae.
Five patients died while on study. All deaths were due to disease progression.

<u>Phase II Stage</u>
Arm 1 (24-hour Infusion Fortnightly)
Fourteen patients in this arm were treated with elisidepsin and thus were evaluable for safety.
All elisidepsin-related AEs were grade 1. The most common was fatigue (14.3% of patients/11.1% of cycles). All other related AEs occurred in one patient (7.1%) and 1-5 cycles (2.8-13.9%) each.
Regardless of relationship, most hematological abnormalities were grade 1 or 2. Severe abnormalities were grade 3 only and comprised lymphopenia (28.6% of patients/11.8% of cycles), thrombocytopenia (14.3% of patients/5.9% of cycles), anemia (7.1% of patients/2.9% of cycles) and neutropenia (7.1% of patients/2.9% of cycles). All patients with severe anemia and lymphopenia already had these abnormalities at baseline. No episodes of febrile neutropenia were reported.
Most biochemical abnormalities regardless of relationship were also grade 1 or 2. The most common severe abnormality was grade 3 ALT increase (21.4% of patients/8.8% of cycles), followed by grade 3 GGT increase (14.3% of patients/5.9% of cycles), grade 3 AST increase (7.7% of patients/3.0% of cycles) and grade 3 AP increase (7.1% of patients/2.9% of cycles). Grade 3 ALT increase generally appeared on Day 14 (range, 4-29 days) and returned to grade ≤ 1 after a median of five days (range, 1-8 days). The single episode of grade 3 AST increase appeared on Day 29 and returned to grade ≤ 1 within one day. No severe increases in creatinine or total bilirubin levels were found.
No elisidepsin-related SAEs were reported. Twelve patients died during the study period, all due to disease progression.

Arm 2 (3-hour Infusion Weekly)
All 18 patients in this arm were treated with elisidepsin and thus were evaluable for safety.
All elisidepsin-related AEs were grade 1 or 2; the most common were pruritus (44.4% of patients/30.2% of cycles) and fatigue (22.2% of patients/20.9% of cycles).
Most hematological abnormalities were grade 1 or 2, regardless of relationship. Severe abnormalities consisted of grade 3 lymphopenia (11.1% of patients/7.3% of cycles)

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	and grade 3 anemia (11.1% of patients/4.9% of cycles). Both patients with grade 3 anemia in this arm already had grade 1/2 anemia at baseline. No cases of febrile neutropenia were found. Regardless of relationship, most biochemical abnormalities were grade 1 or 2 and none reached grade 4. The most common severe abnormality was grade 3 GGT increase (50.0% of patients/46.3% of cycles), followed by transient grade 3 ALT increase (27.8% of patients/12.2% of cycles), grade 3 AP increase (11.1% of patients/9.8% of cycles) and grade 3 AST increase (5.6% of patients/2.4% of cycles). Grade 3 ALT increase appeared on Day 13 (range, 4-22 days) and returned to grade ≤ 1 within nine days (range, 1-12 days), while the single episode of grade 3 AST increase appeared on Day 13 and returned to grade ≤ 1 within one day. No patients had severe increases in creatinine or total bilirubin levels. No elisidepsin-related SAEs were reported. Thirteen patients died during the study period: 12 due to disease progression and one due to grade 4 embolism unrelated to elisidepsin.	
Results (5): Efficacy	Phase I stage *Arm 1 (24-hour Infusion Fortnightly)* None of the six patients included and treated in this arm had CR or PR. Two patients treated at the optimal dose were progression-free at Week 16 ± 1. *Arm 2 (3-hour Infusion Weekly)* None of the six patients included and treated in this arm had CR or PR, or were progression-free at Week 16 ± 1. Phase II stage *Arm 1 (24-hour Infusion Fortnightly)* - Primary efficacy endpoint: rate of tumor control None of the 15 patients enrolled in this arm had CR or PR; one patient was progression-free at Week 16 ± 1. The rate of tumor control was 6.7%. - Secondary efficacy endpoints The PFS-6 was 6.7% and the 1-yr PFS was 0%. The rate of response was 0%; no median duration of tumor response could be calculated owing to the lack or response. The median PFS was 1.8 months (95% CI, 1.5-2.1 months). The 1-yr OS was 0% and the median OS was 5.2 months (95% CI: 1.5-8.0 months). *Arm 2 (3-hour Infusion Weekly)* - Primary efficacy endpoint: rate of tumor control None of the 18 patients enrolled in this arm had CR or PR, or were progression-free at Week 16 ± 1. The rate of tumor control was 0%. - Secondary efficacy endpoints Both the PFS-6 and the 1-yr PFS was 0%. The rate of response was 0%; no median duration of tumor response could be calculated owing to the lack or response. The median PFS was 1.8 months (95% CI, 1.5-1.8 months). The 1-yr OS was 11.1% and the median OS was 5.5 months (95% CI, 3.6-11.4 months).	
Results (6): Pharmacokinetics	The PK profile of elisidepsin administered at a dose of 8.0 or 10.0 mg FD as a 24-hour infusion fortnightly q4wk to patients with unresectable, locally advanced or metastatic esophageal, esophagogastric junction or gastric cancer (Arm 1) was characterized by a mean clearance (CL) of 14 l/h, a mean terminal half-life (HL) of 58 h and a mean volume of distribution at steady-state (V_{ss}) of 353 l. In patients treated with elisidepsin at 3.0 or 3.75 mg FD as a 3-hour infusion weekly q4wk (Arm 2), the PK profile showed a mean CL of 14 l/h, a mean HL of 44 h and a	

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	mean V_{ss} of 357 l. No differences between tumor types were found in either treatment arm. Overall, the values of the PK parameters found for these two elisidepsin schedules were similar to those obtained in patients with different solid tumors treated with a comparable dose and the same schedule from a phase I study.	
Results (7): Pharmacogenomics	The PGx substudy was finally not conducted owing to the low clinical benefit observed with the two elisidepsin schedules evaluated in the present study.	
Conclusions	The first stage of this phase Ib-II clinical trial established 10.0 mg FD as the optimal dose for elisidepsin given as a 24-hour infusion fortnightly q4wk, and 3.75 mg FD as the optimal dose when given as a 3-hour infusion weekly q4wk, to adult patients with unresectable, locally advanced or metastatic esophageal, esophagogastric junction or gastric cancer. The second stage primarily assessed the efficacy of both schedules at the optimal doses determined in the first stage. Tumor control was found in 6.7% of patients given elisidepsin as a 24-hour infusion fortnightly, and in none of those given elisidepsin as a 3-hour infusion weekly. Both schedules were generally well tolerated, and most adverse events were mild or moderate, reversible and predictable. The PK profiles obtained for both schedules were similar to those reported previously in patients with solid tumors treated with a comparable dose and the same schedule. In conclusion, no recommendation may be given for further evaluation of elisidepsin given as a 24-hour infusion fortnightly or as a 3-hour infusion weekly in the treatment of unresectable, locally advanced or metastatic esophageal, esophagogastric junction or gastric cancer.	
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