The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: VEG111109

Title : An open-label, multicenter, phase I/II study of pazopanib in combination with paclitaxel in first-line treatment of subjects with stage IIIBwet/IV non-small cell lung cancer

Rationale: Pazopanib is an anti-angiogenic tyrosine kinase inhibitor, which has demonstrated activity in non-small cell lung cancer (NSCLC), with 86% of subjects with early stage NSCLC who participated in a pre-operative study experiencing volumetric reduction of their tumor after a median duration of 16 days treatment with single-agent pazopanib. The combination of pazopanib with the third-generation chemotherapy agent, paclitaxel, presents the possibility of a new non-platinum doublet combination in the frontline treatment of advanced or metastatic NSCLC.

Phase: I/II (Data for Phase I of the study is presented; the Phase II part of the study was not performed)

Study Period: 09 July 2009 – 25 October 2012

Study Design: This was an open-label, multicenter, Phase I/II study of pazopanib in combination with paclitaxel administered once every 3 weeks in the first-line treatment of subjects with Stage IIIBwet, Stage IV NSCLC, or previously untreated advanced solid tumors for which there was no standard therapy or for which paclitaxel was standard therapy. The Phase II part of the study was not initiated, as documented in a protocol amendment, due to a strategic decision not to pursue the development of the pazopanib/paclitaxel combination in this indication.

Centres: Two centers in the United Kingdom and two centers in the United States of America

Indication: Advanced NSCLC or previously untreated advanced solid tumors

Treatment: Pazopanib was administered orally once daily until disease progression, unacceptable toxicities, or death, and paclitaxel was administered as a 3-hour intravenous (IV) infusion on Day 1 of each 3-week treatment cycle for up to 6 cycles. In order to assess the pharmacokinetic (PK) profile of paclitaxel alone and in combination with pazopanib, treatment with pazopanib was initiated on Day 2 of the study. The initial dose level tested in Cohort 1 was pazopanib 800 mg once daily plus paclitaxel 135 mg/m^2 once every 3 weeks. All subjects were required to receive premedication according to the prescribing information before receiving paclitaxel.

Primary Objectives: To assess the safety and tolerability, and to determine the maximum tolerated regimen (MTR) of pazopanib in combination with paclitaxel in subjects with previously untreated advanced solid tumors, including Stage IIIBwet or Stage IV NSCLC.

Secondary Objectives:

- To determine the effect of pazopanib administered once daily on the PK of paclitaxel administered as a 3-hour IV infusion once every 3 weeks.
- To estimate the PK of pazopanib in the presence of paclitaxel administered as a 3-hour IV infusion.
- To assess the clinical activity of pazopanib in combination with paclitaxel.

Statistical Methods:

Safety: The planned sample size was based on a traditional 3 + 3 design and was determined by the number of cohorts needed to determine the MTR of pazopanib and paclitaxel in combination. The total number of subjects enrolled in Phase I was dependent upon the number of subjects who experienced a dose-limiting toxicity (DLT) within a given cohort and the number of dose escalations undertaken. The Safety Population consisted of all subjects who received at least one dose of pazopanib and one dose of paclitaxel within at least one cycle of treatment. The MTR was defined as a regimen where no more than 1 out of 6 subjects experienced DLTs and was confirmed with safety and tolerability results from 6 additional subjects.

Pharmacokinetics: The PK Concentration Population consisted of all subjects for whom a PK sample was obtained and analyzed. This population was a subset of the Safety Population and was used to assess PK. Pharmacokinetic parameters were listed and summarized for paclitaxel and pazopanib. The paclitaxel PK parameters, area under the plasma drug concentration curve (AUC) and maximum observed plasma drug concentration (Cmax), from subjects in the expanded cohort were statistically analyzed by performing an analysis of variance (ANOVA) on log-transformed data. The ANOVA used a mixed-effects model with subject as a random effect and treatment as a fixed effect. The test

treatment was pazopanib plus paclitaxel and the reference treatment was paclitaxel alone.

Clinical activity: The best objective response was summarized. The best objective response rate (ORR) was defined as the percentage of subjects achieving either a complete or partial response (CR or PR) per the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.0). A determination of stable disease was required to be confirmed no sooner than 6 weeks after the initial observation of stable disease.

Study Population: Subjects at least 18 years of age, with advanced solid tumor that was previously untreated, for which there was no standard therapy or for whom paclitaxel was standard therapy, an Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease as defined by the RECIST criteria (version 1.0), and a predicted life expectancy of at least 12 weeks.

Number of Subjects:	**Cohort 1: Pac 135/ Paz 800**	**Cohort 2: Pac 175/ Paz 800**	**Cohort 3: Pac 150/ Paz 800**	**Cohort 4: Pac 175/ Paz 400**
Planned, N	3-6	3-6	3-12	3-6
Enrolled, N[a]	7	5	12	6
Safety Population	6	4	12	6
Completed, n (%)	4 (67)	3 (75)	10 (83)	5 (83)
Total number of subjects withdrawn, n (%)	2 (33)	1 (25)	2 (17)	1 (17)
Reason for study withdrawal, n (%)				
Adverse events	1 (17)	1 (25)	0	1 (17)
Investigator discretion[b]	1 (17)	0	2 (17)	0
PK Population	6	4	12	6

a. Two subjects were enrolled and received treatment with paclitaxel, but did not receive pazopanib. These subjects were not included in the Safety Population since they did not receive at least one dose of paclitaxel and one dose of pazopanib. The denominator for the completed and withdrawn percentage is the number of subjects in the Safety Population

b. Investigator discretion reasons included: patient withdrawn from this study in order to commence on another clinical trial (Cohort 1); subject needed radiation treatment (Cohort 3); progressive disease observed in clinic -subject unable to return for follow-up visits (Cohort 3)

Demographics	**Cohort 1: Pac 135/ Paz 800 (n=6)**	**Cohort 2: Pac 175/ Paz 800 (n=4)**	**Cohort 3: Pac 150/ Paz 800 (n=12)**	**Cohort 4: Pac 175/ Paz 400 (n=6)**
Females: Males	3:3	1:3	7:5	2:4
Mean age in years (sd)	58.8 (11.86)	56.5 (9.26)	62.8 (13.66)	46.2 (11.97)
Mean weight in kg (sd)	80.4 (9.54)	101.0 (17.78)	78.4 (20.94)	82.7 (17.69)
White, n (%)	6 (100)	3 (75)	11 (92)	5 (83)

Primary Outcome: Determination of MTR

Paclitaxel 135 mg/m^2 plus pazopanib 800 mg (Pac 135/ Paz 800) was the initial dose regimen (Cohort 1). Pac 175/ Paz 800 (Cohort 2) exceeded the MTR with 2 of 4 subjects experiencing a DLT. Pac 150/ Paz 800 (Cohort 3) and Pac 175/ Paz 400 (Cohort 4) dose regimens each met the criteria for MTR; Pac 150/ Paz 800 was selected for expansion to a total of 12 subjects due to a slightly better tolerability profile, including longer treatment duration (median treatment duration was 6.9 months for Pac 150/ Paz 800 and 5.0 months for Pac 175/ Paz 400). Pac 150/ Paz 800 was determined to be the MTR for this study.

Dose-limiting Toxicities (DLTs)

	Cohort 1: Pac 135/ Paz 800 (n=6)	**Cohort 2: Pac 175/ Paz 800 (n=4)**	**Cohort 3: Pac 150/ Paz 800 (n=12)**	**Cohort 4: Pac 175/ Paz 400 (n=6)**
Hepatic enzyme increased Grade 4	1	0	0	0
ALT increased Grade 3; AST increased Grade 3; rash Grade 2	0	1	0	0
Rash pruritic Grade 3	0	1	0	0
Total	1 (17%)	2 (50%)	0	0

ALT = alanine aminotransferase

Safety Results:

All AEs and SAEs were collected and recorded from receipt of the first dose of study drug until 28 days after cessation of study drug.

Most Frequent Adverse Events – On Therapy Adverse Events Occurring in >1 Subject within any Treatment Group (in descending order of overall frequency)

	Cohort 1: Pac 135/Paz 800 (n=6)	**Cohort 2: Pac 175/ Paz 800 (n=4)**	**Cohort 3: Pac 150/ Paz 800 (n=12)**	**Cohort 4: Pac 175/ Paz 400 (n=6)**
Subjects with any AEs, n (%)	6 (100)	4 (100)	12 (100)	6 (100)
Alopecia	6 (100)	3 (75)	10 (83)	5 (83)
Fatigue	6 (100)	2 (50)	11 (92)	4 (67)
Hypertension	4 (67)	4 (100)	8 (67)	4 (67)
Nausea	4 (67)	1 (25)	9 (75)	5 (83)
Diarrhea	4 (67)	3 (75)	8 (67)	2 (33)
Vomiting	3 (50)	1 (25)	6 (50)	5 (83)
Dysgeusia	4 (67)	1 (25)	7 (58)	2 (33)
Myalgia	3 (50)	1 (25)	6 (50)	4 (67)
Neutropenia	3 (50)	3 (75)	5 (42)	2 (33)
Arthralgia	3 (50)	2 (50)	4 (33)	3 (50)
Decreased appetite	4 (67)	1 (25)	4 (33)	3 (50)
Hair color changes	4 (67)	2 (50)	4 (33)	2 (33)
Headache	3 (50)	1 (25)	5 (42)	3 (50)
Neuropathy peripheral	4 (67)	1 (25)	4 (33)	3 (50)
Pain in extremity	1 (17)	1 (25)	3 (25)	6 (100)
Rash	1 (17)	2 (50)	6 (50)	2 (33)
Constipation	2 (33)	0	3 (25)	4 (67)
Dizziness	2 (33)	1 (25)	2 (17)	4 (67)
Back pain	0	1 (25)	4 (33)	3 (50)
Alanine aminotransferase increased	2 (33)	1 (25)	3 (25)	1 (17)
Dyspnoea	2 (33)	1 (25)	3 (25)	1 (17)
Oropharyngeal pain	1 (17)	0	3 (25)	3 (50)
Contusion	1 (17)	1 (25)	3 (25)	1 (17)

Oral candidiasis	1 (17)	1 (25)	2 (17)	2 (33)
Aspartate aminotransferase increased	2 (33)	1 (25)	1 (8)	1 (17)
Dry skin	0	2 (50)	1 (8)	2 (33)
Insomnia	1 (17)	1 (25)	1 (8)	2 (33)
Lymphopenia	1 (17)	1 (25)	1 (8)	2 (33)
Muscle spasms	2 (33)	1 (25)	2 (17)	0
Musculoskeletal pain	2 (33)	0	1 (8)	2 (33)
Edema peripheral	3 (50)	0	1 (8)	1 (17)
Upper respiratory tract infection	0	0	3 (25)	2 (33)
Dehydration	1 (17)	0	3 (25)	0
Dysphonia	1 (17)	0	3 (25)	0
Hemoptysis	1 (17)	0	2 (17)	1 (17)
Mouth ulceration	2 (33)	1 (25)	0	1 (17)
Neutrophil count decreased	0	0	4 (33)	0
Paresthesia	0	0	2 (17)	2 (33)
Pruritus	0	1 (25)	2 (17)	1 (17)
Cough	2 (33)	0	1 (8)	0
Dyspepsia	0	0	1 (8)	2 (33)
Epistaxis	1 (17)	0	2 (17)	0
Erythema	2 (33)	0	1 (8)	0
Gamma-glutamyltransferase increased	0	0	2 (17)	1 (17)
Hypotension	0	0	2 (17)	1 (17)
Neuralgia	1 (17)	0	2 (17)	0
Oral pain	0	1 (25)	2 (17)	0
Sinusitis	0	0	2 (17)	1 (17)
Tachycardia	1 (17)	0	2 (17)	0
Urinary tract infection	1 (17)	0	2 (17)	0
Weight decreased	0	0	3 (25)	0
Anemia	0	0	2 (17)	0
Hyperglycemia	0	0	2 (17)	0
Hypokalemia	0	0	2 (17)	0
Muscular weakness	0	0	2 (17)	0
Peripheral sensory neuropathy	0	0	2 (17)	0
Pyrexia	0	0	0	2 (33)
Respiratory tract infection	0	0	2 (17)	0
Rhinitis	0	0	2 (17)	0

Serious Adverse Events (in descending order of overall frequency)
n (%) [n considered by the investigator to be related to study medication]:

	Cohort 1: Pac 135/ Paz 800 (n=6)	**Cohort 2: Pac 175/ Paz 800 (n=4)**	**Cohort 3: Pac 150/ Paz 800 (n=12)**	**Cohort 4: Pac 175/ Paz 400 (n=6)**
Subjects with any SAEs, n (%)	2 (33) [1]	1 (25) [1]	7 (58) [2]	4 (67) [2]
Respiratory tract infection	0	0	2 (17) [0]	0
Alanine aminotransferase increased	0	1 (25) [1]	1 (8) [1]	0
Hepatic enzyme increased	1 (17) [1]	0	1 (8) [1]	0
Viral infection	1 (17) [0]	0	0	0
Hyponatremia	0	0	1 (8) [0]	0
Urinary retention	0	0	1 (8) [0]	0
Nephrolithiasis	0	0	1 (8) [0]	0
Urinary tract infection	0	0	1 (8) [0]	0
Cellulitis	0	0	1 (8) [0]	0

Pneumonia	0	0	0	1 (17) [0]
Subcutaneous abscess	0	0	0	1 (17) [1]
Pain in extremity	0	0	0	1 (17) [0]
Anxiety	0	0	0	1 (17) [0]
Neutropenia	0	0	0	1 (17) [1]
Aphasia	0	0	0	1 (17) [0]

There were no fatal SAEs

Pharmacokinetics (PK), pharmacodynamics (PD), PK/PD Endpoints:

Plasma Pazopanib Pharmacokinetic Parameters After Administration with Paclitaxel on Cycle 2 Day 1

Parameter	n[a]	Paclitaxel Dose (mg/m^2)	Pazopanib Dose (mg)	Cycle 2, Day 1
AUC(0-24) (μg*hr/mL)[b]	5	135	800	1254 (1070, 1472) 17.0
	2	175	800	372, 1201
	10	150	800	683 (520, 897) 49.8
	5	175	400	671 (458, 981) 41.6
C24 (μg/mL)[b]	5	135	800	47.6 (34.0, 66.5) 36.3
	2	175	800	11.9, 44.1
	10	150	800	25.3 (17.9, 35.9) 65.7
	5	175	400	25.4 (14.9, 43.2) 60.6
Cmax (μg/mL)[b]	5	135	800	68.2 (60.3, 77.2) 13.1
	3	175	800	17.3 (4.92 – 58.2)[c]
	10	150	800	35.2 (26.8, 46.3) 49.7
	5	175	400	33.7 (25.1, 45.2) 31.6
tmax (h)[c]	5	135	800	4.0 (1.1 – 24.0)
	3	175	800	7.9 (4.0 – 8.1)
	10	150	800	3.0 (1.2 – 24.0)
	5	175	400	1.9 (1.0 – 24.5)

a. While the PK Population consisted of all subjects for whom a PK sample was obtained and analyzed, not all subjects had PK samples available for Cycle 2 treatment; Cohort 2 had limited PK data available due to DLTs.
b. Data presented as geometric mean (95% Confidence Interval) and CVb%.
c. Data presented as median (range).

Summary of Statistical Analysis of Log-transformed AUC and Cmax to Evaluate the Effect of Pazopanib on Paclitaxel PK Parameters in the Expansion Cohort (Cohort 3)

Parameter	n	Geometric Least Squares Mean		Ratio	90% Confidence Interval
		Paclitaxel	Paclitaxel + Pazopanib		
AUC(0-∞) (μg*h/mL)	9	11.8	15.8	1.34	1.21, 1.48
Cmax (μg/mL)	9	3.32	4.53	1.37	1.25, 1.50

Clinical Activity

Investigator-Assessed Best Confirmed Response (RECIST 1.0)	Cohort 1: Pac 135/ Paz 800 (n=6)	Cohort 2: Pac 175/ Paz 800 (n=4)	Cohort 3: Pac 150/ Paz 800 (n=12)	Cohort 4: Pac 175/ Paz 400 (n=6)	Total (N=28)
Partial Response, n (%)	2 (33)	3 (75)	3 (25)	2 (33)	10 (36)
Stable Disease, n (%)	2 (33)	0	6 (50)	2 (33)	10 (36)
Progressive Disease, n (%)	1 (17)	0	2 (17)	2 (33)	5 (18)
Unknown, n (%)	1 (17)	1 (25)	1 (8)	0	3 (11)
Response rate (CR + PR), n (%)	2 (33)	3 (75)	3 (25)	2 (33)	10 (36)
95% CI	(0.0, 71.1)	(32.6, 100)	(0.5, 49.5)	(0.0, 71.1)	(18.0, 53.5)

Conclusions:

The MTR for this combination was pazopanib 800 mg oral daily plus paclitaxel 150 mg/m^2 IV once every three weeks.

All subjects reported at least one AE, the most frequently reported AEs overall were alopecia, fatigue, hypertension, nausea, diarrhoea, and vomiting. Fourteen (50%) subjects reported at least 1 SAE, with respiratory tract infection the only SAE reported in more than 1 subject. DLTs included rash and ALT elevations.

Concomitant administration of pazopanib and paclitaxel resulted in an increase in systemic exposure to paclitaxel relative to administration of paclitaxel alone.

Investigator-assessed best objective response included PR in 10/28 subjects and stable disease ≥12 weeks in 10/28 subjects.