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.: MD7114987

Title: An open-label, phase 2a study to evaluate pazopanib eye drops administered for 12 weeks to patients with neovascular age-related macular degeneration

Rationale: This study was designed to determine whether pazopanib eye drops have the potential to reduce retinal edema and maintain or improve visual acuity (VA) in subjects with previously untreated subfoveal CNV secondary to age-related macular degeneration (AMD) over 4 weeks and to further characterize the safety and tolerability of pazopanib eye drops administered over a 12-week period.

Phase: 2a

Study Period: 7 July 2011 to 16 April 2012

Study Design: This was a multi-center, open-label, single-arm study in adults with neovascular AMD and a previously untreated subfoveal choroidal neovascularization (CNV) lesion in the study eye. A single regimen of pazopanib eye drops 10 mg/mL (1 drop), administered four times daily (QID) over a 12-week period, was evaluated.

Centres: This study was conducted at 10 sites in the United States, Germany and France.

Indication: Age-related macular degeneration

Treatment: Subjects instilled a single drop (approximately 40 µL) of the pazopanib ophthalmic solution 10 mg/mL to the study eye QID during the non-sleep period.

Objectives: The primary objectives were: (1) to assess the effect of pazopanib eye drops on central retinal thickness (CRT); and (2) to evaluate the effect of pazopanib eye drops on visual acuity (VA)

Primary Outcome/Efficacy Variable: The primary assessments of interest were the change from baseline in CRT, as measured by optical coherence tomography (OCT), and change from baseline in best-corrected visual acuity (BCVA), as determined by electronic ETDRS visual acuity (EVA), after 28 days of treatment (Week 4, Day 29).

Secondary Outcome/Efficacy Variable(s):

- Change from baseline in CRT, central retinal lesion thickness (CRLT), lesion thickness, subretinal fluid thickness and pigment epithelial detachment (PED) thickness as determined by OCT
- Change from baseline in fluorescein angiography (FA) assessments of total lesion size and CNV size at Week 4 visit
- Safety endpoints included complete ophthalmic examination, VA, vital signs (heart rate and blood pressure), clinical laboratory tests, clinical monitoring and adverse event (AE) reporting.
- Plasma pazopanib concentrations were used as the pharmacokinetic endpoint.

Statistical Methods: The change from baseline in BCVA, CRT, CRLT, lesion thickness, subretinal fluid thickness and PED thickness were analyzed separately using a mixed model repeated measures approach and included fixed effect term for time, and baseline value as covariate, and subject as random effect. The mean changes from baseline at each visit were estimated. The analysis used AR(1) covariance matrix in the model. The results of this analysis were presented as point estimates and two-sided 90% confidence intervals, which provide the 95% one-sided confidence boundaries. To assess regression of CNV, the change from baseline in FA assessments of total lesion size and CNV size were also examined. Point estimates and confidence intervals were presented. The parameters described above were listed and summarized by subject and time.

The following populations were assessed:

- Safety Population. The population consisted of any subject who received at least one dose of study medication.
- Intent-to-Treat Population (ITT). The ITT population consisted of any subject who received at least one dose of study medication. This was the primary population for determining efficacy.
- Pharmacokinetic (PK) Population: This population was defined as subjects in the "ITT Population" for whom a PK sample was obtained and analysed. This population was used for listing, summarizing, plotting of individual and mean/median concentration-time profiles.

Study Population: Eligible subjects were males and non-childbearing potential females (≥50 years of age) with diagnosis of AMD and the following characteristics: previously untreated CNV caused by AMD that extended under the geometric center of the foveal avascular zone; CNV comprised ≥50% of lesion area; center subfield thickness (inclusive of subretinal fluid) >320 microns on OCT using only SPECTRALIS (Heidelberg); total lesion area ≤12 disc areas on FA, where the lesion complex includes CNV, blood, blocked fluorescence not from blood, and serous

detachment of the retinal pigment epithelium (RPE); classic CNV comprised <50% of the lesion area; fibrosis comprised ≤25% of lesion area; if no evidence of classic CNV, then presumed to have recent disease progression because of deterioration (≥5 letter decrease in vision or evidence of growth of a CNV lesion on FA) within last 3 months or evidence of hemorrhage from CNV. BCVA score by electronic ETDRS (EVA) in the study eye of between 25 and 73 letters (approximately equivalent to Snellen VA of 20/320 to 20/32) at screening. QTcF <450msec or QTcF <480msec in subjects with Bundle Branch Block.

Subject Disposition: Enough subjects were to be enrolled so that 20 subjects completed the initial 28-day period (Week 4 [Day 29] Visit). Due to lack of efficacy, the study was terminated before the 20 subjects completed the initial 28-day period. A total of 19 subjects were enrolled. Thirteen subjects completed up to at least the Week 4 visit, including 5 who completed the study as planned. A total of 14 subjects were withdrawn, including 9 subjects who reached protocol-defined stopping criteria requiring rescue medication,and 5 subjects who were withdrawn due to termination of the study.

Demographics: All 19 enrolled subjects were included in safety population, ITT population, PK population

Number of Subjects	**Pazopanib 10 mg/mL; QID (N = 19)**
Age in Years, Mean (Range)	76.3 (63 – 87)
Sex, n (%)	
Female:	14 (74)
Male:	5 (26)
BMI,(kg/m^2) Mean (Range)	27.3 (18.1 – 39.9)
Height, (cm) Mean (Range)	163.3 (147 – 180)
Weight, (kg) Mean (Range)	72.7 (49.4 -98.4)
Ethnicity, n (%)	
Hispanic or Latino:	0
Not Hispanic or Latino:	19 (100)
Race, n (%)	
White – White/Caucasian/European Heritage	19 (100)

Primary Efficacy Results:

Primary Endpoint Measured by OCT at Week 4—Study Eyes (Observed Cases)

Parameter (microns) (N=19)	**N**	**Point Estimate**	**SD**	**SE**	**90% CI**
Central retinal thickness	13	37.91	89.692	24.876	(-3.95 , 79.78)

Statistical Analysis of Change from Baseline in BCVA (letters) for Study Eyes (Observed Cases)—All Subjects

Visit	**N**	**n**	**Point Estimate**	**SD**	**SE**	**90% CI**
Week 4	19	13	0.07	9.973	2.766	(-4.61 , 4.75)

Secondary Outcome Variable(s):

Secondary Endpoints Measured by OCT at Week 4—Study Eyes (Observed Cases)

Parameter (microns) (N=19)	N	Point Estimate	SD	SE	90% CI
OCT Endpoints					
Central retinal/lesion thickness	13	31.72	88.289	24.487	(-9.43, 72.86)
Lesion Thickness	13	-11.20	74.458	20.651	(-45.66, 23.27)
Pigment epithelial defect (thickness)	9	7.16	54.843	18.281	(-23.85, 38.16)
Subretinal fluid thickness	12	5.69	67.938	19.612	(-27.20, 38.58)
Central retinal thickness	13	37.91	89.692	24.876	(-3.95 , 79.78)
FA Endpoints					
CNV (mm^2)	13	1.38	2.902	0.805	(-0.07, 2.83)
Total lesion size (mm^2)	13	1.37	2.892	0.802	(-0.07, 2.81)

Summary of Pazopanib Plasma Concentration Data (ng/mL)

Visit	n	Mean	SD	Median	Min	Max
Week 2	19	279.0	171.66	238.0	82	816
Week 3	7	323.9	216.77	268.0	80	780
Week 4	14	360.5	215.80	320.0	71	926
Week 6	1	498.0	-	498.0	498	498
Week 8	1	150.0	-	150.0	150	150
Week 12	6	255.3	170.06	168.5	143	572

Safety Results:

Summary of Number of Subjects with Ocular Adverse Events (Safety Population)

Preferred Term n (%) System Organ Class	Pazopanib 10 mg/mL QID N=19
Study Eye	
Number of Subjects with Ocular AE	**8 (42)**
Eye disorders	6 (32)
Age-related macular degeneration	2 (11)
Macular edema	1 (5)
Ocular hypertension	1 (5)
Retinal hemorrhage	1 (5)
Vitreous floaters	1 (5)
General disorders and administration site conditions	3 (16)
Instillation site pain	3 (16) [1]

1. Considered drug-related by the investigator

Summary of Number of Subjects with Non-Ocular Adverse Events (Safety Population)

Preferred Term, n (%)	Pazopanib 10 mg/mL QID N=19
Number of Subjects with Non-Ocular AE	**9 (47)**
Nausea	1 (5) [1]
Esophageal obstruction	1 (5)
Tooth infection	1 (5)
Urinary tract infection	1 (5)
Skeletal injury	1 (5)
Platelet count decreased	1 (5)
Protein urine present	1 (5) [1]
Red blood cells urine positive	1 (5)
Urine protein/creatinine ratio increased	1 (5) [1]
Arthritis	1 (5)
Tendonitis	1 (5)
Torticollis	1 (5)
Depression	1 (5)
Cough	1 (5)
Dysphonia	1 (5)
Hypertension	1 (5)

1. Considered drug-related by the investigator

Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication]

There were no deaths or serious adverse events during this study.

Conclusion:

- In subjects with previously untreated neovascular AMD, pazopanib eye drops 10 mg/mL QID as monotherapy did not appear to improve BCVA or decrease CRT.
- There was no significant change from baseline in CRLT, retinal morphology, CNV size, or total lesion size.
- In the study eye, 8 out of 19 subjects were reported with 9 ocular AEs. All but one AE was mild to moderate in intensity. There were no SAEs during this study. During the study, 47% of the subjects (9 of 19) reported non-ocular AEs during. AEs but one non-ocular AE was mild to moderate in intensity.
- Steady-state concentrations appeared to have been reached by Week 2 after administration of pazopanib eye drops 10 mg/mL QID to subjects with neovascular AMD.