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

FINAL STUDY REPORT

KF-B-005-04

PHASE II CLINICAL AND PHARMACOKINETIC TRIAL OF ONE-HOUR INFUSION OF KAHALALIDE F WITH A WEEKLY SCHEDULE FOR THE TREATMENT OF PATIENTS WITH NON-SMALL CELL LUNG CANCER, STAGE IIIb WITH PLEURAL EFFUSION AND STAGE IV, AFTER A FIRST LINE OF CHEMOTHERAPY

Investigational Medicinal Product:	KF
Name of test drug:	Kahalalide F
Protocol number:	KF-B-005-04
Study design:	Non-randomized, open-label, single-arm, multicenter, exploratory, phase IIa study
Study start date:	9 September 2004 (First consent signed)
Study completion date:	12 December 2006 (Last follow-up)
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Earlier approved reports:	None
Version:	Final version
Approval date:	22 February 2008

This study was conducted in compliance with Good Clinical Practices (GCP)
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2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Pharma Mar, S.A.</td><td colspan="2">Individual Study Table Referring to Part of the Dossier

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<tr><td>Name of finished product:
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<tr><td>Title of the study</td><td colspan="4">Phase II Clinical and Pharmacokinetic Trial of One-hour Infusion of Kahalalide F with a Weekly Schedule for the Treatment of Patients with Non-small Cell Lung Cancer, Stage IIIb with Pleural Effusion and Stage IV, After a First Line of Chemotherapy</td></tr>
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<tr><td>Publication (references)</td><td colspan="4">Preliminary results of this study were presented at the 31st Congress of the European Society for Medical Oncology (ESMO), Istanbul, Turkey. 2006. “Provencio M, Izquierdo A, Viñolas N, Paz-Ares L, Feliu J, Constenla M, et al. Phase II clinical trial of Kahalalide F (KF) as a second line therapy in patients with advanced non-small cell lung cancer (NSCLC).Abstract No.755P.”</td></tr>
<tr><td>Study period:
- First consent signed
- Last consent signed
- First infusion administered
- Last infusion administered
- Last follow-up</td><td colspan="2">09 September 2004
15 December 2005
22 September 2004
14 November 2006
12 December 2006</td><td colspan="2">Phase of development:
Phase IIa</td></tr>
<tr><td>Study objectives</td><td>Primary objective:</td><td colspan="3">• To assess the antitumor activity of KF 650 μg/m^2 given as a weekly 1-hour intravenous (i.v.) infusion to patients with stage IIIb non-small cell lung cancer (NSCLC) with pleural effusion or with stage IV after a first-line of chemotherapy.</td></tr>
<tr><td></td><td>Secondary objectives:</td><td colspan="3">• To investigate the toxicity profile of this KF schedule in this patient population.
• To evaluate the pharmacokinetics (PK) of this KF schedule in this patient population.</td></tr>
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Name of Sponsor/Company: Pharma Mar, S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	(*For National Authority Use only*)
Name of finished product: Kahalalide F		
Name of active ingredient(s): Kahalalide F		
Methodology	Non-randomized, open-label, single-arm, multicenter, exploratory, phase IIa study	
Number of patients (planned and analyzed)	**Planned number of patients:** A Simon's two-stage minimax design was chosen to evaluate the null hypothesis $p \leq 0.03$ compared to the alternative hypothesis $p \geq 0.15$. The probability of early termination was 0.467. Thus, if the investigational medicinal product (IMP) was not effective, the probability of concluding that it really was effective was 0.080 (with $\alpha = 0.01$), whereas if the IMP was effective, the probability of concluding that it really was not effective was 0.10 (with $\beta = 0.1$, power of 90%). KF was to be tested on 25 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 9 patients were to be evaluated. The Simons's design stated that if the total number of patients with an objective tumor response was ≤2, this schedule was not to be considered for further evaluation. **Patients analyzed:** The study was closed early after 31 patients had been included into the first stage because the efficacy found in the 26 evaluable patients who satisfied all eligibility criteria was considered too low to merit further interest for KF in NSCLC. All patients were included in the safety analysis.	
Diagnosis and main selection criteria	**Inclusion Criteria:** 1. Signed informed consent by the patient before starting any study procedures. 2. NSCLC, stage IIIb with pleural effusion, or stage IV, confirmed histologically. 3. Previous treatment with up to one line of systemic therapy for stage IIIb with pleural effusion or stage IV NSCLC was allowed as long as four weeks had passed since the end of these treatments. 4. Complete recovery from the effects of radiotherapy, if any. Four weeks had to have passed since the completion of radiotherapy. 5. At least one measurable lesion (as per Response Evaluation Criteria In Solid Tumors [RECIST]) located in a non-irradiated area, properly measured within four weeks before inclusion in the study. 6. Age ≥18 years. 7. Performance status (PS) according to Eastern Cooperative Oncology Group (ECOG) ≤2. 8. Life expectancy ≥3 months. 9. Adequate bone marrow, renal and hepatic function (assessed three days before inclusion in the study): a. Neutrophils ≥1.0 x 10^9/l (≥1000/mm^3); b. Platelets ≥75 x 10^9/l (≥7500/mm^3); c. Creatinine ≤2 mg/dl; or creatinine clearance ≥ 40 ml/min; d. Serum bilirubin ≤2 mg/dl; e. Alkaline phosphatase (AP) ≤2.5 x upper limit of normal (ULN); f. Albumin ≥2.5 g/dl; g. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤2.5 x ULN of the laboratory values used at each center (≤5 x ULN, in the event of liver metastases); h. Partial thromboplastin time (PTT) <1.5 x ULN; i. Prothrombin time (PT) <1.5 x ULN. **Exclusion Criteria:** 1. Treatment with any chemotherapeutic or biological agent within four weeks before the first dose. 2. Pregnant or lactating women, or men and women who were not using effective contraceptive methods (contraceptive pill, intrauterine devices, double barrier method). 3. History of other malignant neoplasia (other than non-melanoma skin cancer or properly treated carcinoma *in situ*). 4. Known symptomatic cerebral or leptomeningeal involvement. 5. Other serious diseases or conditions: a. Congestive heart failure, ischemic cardiopathy, arterial hypertension or poorly controlled arrhythmias. b. History of psychiatric disorders that might interfere with adherence to the study. c. Active infection.	

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	d. Recent esophageal hemorrhage. e. Chronic liver disease. 6. Any other clinical condition or important laboratory finding that prevented the patient from participating in the study. 7. Participation in other clinical trials or concomitant treatment with other investigational products in the 30-day period before inclusion into the study. 8. Patients who were unable to guarantee follow-up. 9. Known hypersensitivity to Cremophor or ethanol.	
Test product, dose and mode of administration, batch numbers	KF (Pharma Mar, Colmenar Viejo, Spain) was supplied as a sterile lyophilized powder for concentrate for solution for infusion in vials with two strengths: 0.5 mg and 1 mg. KF had to be administered at a dose of 650 μg/m^2 as a weekly 1-hour i.v. infusion, with no resting period (i.e., weeks without treatment). The infusion rate had to be adjusted so as to insure that the total dose was administered over a period of one hour. Each weekly KF administration was considered a cycle. The batch numbers of the KF used in this study were as follows: • **0.5-mg vials:** #031604MD26/KF, #080403MD24/KF, #082004MD28/KF, #121702MD19/KF, #080205SQ4/KF, and #041505SQ2/KF. • **1-mg vials:** #031104MD25/KF, #081004MD27/KF, #111704BN1/KF, #020105SQ1/KF, #080505SQ5/KF, #082905JH1/KF, #090205JH2/LH, and #060605SQ3/KF.	
Duration of treatment	Any eligible patient who experienced early disease progression prior to the first response evaluation (eight weeks after treatment onset) was to be withdrawn from the study and categorized as "early progression". At the time of any other evaluation, the patients were to be taken off study if they showed objective progression. Regardless of the disease status, treatment always had to be discontinued in case of patient refusal and if excessive toxicity precluded further therapy. If neither of the aforementioned situations occurred, patients were to be treated weekly until objective or clinically significant progression of the disease was observed, unacceptable toxicity appeared, treatment delay >2 weeks (assuming that the patient would remain in the study for an average time of four months), or due to investigator's decision. The sponsor could terminate the study at any time due to any of the following reasons: failure in patient inclusion, protocol deviations, inaccurate or incomplete data, unsafe or unethical practice, doubtful safety or suspected lack of efficacy of KF, or administrative decision.	
Criteria for evaluation	**Efficacy:** Patients evaluable for response had to receive at least eight treatment cycles and had to have at least one disease assessment. The primary efficacy endpoint of this study was the objective response rate evaluated using RECIST and estimated as the percentage of evaluable patients in the study population who achieved complete response (CR) or partial response (PR). Objective tumor measurements were to be assessed at least every eight weeks while on therapy and every three months during follow-up for patients who discontinued due to reasons other than progression. Tumor investigations were performed by computed tomography (CT) and nuclear magnetic resonance (NMR) scans for all measurable lesions, and using appropriate clinical and/or radiological tests for all non-measurable lesions. The secondary efficacy endpoints of this study included evaluation of time to beginning of response, duration of response, and incidence of controlled disease (CR, PR and stable disease [SD] lasting for three months or more). Additionally, an evaluation of time-to-event efficacy endpoints (progression-free survival [PFS] time to progression [TTP] and overall survival [OS]) was to be done. Follow-up of survival was to be finished at six months after the inclusion of the last patient. **Toxicity:** All patients were to be evaluable for toxicity if they had received any KF infusion. Safety parameters included description of treatment-related deaths, premature withdrawals from treatment due to toxicity, description of adverse events (AEs) and serious adverse events (SAEs), evaluation of toxicity according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 3.0) and laboratory abnormalities. **Pharmacokinetic:** Whole blood samples for PK analysis had to be collected during the first and second infusions at different time intervals from the arm contralateral to the one used for infusion. Sample	

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	volume had to be 5 ml for all samples, except for one sample (No. 10), which had to be 8 ml. PK parameters were to be defined.	
Statistical methodology	The Statistical Analysis Plan (SAP) defined two patient populations: the intention-to-treat (ITT) population, which included all patients enrolled who signed the informed consent, and the all-treated (AT) population, which included all patients who received at least one cycle of treatment during the study. Tumor response was to be evaluated in patients who fulfilled all eligibility criteria. Descriptive statistics (mean, median, standard deviation [SDev], 95% confidence interval [CI], and range of values) were to be used in the analysis of demographic data, response rates, toxicities (coded as per NCI-CTC, version 3.0), AEs (coded as per Medical Dictionary for Regulatory Activities [MedDRA]), toxic deaths, SAEs, treatment-related toxicities and treatment discontinuation profiles. In the current study only one objective response (PR) according to RECIST was found in one patient who did not satisfy all eligibility criteria at baseline; therefore, several analyses described in the study protocol (e.g., comparison of null hypothesis to alternate hypothesis, Bayesian analysis, prognostic factors, the Fisher's exact test or the Pearson χ^2 test) were not considered appropriate. Time-to-event efficacy endpoints were to be analyzed according to the Kaplan-Meier method. For the PK analysis, the potential influence of dychotomic demographic and clinical variables on kinetic parameters was to be evaluated. All individual PK parameters were to be tabulated and summarized for each treatment infusion for the evaluable PK population using count (n), mean, SDev, coefficient of variation (CV%), median, geometric mean, minimum and maximum values. Interpatient and intrapatient variability of the PK parameters (terminal half-time [$t_{½}$], total body clearance [CL], and distribution at steady-state [V_{ss}]) were to be assessed by analysis of variance (ANOVA) using general linear models in SAS®. Linear regression of natural log-transformed plasma area under the curve (AUC), maximum plasma concentration (C_{max}), $t_{½}$, CL, and V_{ss} predicted by natural log-transformed demographic and other covariates (liver enzymes, bilirubin, creatinine and its clearance, and total proteins) was to be carried out.	
Results (1): Patient characteristics	A total of 31 NSCLC patients were enrolled at seven Spanish medical centers (five centers did not enrolled any patient). Patients had a median age of 64.0 years (range, 35-78 years) and all were Caucasians. Most patients had ECOG PS 0-1, save for one patient who had a PS score of 2. At study entry, 29 patients (93.5%) had stage IV NSCLC and two patients (6.5%) had stage IIIb NSCLC (with pleural effusion). Epidermoid carcinoma (45.2%) and adenocarcinoma (32.3%) were the most frequently reported tumor types at baseline. All patients had documented metastatic lesions at baseline, with a median of two sites (range, 1-5 sites), and lung was the most common site involved (100.0%) followed by lymph nodes (41.9%). All patients had received prior chemotherapy in the advanced or advanced/neoadjuvant setting. Most patients (n=28, 90.3%) had been previously exposed to one line of chemotherapy (as per protocol) and had received a median of two chemotherapeutic agents (range, 1-6 agents). Thirteen patients (41.9%) had undergone surgery and 12 (38.7%) had received radiotherapy. Seventeen patients (54.8%) entered the study showing signs and symptoms of disease at baseline (median: 1 per patient; range, 0-5), with respiratory disorders (cough and dyspnea), tumor pain and fatigue as the most frequent symptoms. All signs and symptoms observed at baseline were grade 1/2. Grade 1/2 anemia (n=12; 38.7%) and lymphopenia (n=10; 32.3%) were the only hematological abnormalities at baseline, save for one patient who had grade 3 lymphopenia. All biochemical abnormalities at baseline were grade 1, save for GGT increase, which was grade 2 in two patients and grade 3 in one patient. Additionally, one patient had grade 3 hyperkalemia.	
Results (2): Extent of exposure	**Drug exposure** Overall, 402 treatment cycles were administered to 31 patients, with a median of eight cycles per patient (range, 2-56). Most patients received three or eight cycles (four patients each, 12.9%). The median relative calculated dose intensity was 98.0% (range, 50.0-103.9%). **Dose delays and reductions:** A total of 32 of 371 cycles (8.6%) susceptible of delay were delayed in 15 treated patients (48.4%). All cycles were delayed due to non-treatment-related reasons with a median delay length of 4 days (range, 0-34 days).	

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	One of 402 cycles (0.2%) was reduced (from 650 μg/m^2 to 530 μg/m^2) in one patient (3.2%) due to treatment-related increase in transaminases. **Treatment discontinuation:** Most patients discontinued KF treatment because of disease progression (n=24; 77.4%), followed by other reasons (n=3; 9.7%), death as a result of progression of malignant disease (n=2; 6.5%), toxicity (n=1; 3.2%), and patient refusal (n=1; 3.2%).	
Results (3): Efficacy	No objective responses were found among 26 evaluable patients who satisfied all eligibility criteria (primary efficacy endpoint). Seven patients (22.6%) had SD lasting for more than three months, two patients (6.5%) were early discontinuations because they died due to progressive disease (PD), and the other 17 patients (54.8%) had PD. With a median follow-up of 7.4 months (95% confidence interval [CI], 5.9-9.7 months), the median TTP/PFS was 1.8 months (95% CI, 1.4-2.1 months) and the median OS was 7.2 months (95% CI, 3.6-13.5 months).	
Results (4): Safety	All 31 patients were evaluated for extent of drug exposure and safety. Most KF-related AEs that occurred during the study were grade 1/2 in severity and allowed patients to continue on study treatment. Fatigue and pruritus not otherwise specified (NOS) (19.4% of patients each), were the most observed AEs related to KF. Only two patients (6.5%) experienced four treatment-related grade 3 AEs, all during one cycle (0.2%). A total of 29 SAEs were found in 13 patients (41.9%) but none of them were considered to be related to KF. Sixteen deaths occurred up to the date of last follow-up, and all except for one patient, who died due to sepsis, were due to progression of the underlying malignant disease. Concerning the overall laboratory data, anemia, lymphopenia, increases in the levels of transaminases (ALT/AST) and gamma-glutamyltransferase (GGT) were the most frequent hematological or laboratory toxicities after KF administration. The most frequent grade 1/2 hematological abnormalities were anemia, observed in 19 patients (61.3%) and 142 cycles (36.7%), and lymphopenia, observed in 16 patients (51.6%) and 117 cycles (30.2%). Anemia and lymphopenia were the only hematological toxicities that reached grade 3 severity in one patient (3.2%) each, while no grade 4 hematological toxicities were observed. Regarding biochemical abnormalities, 15 patients (48.4%) in 125 cycles (35.5%) had grade 1/2 GGT increase, while 16 patients (51.6%) in 65 cycles (18.0%) and 10 patients (32.2%) in 21 cycles (5.8%) had grade 1/2 ALT and AST increase, respectively. Six patients (19.4%) had grade 3 GGT increase in 16 cycles (4.5%). Four patients (12.9%) and three patients (9.7%) experienced grade 3 ALT and AST increase, respectively, during six cycles each. Only two patients (6.5%) and four patients (12.9%) had grade 4 ALT and AST increases, all during one cycle each (0.2%). All grade 3/4 ALT and AST increases started shortly after the first KF infusion and were transient, as they all appeared and returned to grade ≤2 levels between cycles 1 and 4. Additionally, grade 3 increase in total bilirubin and CPK were observed in one patient and one cycle each. Other biochemical toxicities occurred at lower frequencies and were mild or moderate in nature.	
Results (5): Pharmacokinetics	The PK profile of KF in NSCLC patients was characterized by a narrow distribution and a short body residence. Intrapatient and interpatient variabilities were low for AUC and V_{ss}, and moderate for C_{max}, CL and $t_{½}$. Body size was a predictor of KF clearance and V_{ss}, with clearance increasing with body surface area (BSA) and weight, and V_{ss} increasing with height, weight, and BSA. Males had higher C_{max}, CL, and V_{ss} values than females; however, no statistically significant differences were found. Creatinine clearance was directly related to KF clearance, although this relationship was considered to be biased by the influence of the body size on the calculated creatinine clearance. This PK profile was somewhat different to that found in a phase I study with KF at the same dose; although $t_{½}$ was quite similar, CL and V_{ss} values were higher in this subpopulation of patients with NSCLC.	
Conclusions	In conclusion, KF 650 μg/m^2 given weekly as a 1-hour i.v. infusion to pretreated patients with NSCLC (stage IIIb with pleural effusion or stage IV) was a safe and well tolerated chemotherapy regimen with predictable and manageable toxicity. This trial was early closed after the first stage because of the lack of objective tumor responses as per RECIST, which was the primary endpoint of this study.	
Date of Report (Final version)	22 February 2008	