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: MD7111396

Title : An extension study to protocol MD7108240; pazopanib eye drops in subjects with neovascular age-related macular degeneration

Rationale: The current study MD7111396 was an extension study of study MD7108240

Phase: II

Study Period: 25 June 2008 – 9 September 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 without progression of AMD and/or requiring rescue therapy during the 28-day treatment period in study MD7108240. Subjects restarted the regimen of pazopanib eye drops that they were randomized to in the previous study (MD7108240) and remained masked to their regimens in study MD7111396. Subjects administered their randomized pazopanib eye drops regimen for up to 5 months during the extension phase. Period of time that had elapsed between the 2 studies was variable amongst the subjects enrolled into the extension study. Additionally, the number of days elapsed between the last administered anti-VEGF medication and start of dosing in MD7111396 was variable amongst the 10 subjects who had received anti-VEGF medication since completion of the parent study.

Centres: This study was conducted in 14 centers in the United States, Italy and Australia

Indication: Age-related macular degeneration (AMD)

Treatment: Subjects restarted the regimen of pazopanib eye drops that they were randomized to in the previous study (MD7108240) and remained masked to the regimen which included: A) 5 mg/mL solution TID, B) 2mg/mL solution TID, and C) 5 mg/mL solution once daily. Placebo was used for instruction of eye drop instillation technique and to mask the once daily arm prior to the amendment. Subjects were assigned to one of three treatments in accordance with the randomization schedule in the original protocol.

Objectives: Primary objective was to determine the systemic and local safety and tolerability of repeat topical ocular doses of pazopanib when administered daily to adult subjects with choroidal neovascularisation (CNV) due to neovascular age-related macular degeneration (AMD). A secondary objective was to determine the effect of pazopanib on visual acuity.

Statistical Methods: Safety endpoints were descriptively summarized and were not analyzed statistically. All subjects were included in the safety analysis.

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

Number of Subjects	**5 mg/mL TID**	**2 mg/mL TID**	**5 mg/mL once daily**
Number of subjects randomized to MD7111396, N:	19	15	8
Number of subjects completed, n (%):	12 (63%)	12 (80%)	3 (38%)
Number of subjects withdrawn (any reason), n (%):	7 (37%) [1]	3 (20%)	5 (63%)
Number of subjects withdrawn for SAE, n (%):	0	0	0
Reasons for subject withdrawal, n (%)			
Adverse events	3 (16%) [1]	0	0
Lack of efficacy	0	0	2 (25%)
Lost to follow-up	0	1 (7%)	0
Investigator discretion	3 (16%) [1]	1 (7%)	3 (38%)
Withdrew consent	1 (5%)	1 (7%)	0
Demographics			
Age in Years, Mean (Range)	73.3 (58-88)	76.8 (68-87)	69.9 (60-83)
Sex, n (%)			
Female:	15 (79%)	7 (47%)	5 (63%)
Male:	4 (21%)	8 (53%)	3 (38%)
BMI,(kg/m^2) Mean (Range)	30.3 (20-51)	29.0 20-44	24.5 22-29

Height, (cm) (Mean and Range)	158.9 127-176	166.1 151-187	168.8 162-182
Demographics--Continued	**5 mg/mL TID**	**2 mg/mL TID**	**5 mg/mL once daily**
Weight, (kg) (Mean and Range)	74.9 45-104	80.8 54-118	69.5 62-82
Ethnicity, n (%)			
Hispanic or Latino:	0	0	0
Not Hispanic or Latino:	19 (100%)	15 (100%)	8 (100%)
Race, n (%)			
White – White/Caucasian/European Heritage	19 (100%)	15 (100%)	8 (100%)

1. In the 5 mg/mL TID group, of the 7 subjects who were withdrawn, 3 were withdrawn due to AEs. Of these 3 subjects, only 2 were recorded as having discontinued the study medication due to an AE. The reason for discontinuation of study medication of the additional subject was marked as "investigator discretion" which was due to a new macular hemorrhage. Thus, the total number of subjects who discontinued due to study medication in the 5 mg/mL TID group was recorded as 4 (21%) in the Summary of Investigational Product Status

Summary of Anti-VEGF Intravitreal Prior and Concomitant Medications—Study Eye

	Number of Subjects N = 42	
Treatment	**Prior Medications (between MD7108240 and MD7111396) [1]**	**Rescued during study MD7111396 [2]**
5 mg/mL TID, N=19	6 (32%)	7 (37%)
2 mg/mL TID, N=15	2 (13%)	2 (13%)
5 mg/mL once daily, N=8	2 (22%)	5 (63%)

1. Of the 42 subjects receiving prior medications between the parent and extension studies, 4 received ranibizumab and 6 received bevacizumab.
2. Of the 42 subjects who were rescued during the extension study, 4 received ranibizumab and 10 received bevacizumab.

Safety results:

Summary of Ocular Adverse Events

Adverse Events Preferred Term n (%)	**Pazopanib 5 mg/mL TID N=19**	**Pazopanib 2 mg/mL TID N=15**	**Pazopanib 5 mg/mL once daily N=8**
Number of Subjects with Ocular AE: Study Eye	7 (37%)	2 (13%)	2 (25%)
Number of Subjects with Ocular AE: Fellow Eye	3 (16%)	3 (20%)	0

There were no clinically significant changes in ophthalmic examinations that would preclude continued clinical investigation of pazopanib eye drops.

Summary of Non-Ocular Adverse Events Reported in more than one Subject across all Treatment Groups

Adverse Events Preferred Term n (%)	Pazopanib 5 mg/mL TID N=19	Pazopanib 2 mg/mL TID N=15	Pazopanib 5 mg/mL once daily N=8
Number of Subjects with Non-Ocular AE	**11 (58%)**	**9 (60%)**	**3 (38%)**
Upper respiratory tract infection	1 (5%)	0	2 (25%)
Nasopharyngitis	1 (5%)	1 (7%)	0
Hypercholesterolemia	1 (5%)	1 (7%)	1 (13%)
Seasonal allergy	0	2 (13%)	0

There were no clinically significant findings in vital signs, clinical laboratory parameters, ECGs or LFTs.

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:

There was one ocular SAE of cataract reported in the fellow eye that was not considered drug-related by the investigator. The subject underwent a cataract extraction with intraocular lens placement. Treatment with pazopanib was continued and the event resolved.

There were two non-ocular SAEs in two separate subjects. One subject was reported with a moderate acute coronary syndrome approximately 4 months (111 days) after receiving the first dose of pazopanib 5 mg/mL TID in study MD7111396. The event was considered life-threatening by the investigator, but not drug-related. Dosing with the study medication was interrupted and the subject was hospitalized and underwent cardiac catherterization. The event was reported as improved on an unspecified date. Another subject experienced a severe wrist fracture approximately 4.5 months (132 days) after receiving the first dose of pazopanib 5 mg/mL TID in study MD7111396. The event was not considered drug-related by the investigator and treatment with pazopanib was continued. The event was reported as improved on an unspecified date.