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.

GSK Medicine: Pazopanib

Study Number: MD7110852

Title: MD7110852, A Phase 2b Dose-Ranging Study of Pazopanib Eye Drops versus Ranibizumab Intravitreal Injections for the Treatment of Neovascular Age-Related Macular Degeneration

Rationale: To determine if pazopanib eye drops could maintain or improve visual acuity (VA) and reduce continual need for intravitreal (IVT) injections with ranibizumab for the treatment of age-related macular

Phase: II

Study Period: 01 June 2010 – 05 Oct 2012

Study Design: This was a multicenter, randomized, parallel-group, double-masked eye drops, and active-controlled study. After a 1-2 week screening period, subjects entered a 52-week treatment period with monthly visits with a follow-up safety visit after approximately 2 weeks post treatment. The study had 7 study arms, including 5 pazopanib arms (5 mg/mL 1 drop three-times daily [TID]; 5 mg/mL 1 drop four-times daily [QID]; 10 mg/mL 1 drop twice-daily [BID]; 10 mg/mL 1 drop TID; 10 mg/mL 1 drop QID), an arm with placebo eye drops dosed QID, and a monthly IVT ranibizumab arm.

Throughout the trial, all eye drop subjects (both pazopanib and placebo) had access to known effective therapy (i.e., ranibizumab IVT injections) on an as-needed basis at each monthly visit according to pre-specified re injection criteria. Only the study eye received the study medication eye drops and one drop was to be administered per dose time. Ranibizumab injections were open-label.

Centres: This study was conducted at 77 sites in 9 countries from North America, Europe, Australia and Japan.

Indication: Age-related macular degeneration (AMD)

Treatment: Subjects who met all eligibility criteria at the Baseline Visit were sequentially assigned according to a computer generated randomization list (1:1:1:1:1:1:1) to one of the 7 investigation product (IP) treatment arms listed in the table below: The ratio of treatment allocations was managed by regional-based randomization using an interactive voice response system (IVRS).

Treatment	IP Eye Drops pazopanib or placebo eye drops double masked for QID dosing	IP Injections open-label ranibizumab
pazopanib eye drops	5 mg/mL TID	as-needed[1]
pazopanib eye drops	5 mg/mL QID	as-needed[1]
pazopanib eye drops	10 mg/mL BID	as-needed[1]
pazopanib eye drops	10 mg/mL TID	as-needed[1]
pazopanib eye drops	10 mg/mL QID	as-needed[1]
placebo eye drops as-needed ranibizumab control	placebo QID	as-needed[1]
ranibizumab injections monthly ranibizumab control	no eye drops used	every 4 weeks

1. Open-label ranibizumab was administered as needed if re-injection criteria are met.

Objectives: The primary objective was to evaluate whether daily-dosed pazopanib eye drops could maintain or possibly improve vision, while reducing the continued need for IVT injections.

Primary Outcome/Efficacy Variable: The primary endpoint was change from baseline in best-corrected visual acuity (BCVA) as measured by the number of letters read on the Early Treatment of Diabetic Retinopathy Study (ETDRS) grading charts at Week 52.

Secondary Outcome/Efficacy Variable(s): Secondary endpoints included:

- Number of ranibizumab re-injections over 28 and 52 weeks
- Time to first ranibizumab re-injection
- Change from baseline in BCVA over time
- Visual acuity response over time (this will include the proportions of subjects with BCVA of various 5-letter thresholds gained or lost from baseline, and the proportions of subjects whose BCVA never declined at any time point below various 5-letter thresholds from baseline)
- Change from baseline in center point thickness (CPT) over time
- Presence of and change in intraretinal (IR) or subretinal (SR) fluid, intraretinal cysts or serous retinal pigment

epithelial detachment (PED) over time

- Change from baseline in the area of choroidal neovascularization (CNV)
- Change from baseline in the area of the CNV lesion complex (i.e. CNV, blood, PED, and fibrosis)
- Change from baseline in the area of fluorescein leakage
- Change in area of serous sensory retinal detachment (SSRD)
- Change from baseline in the area of fibrosis
- Plasma concentrations of pazopanib
- Safety endpoints including complete ophthalmic examination, vital signs (heart rate and blood pressure), cardiac monitoring (electrocardiogram), clinical laboratory tests, clinical monitoring and adverse event reporting

Statistical Methods: The primary comparisons of interest for BCVA were between each pazopanib arm and the monthly ranibizumab arm, as well as between each pazopanib arm and the placebo arm (i.e., the AS-NEEDED ranibizumab arm). This was through estimation only; no formal testing of the mean changes in BCVA was planned. Estimates for BCVA were evaluated within the framework of non-inferiority to comparator arms, although confidence intervals were not adjusted for multiple comparisons. The primary comparison of interest for injection rates was between each pazopanib arm and the placebo arm.
The change from baseline in BCVA was analyzed using mixed model repeated measures (MMRM) approach. Number of injections was analyzed as the probability of receiving an injection at a scheduled visit.

Study Population: Eligible subjects were males and non-childbearing potential females (≥50 years of age) with diagnosis of AMD with subfoveal CNV secondary to AMD in need of re-injection and optical coherence tomography (OCT) evidence of SR fluid, central IR fluid and/or IR cysts. All subjects exhibited prior response to anti-VEGF IVT injection with ≥3 injections and required continued anti-VEGF therapy according to the Investigator. Other criteria included a total lesion area ≤12 disc areas with CNV contributing ≥50% of the total lesion area. If non-CNV lesion components were present, then the following limitations must have been met: serous retinal PED, fibrosis, atrophic scar and SR hemorrhage combined were <50% of the total lesion area, fibrosis alone was ≤25% of the total lesion area, and if SR hemorrhage involved the fovea, then subfoveal hemorrhage was ≤1 disc area. QTcF or QTcB <450msec or QTcF or QTcB <480msec in subjects with Bundle Branch Block.

Number of Subjects:	**Total**
Randomised, N	510
Completed, n (%	463 (91%)
Total Number Subjects Withdrawn, N (%)	47 (9%)
Withdrawn due to Adverse Events n (%)	25 (5%)
Withdrawn for other reasons (consent withdrawal) n (%)	17 (3%)

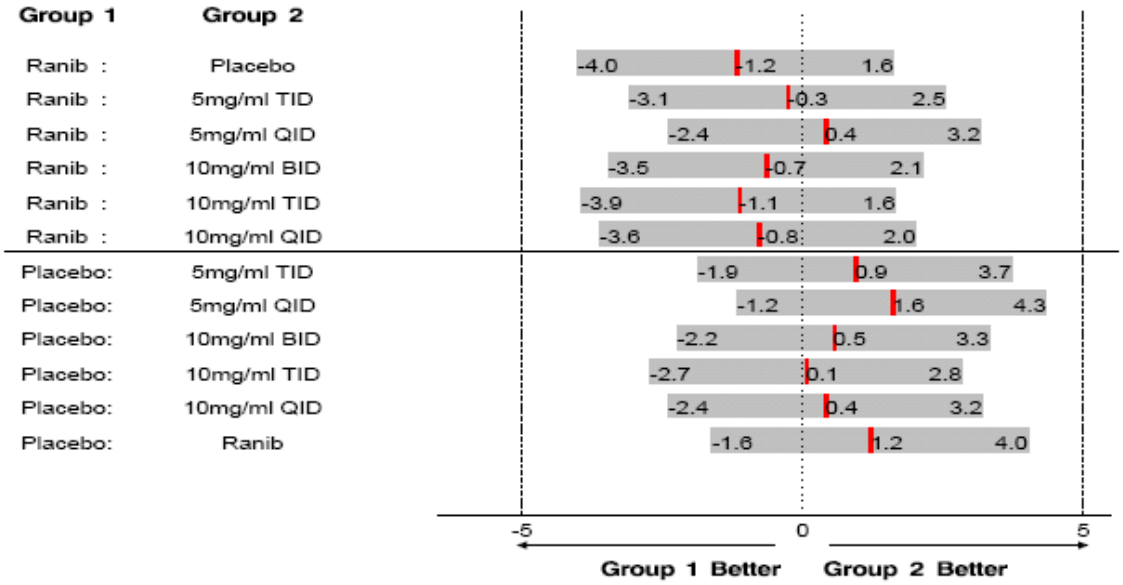
Demographics

Number of Subjects	**Total pazopanib + ranibizumab + placebo regimens (N = 510)**
Age in Years, Mean (Range)	75.3 (52 -95)
Sex, n (%) Female: Male:	 296 (58%) 214 (42%)
BMI,(kg/m^2) Mean (Range)	27.7 (16.3 – 51.9)
Height, (cm) Mean (Range)	166.7 (140 – 203)
Weight, (kg) Mean (Range)	77.2 (39.4 – 157.3)
Ethnicity, n (%) Hispanic or Latino: Not Hispanic or Latino:	 18 (4%) 492 (96%)
Race, n (%) White – White/Caucasian/European Heritage African American/African Heritage Asian	 474 (93%) 1 (<1%) 35 (7%)
Years since 1st AMD treatment, median (Q1, Q3)	1.49 (0.74,2.48)
Years since AMD diagnosis, median (Q1, Q3)	1.64 (0.81,2.71)
Lifetime annualized injection rate in study eye, median (Q1, Q3)	7.82 (5.93,10.22)
6-Month annualized injection rate in study eye, median (Q1, Q3)	8.00 (6.00,10.00)
ETDRS visual acuity score in study eye in study eye, (letters), Mean (range)	67.3 (21 – 94)
Center point thickness by OCT, (microns) Mean (range)	205.9 (1.0 , 694.0)

Distribution of *CFH* Y402H genotypes, n (%)	
C,C	155 (30.4%)
C,T	236 (46.3%)
T,T	119 (23.3%)

Primary Efficacy Results:

Differences in Mean Change from Baseline in Visual Acuity Scores at Week 52 (ITT Population)



Secondary Outcome Results:

Overall, pazopanib eye drops did not demonstrate efficacy at any dose for any of the secondary efficacy endpoints. As-needed ranibizumab injection rates over 52 weeks were similar across all eye drops arms and were not statistically or clinically significantly different for any pazopanib eye drops arm compared to the placebo eye drops arm. Therefore, pazopanib eye drops failed to reduce as-needed ranibizumab injections by ≥50%, the pre-specified criteria for efficacy. Mean plasma pazopanib concentrations following all pazopanib eye drop treatments were approximately proportional to dose and seemed to have achieved steady state by Week 4.

Safety Results:

Adverse events (AEs) were collected from the time of subject consent until study completion. Ocular and non-ocular AEs were reported separately.

The most frequent non-ocular AEs reported (all treatment groups combined) were: nasopharyngitis (12%), hypertension (7%), urinary tract infection (6%), cough (6%), and headache (6%). The frequency of non-ocular drug-related AEs was 4% for all treatment groups combined with a balanced distribution across treatment arms (Source Table 3.21). All but one drug-related AE (dysgeusia, n=2, with pazopanib 5 mg/mL QID) was reported by one subject in each treatment arm.

Most Frequent (≥ 3% of Subjects) Post-Baseline Ocular AEs—n (%)

		Pazopanib Eye Drop						
Preferred Term	**Placebo (N=73)**	**5 mg/mL TID (N=72)**	**5 mg/mL QID (N=74)**	**10 mg/mL BID (N=73)**	**10 mg/mL TID (N=73)**	**10 mg/mL QID (N=72)**	**Rani (N=73)**	**Total (N=510)**
Number of Subjects with Any Ocular AE[a]	**34 (47%)**	**24 (33%)**	**28 (38%)**	**31 (42%)**	**33 (45%)**	**29 (40%)**	**26 (36%)**	**205 (40%)**
Study Eye								
Conjunctival haemorrhage	5 (7)	1 (1)	1 (1)	5 (7)	4 (5)	5 (7)	2 (3)	23 (5)

Eye pain	5 (7)	1 (1)	1 (1)	1 (1)	3 (4)	2 (3)	5 (7)	18 (4)
Vitreous floaters	3 (4)	2 (3)	1 (1)	2 (3)	2 (3)	3 (4)	3 (4)	16 (3)
Vision burred	4 (5)	1 (1)	1 (1)	1 (1)	3 (4)	2 (3)	2 (3)	14 (3)
Visual acuity reduced	2 (3)	3 (4)	1 (1)	1 (1)	3 (4)	1 (1)	3 (4)	14 (3)
Application site pain	0	2 (3)	2 (3)	3 (4)	3 (4)	3 (4)	0	13 (3)
Fellow Eye								
Retinal haemorrhage	2 (3)	3 (4)	2 (3)	1 (1)	4 (5)	0	4 (5)	16 (3)

Two subjects randomized to the pazopanib eye drops 10 mg/mL QID treatment arm developed subepithelial corneal deposits, which persisted after stopping study drug. The event had not resolved for either subject by the end of the study. There were no clinically significant changes in laboratory values, vital signs or ECGs.

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

	Placebo (N=73)	**5 mg/mL TID (N=72)**	**5 mg/mL QID (N=72)**	**10 mg/mL BID (N=73)**	**10 mg/mL TID (N=73)**	**10 mg/mL QID (N=72)**	**Rani (N=73)**	**Total (N=510)**
Any SAE	11 (15%)	10 (14%)	12 (16%)	11 (15%)	10 (14%)	11 (15%)	6 (5%)	71 (14%)
SAE related to study medication	0	0	0	0	0	0	0	0
Fatal SAEs	2 (3%)	1 (1%)	1 (1%)	0	3 (4%)	0	1 (1%)	8 (2%)
Fatal SAEs related to study medication	0	0	0	0	0	0	0	0

Conclusion:

Ocular administration of pazopanib solution, with allowance for as-needed ranibizumab, met the non-inferiority margin (5 letters) of maintaining VA at Week 52 compared to monthly and as-needed ranibizumab. However, pazopanib eye drops did not displace 50% or more as-needed injections, the pre-specified minimal success criteria to demonstrate efficacy. There were no statistically significant differences between pazopanib eye drops and monthly ranibizumab in any OCT or FA parameter, including CRLT, retinal morphology, CNV size, or total lesion size. The safety profile from administration of pazopanib eye drops for up to 52 weeks to AMD subjects who were previously managed by and responsive to anti-VEGF IVT injection therapy was comparable to placebo.