Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	91689 (311523)	EudraCT No. 2007-000583-25 NCT006373770
Study Phase:	III	
Official Study Title:	A randomized, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular age-related macular degeneration (AMD) (VIEW2)	
Therapeutic Area:	Ophthalmology	
Test Product		
Name of Test Product:	VEGF Trap-Eye (BAY86-5321)	
Name of Active Ingredient:	VEGF Trap-Eye (Aflibercept)	
Dose and Mode of Administration:	Year 1 of the study (Baseline to Week 52): •0.5 mg VEGF Trap-Eye administered every month (4 weeks) [0.5Q4] •2 mg VEGF Trap-Eye administered every month (4 weeks) [2Q4]. •2 mg VEGF Trap-Eye administered every 2 months (8 weeks) [2Q8] plus a sham injection at interim 4-week visits (when study drug was not administered), following 3 initial monthly doses. Sham injections were not to be given at Week 52 and during Year 2 of the study. The last mandatory IVT injection during Year 1 was to be performed at Week 48. Year 2 of the study (Week 52 to Week 96/100): In Year 2 (beginning with Week 52, when the first injection according to the modified quarterly dosing schedule was possible), injections were given every 3 month (12 weeks), but could be given more frequently (up to every month [4 weeks]) if pre-specified criteria were met. The last possible study injection could be administered at Week 92. The applied dose per injection remained the same as in Year 1 (i.e. 0.5 mg or 2 mg). For reasons of consistency, the original treatment group designations of the Year 1 of the study were carried over and also used in the Year 2 of the study. No sham injections	

	were applied in Year 2 of the study. Route of administration: intravitreal (IVT)	
Reference Therapy/Placebo		
Reference Therapy:	Ranibizumab	
Dose and Mode of Administration:	Year 1: 0.5 mg administered every month (4 weeks) [RQ4]. During Year 2, ranibizumab was to be administered every 3 months (12 weeks) with a criteria-driven option to dose more frequently up to every month (4 weeks) (i.e. same treatment paradigm as for VEGF Trap-Eye arms). Route of administration. IVT	
Duration of Treatment:	Treatment duration of 23 months (92 weeks) in total	
Studied period:	Date of first subjects' first visit:	11 Apr 2008
	Date of last subjects' last visit:	11 Aug 2011
Premature Study Suspension / Termination:	not applicable	
Substantial Study Protocol Amendments:	A total of 11 Amendments were implemented (3 global, 8 local amendments) The 3 global amendments specified the following major modifications: Amendment 3 (dated 25 Jan. 2008) • Deletion of exclusion criterion no. 17 (prior laser treatment for glaucoma in the study eye) • Reduction of the number of ECG readings during the study from 9 to 4 • Introduction of a more flexible timing of DNA blood sampling (initially to be done at Baseline, now up to visit 6) • Amendment 7 (dated 12 Nov. 2008) • Specification of criteria for treatment discontinuation or withholding according to the summary of product characteristics of ranibizumab (Lucentis®). • (requested by the Swedish Medical Products Agency [MPA]). • Introduction of an 8-week safety follow-up and deletion of the option of a VEGF Trap-Eye injection at Week 96. • (requested by the Swedish Medical Products Agency, MPA). • Introduction of a nasomucosal examination sub-study. • (requested by the Swedish Medical Products Agency, MPA). • Amendment 11 (dated 21 Sep. 2010) • Further specification of two exploratory efficacy variables	

	referring to "moderate" and "severe" vision loss according to the ETDRS letter chart. • Clarification that not every relevant laboratory abnormality or SAE necessarily leads to the subject's withdrawal from study treatment, but only those that warrant withdrawal according to the sponsor's and investigator's judgment. • Correction of the duration of treatment from 24 months to 23 months (96 weeks to 92 weeks).
Study Center(s):	The study was conducted in the following countries (number of recruiting study centers in brackets): Argentina (6), Australia (7), Austria (3), Belgium (1), Brazil (4), Colombia (4), Czech Republic (5), France (10), Germany (21), Hungary (4), India (15), Israel (10), Italy (14), Japan (15), Latvia (2), Mexico (7), Netherlands (4), Poland (7), Portugal (2), Singapore (4), Slovakia (2), South Korea (6), Spain (16), Sweden (3), Switzerland (4), United Kingdom (10).
Methodology:	This was a 2-year study. During Year 1, subjects received an IVT injection (or sham injection, applicable only to the 2Q8 group) in the study eye every month (4 weeks) according to a fixed-dose, proactive treatment regimen until (including) Week 48. Primary efficacy data were evaluated at Week 52, when patients were subsequently allowed to enter Year 2 of the study. From Week 52 onwards, the treatment interval was extended to 3 months (12 weeks) with an option to receive an injection in between, but no more often than every month (4 weeks), if certain criteria were fulfilled (modified quarterly dosing). Thus, while subjects were exclusively treated proactively in Year 1, the treatment schedule in Year 2 comprised a reactive component. The primary analysis was an evaluation of non-inferiority of VEGF Trap-Eye to 0.5 mg ranibizumab. Analysis of the primary variables was performed on Week 52 data while the study was ongoing. Various scenarios were applied as sensitivity analyses. The secondary efficacy analysis was conducted in the full analysis set (FAS) population and tested for superiority of VEGF Trap-Eye over ranibizumab. Subjects who entered Year 2 of the study were evaluated every 4 weeks. The last possible study injection could be administered at Week 92. Afterwards, a mandatory follow-up period of 8 weeks after the last injection was required by regulatory authorities, thereby resulting in final visits at Week 96 (for those patients who had received their last injection before Week 92) or Week 100 (for those patients who were treated at Week 92). All Year-2 analyses were performed in a purely exploratory fashion; no confirmatory tests were planned. Subjects were evaluated every 4 weeks for safety and best corrected visual acuity (BCVA) using the 4 m Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Quality of Life (QoL) was evaluated using the NEI VFQ-25 questionnaire. Overall state of health was assessed using the EQ-5D Health Questionnaire. Optical coherence tomography (OCT) was

	conducted at each visit, and fluorescein angiography (FA) at Screening, Week 24, Week 52, Week 72, and Week 96/100. Only one eye per subject was enrolled in the study. If a subject's fellow (non-study) eye required treatment for AMD at study entry, or during the subject's participation in the study, the fellow eye was allowed to receive any approved treatment for wet AMD (including open-label ranibizumab). Although the fellow eye was allowed to receive treatment, it was not considered an additional study eye. Subjects who received treatment for the fellow eye remained in the study. Safety for the fellow eye was monitored, and systemic adverse events (AEs) were collected. For determining systemic exposure after IVT administration of VEGF Trap-Eye, blood samples were taken 1-4 h after administration at Weeks 0 and 48, at Week 1 and prior to dosing Weeks 0, 4, 12, 48, 52 and 56 (pharmacokinetic [PK] sub-study).
Indication/ Main Inclusion Criteria:	Neovascular AMD of all subtypes All ophthalmic eligibility criteria applied only to the study eye, unless otherwise specified. The reading center confirmed subject eligibility based on angiographic criteria prior to randomization. Key Inclusion Criteria: • Signed Informed Consent. • Men and women ≥ 50 years of age. • Active primary subfoveal choroidal neovascularization (CNV) lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye. • ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye. • Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures. • Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. Able to understand and willing to sign the informed consent form. • The area of CNV must occupy at least 50% of total lesion.
Study Objectives:	Primary: To assess the efficacy of IVT administered vascular endothelial growth factor (VEGF) Trap-Eye compared to ranibizumab (in a non-inferiority paradigm) in preventing moderate vision loss in subjects with all subtypes of neovascular AMD. Secondary: To assess the safety and tolerability of repeated IVT administration of VEGF Trap-Eye in subjects with all subtypes of neovascular AMD for up to 2 years. To assess the effect of repeated IVT administration of VEGF Trap-Eye in vision-related quality of life (QOL) in subjects with all subtypes of neovascular AMD, as assessed using the National Eye Institute 25-

	item visual function questionnaire (NEI VFQ-25). To describe systemic exposure to the study drug.
Evaluation Criteria:	Efficacy (Primary): Primary efficacy variable (Year 1): Proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in the ETDRS letter score compared to baseline. Efficacy (Secondary): Secondary efficacy variables (Year 1): • Change from baseline in BCVA as measured by ETDRS letter score at Week 52 • Proportion of subjects who gained at least 15 letters of vision from baseline to Week 52 • Change in total NEI VFQ-25 score from baseline to Week 52 • Change in CNV area from baseline to Week 52 Exploratory efficacy variables (Year 2): The Year 2-specific exploratory efficacy variables included variables referring to changes in BCVA, central retinal thickness (CRT), retinal fluid status, several parameters measured by FA, and changes in QoL (NEI VFQ-25 subscales and EQ 5D score). Safety: Safety assessments included ophthalmic examinations, the recording and evaluation of clinical AEs, safety laboratory measurements, vital sign assessments, and ECG recordings. Serum samples for potential development of anti-VEGF Trap antibodies were analyzed. A specific evaluation of potential nasomucosal side effects was performed in Year 1 of the study as a sub-study in a subset of subjects from selected centers (ENT substudy).
	Pharmacokinetics: Pharmacokinetic (PK) substudy Other: Pharmacogenetic substudy (optional) – Results will be presented separately. Nasomucosal examination(Ear, Nose and Throat [ENT]) substudy
Statistical Methods:	Efficacy (Primary): Year 1 analysis The primary analysis was a conditional sequence (a- priori ordered hypotheses) of statistical evaluation of non-inferiority of VEGF Trap-Eye to 0.5 mg ranibizumab. The non-inferiority margin was set at 10%. The methodological approach included conditional sequence of calculations of the 95% confidence intervals of the difference between

	the proportions of subjects with maintained vision for the group treated with 0.5 mg ranibizumab and the proportion of subjects with maintained vision for each of the groups treated with VEGF Trap-Eye. The conditional sequence was: 2Q4, 0.5Q4, and 2Q8. VEGF Trap-Eye was to be considered non-inferior to ranibizumab if the confidence interval of the difference lay entirely below 10%, where a positive difference favors ranibizumab. These analyses were based on the per protocol set (PPS). Analysis of the primary variables was performed on Week 52 data while the study was ongoing. Various scenarios were applied as sensitivity analyses. Efficacy (Secondary): Year 1 analysis The secondary efficacy analysis was conducted in the FAS population and tested for superiority of VEGF Trap-Eye over ranibizumab. A conditional sequence of statistical hypotheses (a priori ordered hypotheses) was to control for multiplicity for secondary endpoint analyses. Year 2 analysis In contrast to Year 1 all Year 2 analyses were exploratory, and as such there were no statistical hypotheses. The efficacy analyses were performed in the FAS (for the study period from Baseline to Week 96/100) or in the population of patients who entered Year 2 of study (for the study period from Week 52 to Week 96/100). Exploratory tests for group comparisons vs. ranibizumab with treatment contrasts and 95% CIs were performed where deemed appropriate. Safety: Adverse events were analyzed with tabulated summaries in the SAF for the period from Baseline to Week 96/100 and in the group of patients who entered Year 2 of the study from Week 52 to Week 96/100.
	Pharmacokinetics: Pharmacokinetics (Year 1 analysis) The VEGF Trap concentrations in plasma (free, adjusted bound and total) were described with summary statistics (eg, arithmetic and geometric mean, standard deviation and coefficient of variation and median with minimum and maximum). Other: Other (Year 1 analysis) Frequency tables of the proportion of subjects developing antibodies to VEGF Trap as well as the proportion of subjects developing neutralizing antibodies to VEGF Trap were generated by treatment group. Subjects with detectable antibodies were listed and examined descriptively.

Number of Subjects:

Planned: Approximately 1200 randomized subjects with a target of 300 subjects per treatment arm.

Analyzed: The analysis sets are shown in the table below.

	RQ4	VEGF Trap-Eye			Total
		2Q4	0.5Q4	2Q8	
Randomized	303	313	311	313	1240
Safety set (SAF)	291	309	297	307	1204
Full analysis set (FAS)	291	309	296	306	1202
Per protocol set (PPS)	269	274	268	270	1081
Subjects entering Year 2	276	281	274	284	1115
Subjects completing the 2-year study	260	256	245	264	1025
Subjects completing 2 years of study medication	256	256	243	262	1017

Study Results

Results Summary — Subject Disposition and Baseline

Year 1 analysis

A total of 2031 subjects were screened for this study (ie, provided written informed consent). 791 subjects were not randomized, most of them (n=678) were screening failures. Thus, 1240 subjects were randomized and 1204 received at least 1 dose of randomized study medication. The number of randomized and treated subjects was similar across the 4 treatment groups.

Of the 1240 randomized subjects, 1115 (89.9%) completed Year 1 of the study. Discontinuation rates were approximately 10% in all groups. The most frequent primary reasons for discontinuation from study were specified as "withdrawal by subject" (50 subjects or 4.0% in total) and "adverse event" (25 subjects or 2.0% in total). There were no relevant differences among the treatment groups with regard to primary reasons for premature discontinuation. Thirty-six of the 125 subjects who prematurely discontinued from study during Year 1 had not received any study drug.

Completion of Year 1 was not necessarily associated with completion of study drug during this period, ie, subjects who discontinued study drug were allowed to remain in the study and undergo the planned evaluations.

The population of "subjects entering Year 2 of the study" comprised 490 (43.9%) male and 625 (56.1%) female subjects who, at Baseline, were between 50 and 93 years of age (median: 75 years). Overall, the 4 treatment groups were homogenous with regard to the analyzed variables. The only exception was the sex distribution in the 0.5Q4 group, where the proportion of male and female subjects was identical, while all other groups included more female subjects. In addition, subjects in the RQ4 group were on average approximately 1 year younger than in the other groups. These differences, however, were not considered meaningful and were already present at randomization.

All subjects who entered the Year 2 of the study had at least 1 finding in medical history. As expected, the most frequent medical history findings referred to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) "eye disorders", which were reported for 99.8% of the study population. Vascular disorders and surgical and medical procedures were reported for 67.1% and 64.9% of the subjects, respectively. All subjects used ophthalmologicals as prior and/or concomitant medication.

The overall discontinuation rate during the 2-year study period was 17.3% (215/1240 randomized subjects). The most frequent primary reasons for discontinuation from the study were specified as "withdrawal by subject" (78 subjects or 6.3% in total) and "adverse event" (53 subjects or 4.3% in total). The proportions of subjects who discontinued from the study primarily due to adverse events were higher in the VEGF Trap-Eye groups than in the ranibizumab group (4.2% - 6.8% in the VEGF Trap-Eye groups vs. 1.3% in the RQ4 group). The differences, however, did not suggest a treatment effect with regard to primary reason for premature discontinuation during either year of the study.

Results Summary — Efficacy

Year 1 analysis

The primary analysis was performed on the PPS applying the last observation carried forward (LOCF) method. The proportions of subjects who maintained vision (less than 15 letters lost) was 94.4% in the RQ4 group, 95.6% in the 2Q4 group, 96.3% in the 0.5Q4 group and 95.6% in the 2Q8 group. Pairwise comparisons between the RQ4 and the different VEGF Trap-Eye groups resulted in treatment differences of -1.2% (95% confidence interval (CI): -4.9 to 2.5%; RQ4 minus 2Q4), -1.8% (95% CI: -5.4 to 1.7%; RQ4 minus 0.5Q4), and -1.1% (95% CI: -4.8 to 2.5%; RQ4 minus 2Q8). Thus the non-inferiority of all VEGF Trap-Eye treatments (including the treatment in the 2Q8 arm with dosing every 2 months [8 weeks]) to the RQ4 treatment was statistically proven, because the 95% CIs for the differences lay consistently below the non-inferiority margin of 10%. In fact, the upper limits of the 95% CIs were all <3%.

The secondary endpoint analyses (LOCF method) were performed in the FAS and tested for superiority of VEGF Trap-Eye over ranibizumab. A conditional sequence of 12 statistical hypothesis tests controlled for multiplicity. The confirmatory test procedure had to stop at the first step (comparison of the change in BCVA as measured by ETDRS letter score from Baseline to Week 52 between the 2Q4 and the RQ4 group), because no statistically significant difference was seen (p=0.076 and p=0.074; Analysis of covariance (ANCOVAs) with and without region-adjustment).

By Week 52, mean ETDRS letter score had increased in all treatment groups by approximately 8-10 letters (LOCF method). The mean increase in ETDRS letter score from Baseline at Week 52 in the FAS (LOCF) was 9.4 +/- 13.5 on RQ4, 7.6 +/- 12.6 on 2Q4, 9.7 +/- 14.1 on 0.5Q4, and 8.9 +/- 14.4 on 2Q8. Similar results were seen in the PPS. In this analysis set, the LS mean changes from Baseline to Week 52 were 9.8 letters in the RQ4 group, 8.2 letters in the 2Q4 group, 10.5 letters in the 0.5Q4 group, and 9.2 letters in the 2Q8 group.

With regard to proportion of subjects who gained at least 15 letters of vision from Baseline: In the FAS, 99 subjects (34.0%) in the RQ4 group, 91 subjects (29.5%) in the 2Q4 group, 103 subjects (34.8%) in the 0.5Q4 group and 96 subjects (31.4%) had gained 15 letters or more in the ETDRS letter score at Week 52 (LOCF method, gain compared to baseline).

In the FAS, the mean NEI VFQ-25 total score at Baseline was >70 in all treatment groups and comparable among them. It was numerically the highest in the 0.5Q4 group (74.0 ± 18.2) and the lowest in the 2Q4 group (70.3 ± 19.4); however, this numerical difference was not clinically meaningful. Up to Week 52, the mean NEI VFQ-25 total score had improved in all groups by approximately 5-6 points.

Mean CNV area at Baseline ranged between 7.58 mm2 (RQ4 group) and 8.24 mm2 (2Q4 group). At Week 52, mean CNV area had decreased to < 3.5 mm2 in all groups. The mean decrease was the lowest in the RQ4 group (-4.16 ± 5.90 mm2) and the highest in the 2Q4 group (5.95 ± 5.04 mm2).

Year 2 analysis

Note: All Year 2 analyses were strictly exploratory. Thus, the interpretation of these results has to be done with caution and at a purely descriptive level.

In the exploratory Year 2 analysis of the original primary efficacy endpoint (subjects maintaining vision from Baseline) the following proportions of FAS subjects who maintained vision at Week 96 (LOCF) were found: RQ4, 93.5%; 2Q4, 91.3%; 0.5Q4, 92.9%; and 2Q8, 93.5%. These results were similar to those observed at Week 52, indicating that efficacy was maintained through Year 2.

The mean increase in ETDRS letter score from Baseline at Week 96 in the FAS (LOCF) was 8.5 +/- 15.0 on RQ4, 6.0 +/- 14.9 on 2Q4, 8.1 +/- 15.8 on 0.5Q4, and 8.1 +/- 15.6 on 2Q8.

Results Summary — Safety

Year 1 analysis

The overall rates of both ocular and non-ocular treatment-emergent AEs/SAEs were similar among the treatment groups. Most of the reported TEAEs were regarded as "mild" and resolved within the observation period with no need to interrupt or permanently discontinue the study treatment. The occasionally observed slight numerical differences (mostly by <5%-points) were considered chance findings, which were clinically not relevant, since they were rather small, and no consistent event pattern was found for these differences. The ocular TEAEs in the study eye appeared to be mostly procedure-related events or associated with the underlying study disease. No cases of endophthalmitis or uveitis were reported, and events related to any eye infections and inflammatory reactions were uncommon.

Adverse events from Baseline to Week 52 (SAF)

Number of subjects with:	Ranibizumab 0.5Q4 (N = 291) n (%)	VEGF Trap-Eye 2Q4 (N = 309) n (%)	VEGF Trap-Eye 0.5Q4 (N = 297) n (%)	VEGF Trap-Eye 2Q8 (N = 307) n (%)	VEGF Trap-Eye Combined (N = 913) n (%)
Any TEAE	250 (85.9)	277 (89.6)	262 (88.2)	277 (90.2)	816 (89.4)
Any ocular TEAE	210 (72.2)	216 (69.9)	206 (69.4)	220 (71.7)	642 (70.3)
Study eye	187 (64.3)	191 (61.8)	182 (61.3)	198 (64.5)	571 (62.5)
Fellow eye	124 (42.6)	110 (35.6)	118 (39.7)	123 (40.1)	351 (38.4)
Any drug-related TEAE	26 (8.9)	23 (7.4)	30 (10.1)	34 (11.1)	87 (9.5)
Any drug-related ocular TEAE in the study eye	23 (7.9)	16 (5.2)	29 (9.8)	25 (8.1)	70 (7.7)
Any injection-related ocular TEAE in the study eye	93 (32.0)	101 (32.7)	90 (30.3)	89 (29.0)	280 (30.7)
Any severe ocular TEAE	11 (3.8)	15 (4.9)	24 (8.1)	17 (5.5)	56 (6.1)
Any non-ocular TEAE	181 (62.2)	231 (74.8)	206 (69.4)	213 (69.4)	650 (71.2)
Any drug-related non-ocular TEAE	4 (1.4)	8 (2.6)	7 (2.4)	8 (2.6)	23 (2.5)
Any severe non-ocular TEAE	15 (5.2)	19 (6.1)	25 (8.4)	27 (8.8)	71 (7.8)
Any AE-related deaths*	2 (0.7)	3 (1.0)	2 (0.7)	2 (0.7)	7 (0.8)
Any SAEs	36 (12.4)	50 (16.2)	42 (14.1)	50 (16.3)	142 (15.6)
Any treatment emergent SAEs	35 (12.0)	49 (15.9)	41 (13.8)	48 (15.6)	138(15.1)
Any TEAEs leading to withdrawal from the study	3 (1.0)	9 (2.9)	10 (3.4)	10 (3.3)	29 (3.2)
TEAEs leading to discontinuation of study drug	4 (1.4)	12 (3.9)	14 (4.7)	10 (3.3)	36 (3.9)
Any APTC event	4 (1.4)	4 (1.3)	5 (1.7)	8 (2.6)	17 (1.9)

Note: Percentage values (rounded to one decimal place) were calculated by author.

*: 2 of the total of 9 deaths were not considered "treatment-emergent" since the underlying fatal event started >30 days after the last administration of the study drug

Events potentially pointing to signs of systemic VEGF inhibition, such as non-ocular hemorrhages or proteinuria were uncommon in their appearance and without apparent differences. Likewise, events related to arterial hypertension occurred in similar frequency across the treatment groups. Descriptively, slightly higher frequencies in the VEGF Trap-Eye groups were seen for the SOC "cardiac disorders", but an additional analysis of arterial thromboembolic events (ATE) events using the APTC endpoint did not show group differences. Overall, the pattern/frequency distribution of non-ocular TEAEs was regarded as similar among the treatment groups. Also the analyses of adverse events of interest did not show relevant differences between VEGF Trap-Eye and ranibizumab. Overall, the pattern/frequency distribution of non-ocular TEAEs was regarded as similar among treatment groups, and no apparent dose-relationship was noted.

A total of 9 deaths were reported. The underlying AEs were not considered study drug-related or injection-related. These deaths were equally distributed across the treatment groups, as were the other serious ocular and non-ocular TEAEs. Serious ocular or non-ocular AEs associated with the study drugs or the injection procedure (as judged by site investigators) were uncommon.

Adverse events during Year 1 (safety analysis set)

A total of 1134 study subjects (94.2% of the 1204 study participants) experienced at least one TEAE during the entire study period from Baseline to Week 96/100. An overview of the overall adverse event experience over the entire study period of 2 years is provided in the following safety table. Numerical differences of ≥5.0% between the ranibizumab group and the VEGF Trap-Eye combined group were observed for "any non-ocular TEAEs" (ranibizumab: 76.6% vs. VEGF Trap-Eye combined: 81.8%). Overall, and in accordance with the previously reported 1-year data, differences among treatment groups were small for the various categories of AEs, and no dose-response was observed.

Adverse events from Baseline to Week 96/100 (SAF)

Number of subjects with:	Ranibizumab 0.5Q4 (N = 291) n (%)	VEGF Trap-Eye 2Q4 (N = 309) n (%)	VEGF Trap-Eye 0.5Q4 (N = 297) n (%)	VEGF Trap-Eye 2Q8 (N = 307) n (%)	Combined (N = 913) n (%)
Any TEAE	270 (92.8)	291 (94.2)	277 (93.3)	296 (96.4)	864 (94.6)
Any ocular TEAE	243 (83.5)	251 (81.2)	242 (81.5)	248 (80.8)	741 (81.2)
Study eye	222 (76.3)	228 (73.8)	212 (71.4)	229 (74.6)	669 (73.3)
Fellow eye	158 (54.3)	154 (49.8)	152 (51.2)	161 (52.4)	467 (51.2)
Any drug-related TEAE	32 (11.0)	33 (10.7)	43 (14.5)	42 (13.7)	118 (12.9)
Any drug-related ocular TEAE in the study eye	25 (8.6)	23 (7.4)	37 (12.5)	33 (10.7)	93 (10.2)
Any injection-related ocular TEAE in the study eye	105 (36.1)	112 (36.2)	103 (34.7)	103 (33.6)	318 (34.8)
Any severe ocular TEAE	20 (6.9)	22 (7.1)	27 (9.1)	26 (8.5)	75 (8.2)
Any non-ocular TEAE	223 (76.6)	257 (83.2)	233 (78.5)	257 (83.7)	747 (81.8)
Any drug-related non-ocular TEAE	8 (2.7)	11 (3.6)	11 (3.7)	12 (3.9)	34 (3.7)
Any severe non-ocular TEAE	29 (10.0)	37 (12.0)	42 (14.1)	46 (15.0)	125 (13.7)
Any AE-related deaths	4 (1.4)	5 (1.6)	10 (3.4)	6 (2.0)	21 (2.3)
Any SAEs	64 (22.0)	81 (26.2)	71 (23.9)	80 (26.1)	232 (25.4)
Any drug-related SAEs	1 (0.3)	6 (1.9)	1 (0.3)	6 (2.0)	13 (1.4)
Any TEAEs leading to withdrawal from the study	7 (2.4)	19 (6.1)	29 (9.8)	18 (5.9)	66 (7.2)
TEAEs leading to discontinuation of study drug	8 (2.7)	20 (6.5)	28 (9.4)	17 (5.5)	65 (7.1)
Any APTC event	7 (2.4)	6 (1.9)	10 (3.4)	11 (3.6)	27 (3.0)

TEAE: Treatment-emergent adverse event

The 3 most common ocular TEAEs in the study eye occurring in the total study population (N=1204) from Baseline to Week 96/100 were "retinal hemorrhage" (17.2%), "visual acuity reduced" (13.4%), and "macular degeneration" (11.1%). Individual ocular TEAEs in the study eye were balanced among the treatment groups and were generally consistent with disease progression, or expected adverse consequences of the injection procedure.
Overall, pattern and frequencies of non-ocular TEAEs were similar among treatment groups, and no apparent dose-response was found.
In consistence with the analyses of all TEAEs, the analyses of drug-related ocular and non-ocular events and injection-related ocular events or serious adverse events did not point to clinically meaningful imbalances among the treatment groups.
Two deaths were considered drug-related by the reporting investigators: "cerebrovascular accident" and "ischemic stroke", respectively. A review of the individual medical history of these patients, however, revealed medical conditions that might serve as reasonable alternative explanations for these fatal events. Overall, the absolute number of deaths was too low to allow specific conclusions, but, based on the present data, deaths appeared to be similarly distributed across all treatment groups and not unexpected in the study population.
The additional safety analyses using several sets of pre-specified adverse events of interest and adjudicated APTC events over 2 years did not indicate relevant differences among the treatment groups or specific risks of treatment with VEGF Trap-Eye in terms of potential systemic adverse reactions.
As an overall conclusion for the comprehensive set of the adverse event subgroup analyses, the results of the treatment group comparisons within subgroups were similar to those seen in the entire study population (where sample sizes were large enough to allow for a reasonable assessment).

Anti-Drug Antibodies (complete study period)
By the end of Week 96/100, a total of 47 subjects were positive in the antidrug antibody (ADA) assay: 9 subjects (3.1%) in the RQ4 group, 17 subjects (5.5%) in 2Q4 group, 17 subjects (5.7%) in 0.5Q4 group, and 4 subjects (1.3%) in 2Q8 group. Treatment-emergent positive responses were observed in 27 of these subjects (RQ4: 5 subjects [1.7%], 2Q4: 9 subjects [2.9%], 0.5Q4: 10 subjects [3.4%], and 2Q8: 3 subjects [1.0%]). The slight increase from 42 positive subjects by the end of Year 1 to 47 positive subjects by the end of Year 2 indicated that most subjects, who exhibited a positive response in the ADA assay, did so within Year 1 of the study. Titers were low and stable, with minor increases in titers observed in only a few subjects during Year 2. The maximum titer in Year 1 and in Year 2 was 1:960. No neutralizing antibodies were detected in any of the positive study subjects. As far as assessable because of the relatively small number of subjects with positive ADA assays, there were no obvious differences to the incidences and event patterns observed in all study subjects, suggesting that the ADA assay-positive subjects were not prone to more or more complicated adverse events.

ENT Substudy (complete study period)
The enhanced monitoring and AE reporting for ENT-specific AEs in 160 subjects (ENT sub-study, performed by ENT specialist at baseline, Week 12, and Week 52) resulted in inciden-ces and event patterns that were similar across the treatment groups and not indicative of any increased risk of nasal mucosal affections associated with VEGF Trap-Eye. This observation was supported by an additional modified standardized MedDRA term search for respective symptoms in the remaining 1044 subjects, where no relevant differences among the treatment groups were found up to Week 96/100.

Results Summary — Pharmacokinetics
Year 1 analysis The systemic exposure to free and adjusted bound VEGF Trap after IVT administration of 0.5 or 2 mg VEGF Trap-Eye was considered to be low that only minor parts of the available systemic endogenous VEGF were expected to be bound to VEGF Trap, and that considerable amounts of free endogenous VEGF were present systemically throughout the study period. Consistent with these findings, there was no evidence of a dose- or exposure-related trend in the safety data. Year 2 analysis In comparison to the Year 1 PK analyses, just one additional sample time point at Week 56 was added to the PK data base. The numbers of patients with free or adjusted bound VEGF Trap plasma concentrations greater than the lower limit of quantitation as well as the calculated mean plasma concentrations at this time were not relevantly different from the preceding sample time points, and overall, the conclusions derived from Year 1 analyses were still valid even after the inclusion of the Week 56 sample data.

Results Summary — Other
not applicable

Conclusion(s)
All VEGF Trap-Eye treatment regimens (2Q4, 0.5Q4 and 2Q8) were shown to be non -inferior to the ranibizumab treatment (RQ4) in maintaining vision at Week 52. This similarity of results was maintained up to Week 96, with overall approximately 5 fewer injections in the 2Q8 arm than in the Q4 arms. The improvements in BCVA achieved during Year 1 (with fixed dosing) were largely maintained through Year 2 (with modified quarterly dosing) in all VEGF Trap-Eye treatment groups. However, there were on group level some slight declines in visual acuity and morphological parameters observed, suggesting that a proactive dosing strategy delivers more stable and predictable results than the modified quarterly dosing paradigm, which included some reactive treatment component for those subjects that did not well under the quarterly (12-weekly) interval. Data clearly show that VEGF Trap-Eye treatment regimen 2Q8 is as efficacious as ranibizumab treatment (RQ4). The analyses of exposure data of the second year of treatment support the 2mg dose at a dosing interval of every 2 months or even longer. VEGF Trap-Eye was generally safe and well tolerated over 2 years of treatment, without notable differences in the safety profile compared to ranibizumab 0.5Q4 in ocular or non-ocular TEAEs. Most common TEAEs were typical of injection procedure or underlying disease

Publication(s):	Heier JS, et al. Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration. Ophthalmology 2012; 119: 2537-2548. PMID: 23084240
Date Created or Date Last Updated:	24 Jan 2013 Date of CSR 13 June 2012

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