2 SYNOPSIS

NAME OF SPONSOR COMPANY: Protherics Medicines Development, Ltd.	Individual study table referring to Part of the Dossier	(*For National Authority use only*)
NAME OF FINISHED PRODUCT: Prolarix™	Volume:	
NAME OF ACTIVE INGREDIENT: Tretazicar and Caricotamide	Page:	

Title of Study: A Phase 2 Study of the Anti-Tumour Activity and Safety of Prolarix™ in Hepatocellular Carcinoma (HCC)

Investigators and/or Study Centers: Five investigators were intended to participate in the study. However, only a single subject was enrolled at one study center prior to premature termination of the study.

Publications: None

Study Period: **Date of enrollment of first subject:** 09 October 2008 **Date of study termination:** 01 September 2009	**Phase of Development:** Phase 2

Primary Objective: The primary objective of this study was to evaluate the overall response rate (ie, proportion of subjects with complete response and partial response) to treatment with Prolarix at the maximum tolerated dose [MTD] determined in a previous Phase 1 study.

Methodology: This was an open-label study designed to evaluate the anti-tumour activity and safety of Prolarix in subjects with advanced hepatocellular carcinoma (HCC). Study drug was to be administered once every 21 days until disease progression occurred or until 6 cycles of treatment had been completed. Subjects were to receive 200 mg/m^2 caricotamide over a 4-hour infusion with 26.6 mg/m^2 tretazicar given over 15 minutes at the midpoint of the caricotamide infusion (1 hour 45 minutes) on Day 1 of each 21-day cycle. The tolerability of Prolarix was to be established by evaluating the toxicities at each cycle. Subjects who had not progressed at the end of the treatment period were to enter a follow-up period in which they would continue receiving study drug using the same schedule as the treatment period until disease progression. During the treatment and follow-up periods subjects were to undergo evaluation for safety at every visit. Tumour measurements were to be performed by computed tomography (CT) scan at Screening (within –28 days) and within 5 days prior to every odd numbered cycle after Cycle 1.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 20 subjects were planned to be enrolled to obtain 14 evaluable subjects for post-treatment tumour response.
Analyzed: One subject had been treated at the time the study was terminated.

Diagnosis and Main Criteria for Inclusion: Main inclusion criteria included age ≥18 years; histologic or cytologic diagnosis of HCC considered unsuitable for resection or other potentially curative options; presence of a measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) on CT scan in at least one site which had not received radiation or any other local therapy; Eastern Cooperative Oncology Group (ECOG) Performance status of 0 or 1; no other active malignancy within the previous 3 years (except non-melanomatous skin cancer or carcinoma *in situ* of the breast, bladder or uterine cervix); life expectancy >3 months; adequate bone marrow function (ie, haemoglobin ≥9 g/dL, granulocytes ≥1500/mm^3, platelets ≥75,000/mm^3); prothrombin time (PT)-international normalised ratio (INR) ≤2.3 or PT ≤6 seconds above control; adequate renal function (ie, normal serum creatinine clearance or calculated creatinine clearance ≥60 mL/min); adequate hepatic function (ie, bilirubin ≤2x upper limit of normal; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤5xULN). Main exclusion criteria included prior or current systemic pharmacotherapy for HCC; an absolute contraindication to receiving CT contrast media; Child-

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Pugh Class C hepatic impairment; major variceal bleeding within the previous 30 days; and known history of human immunodeficiency virus/AIDS infection.

Test Product, Dose and Mode of Administration, Batch Number: Prolarix is a therapy that comprises tretazicar as prodrug and caricotamide as co-substrate for the endogenous enzyme, NQO2. A dose of 200 mg/m^2 caricotamide is administered over a 4-hour infusion with 26.6 mg/m^2 tretazicar IV infusion given over 15 minutes at the midpoint of the caricotamide infusion (1 hour 45 minutes). Prolarix was to be administered on Day 1 of each 21-day cycle until disease progression or until 6 cycles had been completed. The batch number for tretazicar was 742559 and the batch number for caricotamide was P08307.

Reference Therapy, Dose and Mode of Administration, Batch Number: No reference therapy was evaluated.

Duration of Treatment: Subjects were to receive infusion of Prolarix at 21-day intervals until disease progression or until 6 cycles had been completed. Subjects who had not progressed at the end of the treatment period were to enter a follow-up period in which they would continue to receive study drug using the same schedule as the treatment period until disease progression.

CRITERIA FOR EVALUATION

Efficacy: Overall tumour response was to be based on the best tumour response in all subjects. Tumour responses for targeted and non-targeted tumours were to be defined using RECIST criteria with the modification that confirmatory CT was not required to define tumour response.

Safety: Safety measurements included adverse events, laboratory tests (haematology, chemistry, urinalysis, creatine phosphokinase MB (CK-MB) and troponin I), vital signs, electrocardiograms (ECG), weight, physical examinations, and toxicity evaluations. Toxicities were evaluated at each course of therapy using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 grading system.

STATISTICAL METHODS: No statistical analyses were performed because only one subject participated prior to termination of the study.

SUMMARY AND CONLUSIONS

This study was terminated prematurely by the sponsor for business reasons. One subject participated in the study prior to study termination. This was a 53 year-old white male, Child-Pugh Class B, with a history of type 2 diabetes, hypertension, cirrhosis, Quincke edema, non-alcoholic steato-hepatitis, and non-resectable hepatocellular carcinoma of 12 cm in the right lobe of the liver with two satellite lesions and right portal vein tumour thrombus. The subject was screened for the study on 16 October 2008 and received the first dose of study drug on 27 October 2008. The subject experienced numerous adverse events between screening and receipt of study drug. These consisted of hyperkalaemia, hyponatraemia , haematoma, increased creatinine, increased urea, dehydration requiring hospitalization, renal disorder, exertional dyspnoea, hyperkalaemia, abdominal pain, and anaemia. All of the adverse events that occurred prior to study drug dosing were considered by the investigator to be unrelated to the study drug. On 27 October 2008 the subject received his first dose of study drug: 384 mg caricotamide administered over a 4-hour infusion with 51 mg tretazicar IV infusion given over 15 minutes at the midpoint of the caricotamide infusion (1 hour 45 minutes). On 28 October 2008, he developed gastrointestinal toxicity resulting in hospitalization considered by the investigator to be possibly related to study treatment and manifested by dehydration, nausea, anorexia, fatigue, vomiting, diarrhea, and deterioration in performance status to ECOG 3. On

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4 November 2008 he developed dehydration again for which he was rehospitalized, hyperkalaemia, deterioration of renal function (increased creatinine and urea) and evidence of hepatic encephalopathy. He developed anxiety on 10 November 2008 and pleural effusion on 11 November 2008. Hepato-renal syndrome was diagnosed on 12 November 2008. Despite hydration and albumin infusion the patient's condition progressively deteriorated. Further treatment with Prolarix was withheld and he was discharged from the hospital on 17 November 2008. The patient expired at home on 24 November 2008. The cause of death was hepato-renal syndrome, which the investigator considered to be unrelated to Prolarix administration.		
Date of the Report: 23 April 2010		