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: MD7108240

Title : A double-masked, randomized, parallel-group study to investigate the pharmacodynamics, safety, and systemic pharmacokinetics of pazopanib eye drops, administered for 28 days to adult subjects with choroidal neovascularization due to neovascular age-related macular degeneration (AMD)

Rationale: This study was the first administration of pazopanib eye drops to adult subjects with neovascular AMD

Phase: II

Study Period: 18 February 2008 - 27 January 2009

Study Design: This was a multi-center, double-masked, randomized, parallel-group dose-ranging study of repeat topical ocular doses of pazopanib in subjects with primary or recurrent active subfoveal neovascular AMD. This study did not include a control treatment group (e.g. placebo or active comparator), and instead was benchmarked to optical coherence tomography (OCT) changes observed following treatment with other anti-angiogenic agents in a similar subject population over the same treatment period.

Centres: This study was conducted in 22 centers in the United States, Belgium, Italy and Australia.

Indication: Age-related macular degeneration (AMD)

Treatment: Subjects were assigned to one of three treatments in accordance with the randomization schedule in the original protocol. After the protocol was amended due to feasibility to remove the 5 mg/mL once daily arm (Regimen C), subjects were assigned to one of two treatments in accordance with an updated randomization schedule. Subjects were stratified with two strata: treatment naïve subjects and previously treated subjects. Subjects received 2 mg/mL three times daily (TID), 5 mg/mL TID or once daily.

Treatment Group	Dosing Regimen
A	5 mg/ml pazopanib TID for 28 days
B	2 mg/ml pazopanib TID for 28 days
C [a]	5 mg/ml pazopanib once daily for 28 days (discontinued)

a. Sixteen (16) subjects received 5 mg/mL once daily prior to the protocol amendment which eliminated this arm.

Objectives: The primary objective was to determine the effect of repeat topical ocular doses of pazopanib on central retinal lesion thickness (CRLT), when administered daily for 28 days to adult subjects with subfoveal CNV due to neovascular (wet) AMD. A secondary objective was to determine the effect of pazopanib on visual acuity.

Statistical Methods: The change from baseline in CRLT as measured by OCT at Day 29 for each of the 2 mg/ml TID and 5 mg/ml TID treatment arms was analyzed by an analysis of covariance (ANCOVA) model with treatment as a fixed effect term, and baseline CRLT measured by OCT as a covariate. Hochberg's step-up test procedure was used to adjust the multiple testing of hypotheses. The p-values for each individual hypothesis were calculated as follows. If the estimates of change from baseline in CRLT were negative, then the one-sided p-values were the two-sided t-test of each treatment arm from this analysis divided by 2. If the estimates of change from baseline in central retinal lesion thickness were positive, then the one-sided p-values were 1- p-values of the two-sided t-test of each treatment arm from this analysis divided by 2. This analysis was performed using both last observation carried forward (LOCF) and observed cases (OC) datasets.

Demographics: Eligible subjects were males and non-childbearing potential females (≥ 50 years of age) with diagnosis of AMD with subfoveal CNV

Number of Subjects:

Number of Subjects	**5 mg/mL TID N = 27**	**2 mg/mL TID N= 27**	**5 mg/mL once daily N = 16**
Age in Years, Mean (Range)	72.6 (57 – 87)	76.5 (64 – 88)	71.5 (60 – 83)
Sex, n (%)			
Female:	20 (74%)	14 (52%)	9 (56%)
Male:	7 (26%)	13 (48%)	7 (44%)
BMI,(kg/m^2) Mean (Range)	29.1 (20 – 51)	27.5 (20 – 44)	24.7 (22 – 29)
Height, (cm) (Mean and Range)	160.6 (127 – 183)	166.4 (151 – 188)	165.8 (150 – 182)
Weight, (kg) (Mean and Range)	73.9 (45 – 104)	76.5 (54 – 118)	67.8 (57 – 82)
Ethnicity, n (%)			
Hispanic or Latino:	0	2 (7%)	1 (6%)
Not Hispanic or Latino:	27 (100%)	25 (93%)	15 (94%)
Race, n (%)			
White – White/Caucasian/European Heritage	27 (100%)	27 (100%)	16 (100%)

BMI = body mass index

Primary Outcome: Pharmacodynamics (PD)

Statistical Analyses of Change from Baseline in CRLT as Measured by OCT (microns) at Day 29 (PD Population)

Treatment	N	n	Point Estimate	SE	95% CI	Two-sided P-Value	One-sided P-value
LOCF Data							
5 mg/mL TID	26	26	5.83	18.332	(-31.05, 42.71)	0.7518	0.6241
2 mg/mL TID	24	24	11.87	19.081	(-26.52, 50.26)	0.5369	0.7315
LOCF Data excluding potential outlier subject 611201							
5 mg/mL TID	25	25	-0.82	18.114	(-37.28, 35.64)	0.9640	0.4820
2 mg/mL TID	24	24	19.90	18.496	(-17.33, 57.13)	0.2876	0.8562
OC Data							
5 mg/mL TID	26	26	5.76	18.566	(-31.65, 43.18)	0.7577	0.6212
2 mg/mL TID	24	21	5.20	20.662	(-36.44, 46.84)	0.8026	0.5987
OC Data excluding potential outlier subject 611201							
5 mg/mL TID	25	25	-0.55	18.300	(-37.46, 36.35)	0.9760	0.4880
2 mg/mL TID	24	21	13.97	20.008	(-26.38, 54.32)	0.4889	0.7556

LOCF = last observation carried forward
OC = observed cases

Secondary Outcomes: Visual Acuity

Statistical Analysis of Change from Baseline in Best Correct Visual Acuity Score

Treatment	N	n	Point Estimate	SE	95% CI	P-Value
Overall						
5 mg/mL TID	26	26	4.32	1.290	(1.74, 6.91)	**0.0015** [a]
2 mg/mL TID	24	22	0.76	1.403	(-2.05, 3.57)	0.5921
5 mg/mL once daily	14	11	0.09	1.988	(-3.89, 4.07)	0.9646
Subjects with a 'YES' for RAP/RCA NONE field from DARC FA form in study eye at screening						
5 mg/mL TID	25	25	4.75	1.213	(2.32, 7.19)	**0.0003** [a]
2 mg/mL TID	23	21	1.64	1.326	(-1.02, 4.30)	0.2208
5 mg/mL once daily	13	10	-0.04	1.927	(-3.90, 3.83)	0.9847
Subjects with a 'YES' for eligible field from DARC FA form in study eye at screening						
5 mg/mL TID	19	19	3.53	1.376	(0.75, 6.31)	**0.0142** [a]
2 mg/mL TID	19	18	0.85	1.419	(-2.02, 3.71)	0.5547
5 mg/mL once daily	10	7	0.26	2.287	(-4.37, 4.88)	0.9114

a. Statistically significant
RAP/RCA = Retinal Angiomatous Proliferation / Retinal Choroidal Anastomosis
DARC = Digital Angiography Reading Center
FA = Fluorescein Angiography

Secondary Outcome: Pharmacokinetics

Summary of Selected Plasma Pazopanib Pharmacokinetic Parameters (PK Population)[a]

Dose Level	Day	N	AUC(0-t) (ng·hr/mL)	AUC(0-6) (ng·hr/mL)	Cmax (ng/mL)	tlast (hr)[b]	tmax (hr)[2]
2 mg/mL TID	15	24	120 (76.2)[3]	125 (77.0)[d]	21.1 (75.5)[c]	6.00 (5.50 – 7.50)[3]	2.97 (0 – 6.42)[c]
	22	1	96.1 (NA)	96.1 (NA)	17.7 (NA)	6.00 (6.00 - 6.00)	3.00 (3.00 – 3.00)
5 mg/mL TID	15	24	322 (85.5)	312 (87.9)[e]	56.1 (85.4)	6.00 (5.25 – 7.27)	3.00 (0 – 6.00)
	22	NA	NA	NA	NA	NA	NA

a. Geometric mean (CVb%)
b. Median (range)
c. n = 23
d. n = 21
e. n = 22
NA = Not applicable

Safety results:

Summary of Ocular Adverse Events (Safety Population)

Adverse Event, Preferred Term	Pazopanib 5 mg/mL TID N=27	Pazopanib 2 mg/mL TID N=27	Pazopanib 5 mg/mL once daily N=16
Ocular AEs			
Number of Subjects with **Ocular** AE: Study Eye	9 (33%)	2 (7%)	3 (19%)
Number of Subjects with **Ocular** AE: Fellow Eye	2 (7%)	0	1 (6%)

Summary of Non-Ocular Adverse Events (Safety Population)

Adverse Event, Preferred Term	Pazopanib 5 mg/mL TID N=27	Pazopanib 2 mg/mL TID N=27	Pazopanib 5 mg/mL once daily N=16
Number of Subjects with any **Non-ocular** AE	10 (37%)	5 (19%)	2 (13%)
Number of Subjects with any **Non-ocular** AE related to investigational product	1 (4%)	0	2 (13%)
Non-ocular AEs in more than one subject:			
Headache	3 (11%)	1 (4%)	0
Cough	2 (7%)	0	0
Nausea	2 (7%)	0	0
Nasopharyngitis	1 (4%)	1 (4%)	0
Oropharyngeal pain	1 (4%)	0	1 (6%)[a]
Hypertension	1 (4%)	0	1 (6%)[a]

a. considered by the investigator to be drug-related

Serious Adverse Events, n=1 (1.43%): No fatal SAEs were reported. One subject (70-year-old female) was reported with a SAE of severe atrial fibrillation after receiving pazopanib 2 mg/mL TID. She had a history of supraventricular tachycardia. The subject experienced rapid erratic heartbeat after receiving 2 of 3 daily doses of study medication on the first day of dosing and was hospitalized for the event 2 days later. Study medication was discontinued. The investigator did not consider the event related to the study medication. The subject voluntarily withdrew consent from the study.

Publications: None