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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Macugen® / Pegaptanib sodium

PROTOCOL NO.: A5751017

PROTOCOL TITLE: A 102-Week, Open Label, Multicenter Trial to Investigate the Efficacy of Macugen for the Preservation of Visual Function in Subjects With Neovascular Age-Related Macular Degeneration (AMD) and to Assess the Benefit of Treating Early Choroidal Neovascularization (CNV)

Study Centers: A total of 58 study centers took part in the study and enroll subjects;
4 centers each in Austria, Czech Republic, Poland, Portugal, Germany, Turkey and Spain
3 centers in Belgium, 5 centers each in Canada and Italy, 1 center each in Denmark and Finland, 7 centers in France, 2 centers in Greece, and 6 centers in the United Kingdom (UK).

Study Initiation Date and Final Completion Dates: 07 July 2006 to 07 August 2009

The study was prematurely terminated.

Phase of Development: Phase 3b/4

Study Objectives:

Primary Objective:

- To assess the efficacy of pegaptanib 0.3 mg for the preservation of vision in subjects with early choroidal neovascularization (CNV) lesions and established CNV lesions.

Secondary Objectives:

- To assess the efficacy of pegaptanib 0.3 mg for the preservation of visual function and quality of life (QoL) measurements in subjects with neovascular age-related macular degeneration (AMD).

- To assess the safety of pegaptanib 0.3 mg in subjects with early CNV lesions and established CNV lesions.

METHODS

Study Design: This was a Phase 3b/4, open-label, multicenter study in which all subjects were treated in the study eye (ie, an eye affected by macular degeneration and a loss of visual

acuity) with pegaptanib 0.3 mg every 6 weeks for 48 weeks. All subjects completing the first year of therapy (54 weeks [ie, 6 weeks after treatment at Week 48]) continued treatment with pegaptanib 0.3 mg administered every 12 weeks (ie, Weeks 60, 72, 84, and 96) in the second year of the study (Weeks 54 to 102). Any subject experiencing a ≥15 letter drop in visual acuity (VA) from Baseline in the study eye in the first year of the study (to 54 weeks) or a >5 letter drop in VA in the second year of the study (54 to 102 weeks) from the VA score recorded at 54 weeks in the study eye could have been treated at the discretion of the investigator with salvage therapy. Salvage therapy was defined as treatment by any agent(s) that are considered as the standard of care for the treatment of neovascular AMD that, in the opinion of the Investigator, would result in improvement of the subject's vision, while continuing pegaptanib therapy. Salvage therapy was administered by intravitreal injection every 3 weeks after a pegaptanib injection in the first year of the study (54 weeks) or in the second year (Weeks 54 to 102), as required. It was recommended that subjects requiring treatment for neovascular AMD in the nonstudy eye during the study be treated with an approved (non-investigational or off-label) therapy.
The efficacy of pegaptanib (0.3 mg) was evaluated for preservation of vision in subjects with a macular degeneration disease (eg, neovascular AMD). AMD presents clinically with either 1 of 2 types of retinal lesions: 1) neovascular (wet, exudative), or 2) non-neovascular (non-exudative/dry, atrophic). Pathological neovascularization (ie, choroidal neovascularization, or CNV) is associated with the development of abnormal new blood vessels proliferating under and/or within the retina, and promoting development of AMD lesions. This study examined the effect of Macugen (0.3 mg) on early and late CNV in subjects with AMD.

"Early" CNV was characterized as having new-onset pathologic neovascularization, which is associated with relatively minimal vision loss and a greater chance of vision gain versus subjects with "late" or established CNV. Late CNV was characterized by occult, recent disease progression, or by classic AMD components (eg, retinal atrophy, dry, non-neovascular lesions). For this study, classification of CNV as either early or late occurred at Baseline with enrolled subjects. Subjects with early CNV lesions were distinguished from subjects with established CNV lesions based on the stage of evolution of their CNV as determined by fluorescein angiography (FA) and, where available, indocyanine green angiography as assessed by the Investigator at Baseline. The maximum time between subject enrollment and initiation of treatment was 14 days.

A decision was made (08 May 2009) by the Sponsor to terminate this study early because the study had achieved the primary objective prior to termination. However, the study was not terminated early for safety reasons. This decision was based on the recommendation received in May 2009 from the Global Retinal Asset Team. The decision to terminate the study after completion of Year 1 was based on all active subjects completing Year 1 and the majority of subjects completing Year 2. Table 1 provides an overview of the schedule of activities for this study.

Table 1. Schedule of Activities

Window of ±5 Days; Subsequent Visits Calculated From V 2, D 1	V 1 Screening/ Baseline (D -14 to D 0)	V 2 D 1	V 3 W 6	V 4 W 12	V 5 W 18	V 6 W 24	V 7 W 30	V 8 W 36	V 9 W 42	V 10 W 48	V 11 W 54	V 12 W 60	V 13 W 72	V 14 W 84	V 15 W 96	V 16 W 102
Strata assignment	X[a]	X[a]														
Informed consent	X															
Inclusion/exclusion criteria	X															
Urine pregnancy test		X[b]														X[b]
Medical/ophthalmic history	X															
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pegaptanib injection		X	X	X	X	X	X	X	X	X	[c]	X	X	X	X	
Telephone safety check		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	[c]	X[d]	X[d]	X[d]	X[d]	
Distance visual acuity	X[e]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[e]	X[f]	X[f]	X[f]	X[f]	X[e]
Near visual acuity	X[e]		X[f]	X[f]			X[f]				X[e]					X[e]
Reading speed assessment (Bailey-Lovie reading chart)	X[e]						X[f]				X[e]					X[e]
Contrast sensitivity (Pelli Robson chart)	X[e]						X[f]				X[e]					X[e]
Tonometry	X[g]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[g]	X[h]	X[h]	X[h]	X[h]	X[g]

Table 1. Schedule of Activities

Window of ±5 Days; Subsequent Visits Calculated From V 2, D 1	V 1 Screening/ Baseline (D -14 to D 0)	V 2 D 1	V 3 W 6	V 4 W 12	V 5 W 18	V 6 W 24	V 7 W 30	V 8 W 36	V 9 W 42	V 10 W 48	V 11 W 54	V 12 W 60	V 13 W 72	V 14 W 84	V 15 W 96	V 16 W 102
Ophthalmic examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color fundus photography	X										X					X
Fluorescein angiography	X										X					X
ICG angiography[i]	X[i]										X[i]					X[i]
Corneal specular microscopy[i]	X[i]					X[i]					X[i]					
NEI-VFQ and EQ-5D[j]	X[j]	X[j]									X[j]					X[j]
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D = day; EQ-5D = Euro Quality of Life (QOL); ICG = indocyanine green angiography; IEC = Independent Ethics Committee NEI-VFQ = National Eye Institute – Visual Functioning Questionnaire, V = Visit; W = week.

a. Strata assignment was determined at any time from screening/baseline, but was required to be completed before the first treatment on V 2, D 1.
b. Urine pregnancy tests for women of childbearing potential only; allowed to be repeated as per request of IECs or if required by local regulations.
c. No injection scheduled as all subjects continued study on an every 12-week injection regimen.
d. Telephone safety check was made 3 days after injection (+2-day time window).
e. Assessments was performed on both eyes.
f. Assessments were performed on study eye only.
g. Applanation tonometry was performed at V 1/Screening, V 11/W 54, and V 16/W 102.
h. Tonometry was performed before injection and at least 30 minutes after injection.
i. Based upon availability of equipment.
j. Questionnaires were administered by a telephone interview performed by the Call Center at any time from screening/baseline, but were required to be completed before the first treatment on V 2, D 1 and before the ophthalmic assessments at V 11, W 54 and V 16, W 102.

Number of Subjects (Planned and Analyzed): A total of 370 subjects with neovascular AMD were planned to be enrolled into 1 of 2 strata, 185 subjects with early CNV lesions and 185 subjects with established CNV lesions. Of the 330 subjects screened for the study, 107 subjects were assigned to the early AMD group and 181 subjects were assigned to the established AMD group. Each subject was assigned to strata (early AMD or established AMD) based on the Investigator's assessments. Of the 107 subjects treated in the early AMD group, all were analyzed for efficacy and safety. Of the 179 subjects treated in the established AMD group, 178 (98.3%) were analyzed for efficacy and 179 (98.9%) were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: For general ophthalmic inclusion, evidence of neovascular AMD in at least 1 eye was required for study inclusion. In subjects with bilateral neovascular AMD, only one eye (the "study" eye) would be eligible for enrollment. Baseline refractory (VA) needed to be≥ 20/320, or better than 25 early treatment of diabetic retinopathy studies (ETDRS) letters in the study eye. Total lesion area in the study eye (including CNV and associated lesion components) must have been <12 disc areas. For subjects with early CNV lesions, visual symptoms secondary to neovascular AMD, evidence of CNV or CNV, baseline protocol refraction VA >54 letters or equivalent were required for study inclusion. For subjects with established CNV lesions, classic CNV on FA representing >50% of the total lesion size or occult representing <50% of the total CNV lesion size on FA was required to be eligible for inclusion.

Exclusion criteria for all subjects included previous treatment for CNV secondary to AMD, including any prior photodynamic therapy with verteporfin, thermal laser photocoagulation, external beam radiation or transpupillary thermotherapy to the study eye. Subjects having subfoveal fibrosis/ scar or atrophy representing >25% of the total lesion size were not eligible for enrollment in the study.

Study Treatment: Pegaptanib was administered as 90 µl (nominal delivered volume) intravitreous injections every 6 weeks from Day 1 to Week 48. After Week 54, subjects continued treatment with pegaptanib 0.3 mg every 12 weeks to Week 102 (ie, Weeks 60, 72, 84, and 96).

Efficacy and Safety Endpoints:

Primary Endpoint:

The mean change in distance VA from Baseline to Week 54 in subjects with early CNV lesions and established CNV lesions by assessing best corrected distance VA as measured by EDTRS score.

Secondary Endpoints:

- The mean change in distance VA from Baseline to 102 weeks and from Weeks 54 to 102 in subjects with early CNV lesions and established CNV lesions.

- The mean change in near VA from baseline in subjects with early CNV lesions and subjects with established CNV lesions at 54 and 102 weeks. The mean change in near VA from Weeks 54 to 102 in subjects with early CNV lesions and subjects with established CNV lesions.

- The mean change in reading speed from baseline in subjects with early CNV lesions and subjects with established CNV lesions at 54 and 102 weeks and from Weeks 54 to 102.

- The mean change in contrast sensitivity from baseline in subjects with early CNV lesions and subjects with established CNV lesions at Weeks 54 and 102.

- The mean change in National Eye Institute – Visual Functioning Questionnaire; (NEI-VFQ) composite score and the 12 subscale scores and Euro Quality of Life (EQ5D) score from baseline in subjects with early CNV lesions and subjects with established CNV lesions at Weeks 54 and 102.

- Safety Endpoints: Safety assessments included all adverse events (AEs) as observed/reported from Baseline (except those related to progression of neovascular AMD, ie, decrease in VA, increase in CNV size, lipid exudation, or subretinal hemorrhage).

Safety Evaluations: Evaluation of subjects for safety and tolerability were assessed by ongoing AE assessments. Serious AEs (SAEs), AEs considered related to study medication, AEs that resulted in subject discontinuation, and corneal specular microscopy results were summarized. VA, slit lamp bio microscopy, and ophthalmoscopy were performed throughout the study to document disease progression, changes in disease status, or to monitor the use of salvage therapy as needed.

Statistical Methods: The safety population on which the safety analyses were based included all enrolled subjects who receive at least 1 pegaptanib injection. The modified intent-to-treat (MITT) population included all subjects in the safety population who had a baseline distance VA measurement and at least 1 postbaseline VA measurement. Subjects were analyzed within the stratum to which they were assigned by the Investigators at the beginning of the study for statistical analyses. Efficacy analyses were performed on the MITT population unless otherwise specified.

A total of 370 subjects were planned to receive pegaptanib in the study, 185 subjects with early CNV lesions and 185 subjects with established CNV lesions. The strata (early CNV lesions or established CNV lesions) to which the subjects were assigned were based on the Investigator's assessments. All efficacy endpoints were analyzed based on the MITT population unless otherwise specified.

The mean change from Baseline in distance VA at Week 54 was provided for early CNV lesion subjects and established CNV lesion subjects. Corresponding 95% confidence intervals (CIs) were provided for these means. Mean changes from Baseline in distance VA, near VA, reading speed, contrast sensitivity, NEI-VFQ composite and subscale scores, and EQ-5D index scores at Weeks 54 and 102 were computed along with 95% CIs.

Mean change from Baseline in distance VA for early CNV lesions and established CNV lesions were computed at each visit. The summaries were provided using both the observed cases (OC) at each visit and the last observation carried forward (LOCF) approach. The proportion of subjects with severe vision loss (loss of ≥30 letters), responders (loss of <15 letters), maintainers (gain of ≥0 letters), and gainers (gain of ≥15 letters) and subjects who progressed to legal blindness (subjects with baseline VA >20/200 who progressed to VA ≤20/200) at Weeks 54 and 102 were computed at Week 54 and 102 for the 2 strata. Median time to loss of ≥15 letters from baseline were calculated using Kaplan-Meier estimates for subjects with early lesions and established CNV lesions.

The proportion of subjects requiring salvage therapy in addition to treatment with pegaptanib in subjects with early CNV lesions and established CNV lesions were provided. This endpoint was analyzed based on the study eye of all treated subjects.

The Medical Dictionary for Regulatory Activities (MedDRA, Version 12.0) coding system was used for classifying AEs. Analysis of AEs was based on all treated subjects and on all eyes.

RESULTS

Subject Disposition and Demography: One hundred seven subjects were assigned to the early AMD group and 181 subjects were assigned to the established AMD group; a total of 330 subjects were screened for enrollment. Seventy-eight (72.9%) subjects out of the total 107 in the early AMD group completed the study and all subjects in this group were analyzed for efficacy and safety. Of the 179 subjects treated in the established AMD group, 118 (65.2%) subjects completed the study, 178 (98.3%) were analyzed for efficacy, and 179 (98.9%) were analyzed for safety as shown in Table 2. Two subjects were assigned to study treatment, but were withdrawn before the initiation of treatment; 1 subject was no longer willing to participate in the study and 1 subject was withdrawn due to other reason.

Table 2. Subject Evaluation Groups

No. (%) of Subjects	Early AMD	Established AMD
Screened: 330		
Assigned to study treatment	107	181
Treated	107	179[a]
Completed	78 (72.9)	118 (65.2)
Discontinued	29 (27.1)	61 (33.7)
Subject died[b]	1 (0.9)	4 (2.2)
Related to study drug	13 (12.1)	29 (16.2)
Adverse event	1 (0.9)	4 (2.2)
Lack of efficacy	7 (6.5)	19 (10.6)
Other	5 (4.7)	6 (3.4)
Not related to study drug	15 (14.0)	28 (15.6)
Adverse event	8 (7.5)	10 (5.6)
Lost to follow-up	1 (0.9)	3 (1.7)
Other	0	3 (1.7)
Subject no longer willing to participate	6 (5.6)	12 (6.7)
Analyzed for efficacy		
MITT	107 (100.0)	178 (98.3)
Analyzed for safety		
Adverse events	107 (100.0)	179 (98.9)
Safety population	107 (100.0)	179 (98.9)

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
AMD = age-related macular degeneration; MITT = modified intent-to-treat.

a. Two subjects were assigned to study treatment, but were withdrawn before the initiation of treatment; one Subject was no longer willing to participate in the study and one more Subject was withdrawn due to other reason.

b. Subject deaths reported during this study: One Subject (established AMD; myocardial infarction); one subject (established AMD, bronchopneumonia); one subject (established AMD, heart failure); one subject (established AMD, stroke); and one subject (early AMD, reason not stated).

More females were enrolled in the early AMD group (59 of 107 total subjects) and in the established AMD group (108 of 179 total subjects) than males. The mean age of male and female subjects was similar, with an overall range of 52 to 94 years. The majority of subjects (263 of 286 total subjects, from both early and established AMD groups) were White, as shown in Table 3.

Table 3. Demographic Characteristics

No. (%) of Subjects	Early AMD			Established AMD		
	Male	Female	Total	Male	Female	Total
No. of subjects	48	59	107	71	108	179
Age (years):						
45-64	6 (12.5)	6 (10.2)	12 (11.2)	9 (12.7)	15 (13.9)	24 (13.4)
≥65	42 (87.5)	53 (89.8)	95 (88.8)	62 (87.3)	93 (86.1)	155 (86.6)
Mean	74.6	72.9	73.7	73.4	74.6	74.1
SD	7.9	7.3	7.6	7.1	8.6	8.0
Range	54-93	52-88	52-93	54-86	52-94	52-94
Race:						
White	45 (93.8)	53 (89.9)	98 (91.6)	68 (95.8)	97 (89.8)	165 (92.2)
Other	0	3 (5.1)	3 (2.8)	1 (1.4)	9 (8.3)	10 (5.6)
Unspecified	3 (6.3)	3 (5.1)	6 (5.6)	2 (2.8)	2 (1.9)	4 (2.2)

AMD = age-related macular degeneration; No. = number; SD = standard deviation.

Efficacy Results:

Primary Endpoint: Decreases in the mean change in distance VA from Baseline to Week 54 for the MITT population (LOCF) were noted in the early AMD group (-4.30 letters) and in the established AMD group (-5.51 letters) (Table 4). Slightly lower decreases in mean change in distance VA from Baseline to Week 54 for the observed cases (OC) were noted in the early AMD group (-1.93 letters) and in the established AMD group (-4.08 letters).

Table 4. Mean Change in Distance Visual Acuity From Baseline to Week 54: MITT Population; LOCF

Visit	Statistics	Early AMD N=107	Established AMD N=178
Baseline	n	107	178
	Mean[a]	68.19	55.50
	SD	8.54	14.86
	95% CI	(66.55, 69.82)	(53.30, 57.70)
	Median[a]	69.00	58.00
	Minimum, maximum[a]	46.00, 85.00	12.00, 85.00
Week 54	n	107	178
	Mean[a]	63.89	49.99
	SD	16.20	18.99
	95% CI	(60.78, 66.99)	(47.18, 52.80)
	Median[a]	68.00	51.00
	Minimum, maximum[a]	0.00, 85.00	0.00, 85.00
Change from Baseline at Week 54	n	107	178
	Mean[a]	-4.30	-5.51
	SD	14.57	15.08
	95% CI	(-7.09, -1.51)	(-7.74, -3.28)
	Median[a]	-2.00	-3.00
	Minimum, maximum[a]	-63.00, 19.00	-59.00, 44.00

Only the data collected under pegaptanib exposure were used for the analysis (ie, the VA assessments performed after the first salvage therapy administration were not included). For subjects requiring salvage therapy, the last available assessment preceding the first salvage therapy administration was carried over to all subsequent visits.
AMD = age-related macular degeneration; CI = confidence interval; ETDRS = early treatment of diabetic retinopathy study, LOCF = last observation carried forward, MITT = modified intent-to-treat, n = number of subjects with indicated observation; N = total number of subjects; SD = standard deviation.
a. Mean change in distance VA was based on a gain or loss of letters using ETDRS.

Secondary Endpoints: Decreases in the mean change in distance VA from Baseline to Week 102 for the MITT population (LOCF) were noted in the early AMD group (-7.91 letters) and in the established AMD group (-8.95 letters). Decreases in the mean change in distance VA from Weeks 54 to 102 for the MITT population (LOCF) were also noted in the early AMD group (-3.61 letters) and in the established AMD group (-3.44 letters) (Table 5).

Table 5. Mean Change in Distance Visual Acuity From Baseline to Week 102: MITT Population; LOCF

Visit	Statistics	Early AMD N=107	Established AMD N=178
Baseline	n	107	178
	Mean[a]	68.19	55.50
	SD	8.54	14.86
	95% CI	(66.55, 69.82)	(53.30, 57.70)
	Median[a]	69.00	58.00
	Minimum, maximum[a]	46.00, 85.00	12.00, 85.00
Week 54	n	107	178
	Mean[a]	63.89	49.99
	SD	16.20	18.99
	95% CI	(60.78, 66.99)	(47.18, 52.80)
	Median[a]	68.00	51.00
	Minimum, maximum[a]	0.00, 85.00	0.00, 85.00
Week 102	n	107	178
	Mean[a]	60.28	46.55
	SD	18.00	19.75
	95% CI	(56.83, 63.73)	(43.63, 49.47)
	Median[a]	63.00	45.00
	Minimum, maximum[a]	0.00, 85.00	0.00, 85.00
Change from Week 54 at Week 102	n	107	178
	Mean[a]	-3.61	-3.44
	SD	9.83	9.81
	95% CI	(-5.49, -1.72)	(-4.90, -1.99)
	Median[a]	0.00	0.00
	Minimum, maximum[a]	-39.00, 17.00	-47.00, 18.00
Change from Baseline at Week 102	n	107	178
	Mean[a]	-7.91	-8.95
	SD	16.14	17.34
	95% CI	(-11.00, -4.81)	(-11.51, -6.39)
	Median[a]	-3.00	-7.00
	Minimum, maximum[a]	-63.00, 20.00	-59.00, 51.00

Only the data collected under pegaptanib exposure were used for the analysis (ie, the visual acuity assessments performed after the first salvage therapy administration were not included). For subjects requiring salvage therapy, the last available assessment preceding the first salvage therapy administration was carried over to all subsequent visits.
AMD = age-related macular degeneration; CI = confidence interval; ETDRS = early treatment of diabetic retinopathy study; LOCF = last observation carried forward; MITT = modified intent-to-treat; n = number of subjects with indicated observation; N = total number of subjects; SD = standard deviation.
a. Mean change in distance visual acuity was based on a gain or loss of letters using ETDRS.

Mean change in near VA for the MITT population (LOCF) is summarized in Table 6. Based on the change from baseline at Weeks 54 and 102, a slight improvement in near VA was noted for subjects in the early AMD group (0.10 and 0.19 logMAR, respectively) and for subjects in the established AMD group (0.15 and 0.22, respectively). The mean change in near VA continued to improve for both groups from Weeks 54 to 102, with 0.10 for subjects in the early AMD group and 0.07 for subjects in the established AMD group (Table 6). Based on the change from Baseline at Weeks 54 and 102, slight improvement in near VA was noted for the OC in the early AMD group (0.07 and 0.20 logMAR, respectively) and for subjects in the established AMD group (0.14 and 0.22, respectively). The mean change in

near VA for the OC continued to improve for both groups from Week 54 to 102, with 0.14 for subjects in the early AMD group and 0.10 for subjects in the established AMD group.

Table 6. Mean Change in Near Visual Acuity: MITT Population; LOCF

Visit	Statistics	Early AMD N=107	Established AMD N=178
Baseline	n	107	178
	Mean	0.46	0.69
	SD	0.20	0.29
	95% CI	(0.42, 0.50)	(0.65, 0.73)
	Median	0.40	0.70
	Minimum, maximum	0.10, 1.00	0.10, 1.60
Week 54	n	104	172
	Mean	0.56	0.84
	SD	0.31	0.41
	95% CI	(0.50, 0.62)	(0.77, 0.90)
	Median	0.50	0.80
	Minimum, maximum	0.10, 1.60	0.20, 1.60
Change from Baseline at Week 54	n	104	172
	Mean	0.10	0.15
	SD	0.27	0.32
	95% CI	(0.50, 0.15)	(0.10, 0.20)
	Median	0.10	0.10
	Minimum, maximum	-0.70, 1.20	-0.80, 1.10
Week 102	n	105	172
	Mean	0.65	0.90
	SD	0.39	0.43
	95% CI	(0.58, 0.73)	(0.84, 0.97)
	Median	0.60	0.90
	Minimum, maximum	0.10, 1.60	0.00, 1.60
Change from Baseline at Week 102	n	105	172
	Mean	0.19	0.22
	SD	0.34	0.36
	95% CI	(0.13, 0.26)	(0.16, 0.27)
	Median	0.10	0.20
	Minimum, maximum	-0.70, 1.30	-0.60, 1.20
Change from Week 54 at Week 102	n	104	172
	Mean	0.10	0.07
	SD	0.24	0.24
	95% CI	(0.05, 0.14)	(0.03, 0.10)
	Median	0.00	0.00
	Minimum, maximum	-0.20, 1.10	-0.60, 1.00

Only the data collected under pegaptanib exposure were used for the analysis (ie, the visual acuity assessments performed after the first salvage therapy administration were not included). For subjects requiring salvage therapy, the last available assessment preceding the first salvage therapy administration was carried over to all subsequent visits. Near visual acuity is in unit of logMAR score using the Bailey-Lovie near word reading chart.
AMD = age-related macular degeneration; CI = confidence interval; LOCF = last observation carried forward; MITT = modified intent-to-treat; n = number of subjects with indicated observation; N = total number of subjects; SD = standard deviation.

Table 7 summarizes changes in reading speed for Weeks 54 and 102 from Baseline for the MITT population (LOCF). The mean and median speed in the early AMD and established AMD groups (MITT population [LOCF]) decreased from baseline at Weeks 54 and 102; at Week 54, a larger decrease in mean and median reading speed was noted for the established AMD group compared with the early AMD group. By Week 102, the mean and median decrease from baseline was larger for the early AMD group compared with the established AMD group. However, based on the maximum reading speeds reported, increases in reading speed were noted at Weeks 54 and 102 for subjects in the early AMD group (68.74 and 65.21 words, respectively) and for subjects in the established AMD group (56.17 and 212.81 words, respectively) (Table 7). The change from reading speed at Weeks 54 and 102 from baseline for the MITT population (OC) showed the same trend as for the MITT population (LOCF).

Table 7. Mean Change in Reading Speed at Weeks 54 and 102 Compared with Baseline; MITT Population (LOCF)

Visit	Examination Status	Early AMD N=107	Established AMD N=178
Baseline	n	106	176
	Mean	56.12	40.88
	SD	22.66	24.60
	95% CI	(51.75, 60.48)	(37.22, 44.54)
	Median	58.03	34.95
	Minimum, maximum	8.00, 120.00	0.00, 112.50
Week 54	n	93	152
	Mean	47.75	28.71
	SD	29.27	25.29
	95% CI	(41.73, 53.78)	(24.65, 32.76)
	Median	45.79	17.61
	Minimum, maximum	3.50, 112.00	0.00, 120.00
Change at Week 54	n	92	151
	Mean	-9.15	-10.98
	SD	28.78	22.31
	95% CI	(-15.11, -3.19)	(-14.57, -7.39)
	Median	-4.86	-10.48
	Minimum, maximum	-81.55, 68.74	-86.74, 56.17
Week 102	n	95	153
	Mean	39.20	27.40
	SD	28.06	30.90
	95% CI	(33.49, 44.92)	(22.46, 32.33)
	Median	39.13	17.14
	Minimum, maximum	0.50, 112.50	0.00, 240.00
Change at Week 102	n	94	152
	Mean	-17.81	-12.23
	SD	28.48	32.08
	95% CI	(-23.65, -11.98)	(-17.37, -7.09)
	Median	-14.20	-13.06
	Minimum, maximum	-91.85, 65.21	-88.31, 212.81

Only the data collected under pegaptanib exposure were used for the analysis, ie, the reading speed assessments performed after the first salvage therapy administration were not included. Reading speed was in unit of words, using modified Bailey-Lovie reading chart.
AMD = age-related macular degeneration; CI = confidence interval; LOCF = last observation carried forward; n = number of subjects with indicated observation; N = total number of subjects; SD = standard deviation.

Table 8 provides a summary of the mean change in contrast sensitivity from Baseline to Weeks 54 and 102 for the MITT population (LOCF). Contrast sensitivity declined slightly but continuously through 102 weeks of treatment in both the early and established AMD groups (Table 8).

The mean change in contrast sensitivity from Baseline to Weeks 54 and 102 for the MITT population (OC) was nearly identical to the MITT population (LOCF); ie, contrast sensitivity declined slightly but continuously through 102 weeks of treatment in both the early and established AMD groups.

Table 8. Mean Change in Contrast Sensitivity From Baseline to Week 54 and Week 102: MITT Population; LOCF

Visit	Statistics	Early AMD N=107	Established AMD N=178
Baseline	n	107	176
	Mean	1.33	1.13
	SD	0.27	0.35
	95% CI	(1.28, 1.38)	(1.08, 1.18)
	Median	1.35	1.20
	Minimum, maximum	0.30, 1.80	0.15, 1.65
Week 54	n	93	153
	Mean	1.28	1.09
	SD	0.34	0.41
	95% CI	(1.21, 1.35)	(1.03, 1.16)
	Median	1.35	1.20
	Minimum, maximum	0.30, 1.65	0.00, 1.95
Change from baseline at Week 54	n	93	152
	Mean	-0.06	-0.03
	SD	0.26	0.33
	95% CI	(-0.11, -0.00)	(-0.08, 0.02)
	Median	0.00	0.00
	Minimum, maximum	-1.05, 0.90	-0.90, 1.05
Week 102	n	94	153
	Mean	1.17	1.02
	SD	0.43	0.45
	95% CI	(1.08, 1.26)	(0.95, 1.10)
	Median	1.35	1.20
	Minimum, maximum	0.00, 1.65	0.00, 1.95
Change from baseline at Week 102	n	94	152
	Mean	-0.16	-0.09
	SD	0.37	0.39
	95% CI	(-0.24, -0.09)	(-0.15, -0.03)
	Median	-0.07	0.00
	Minimum, maximum	-1.35, 1.05	-1.35, 1.05

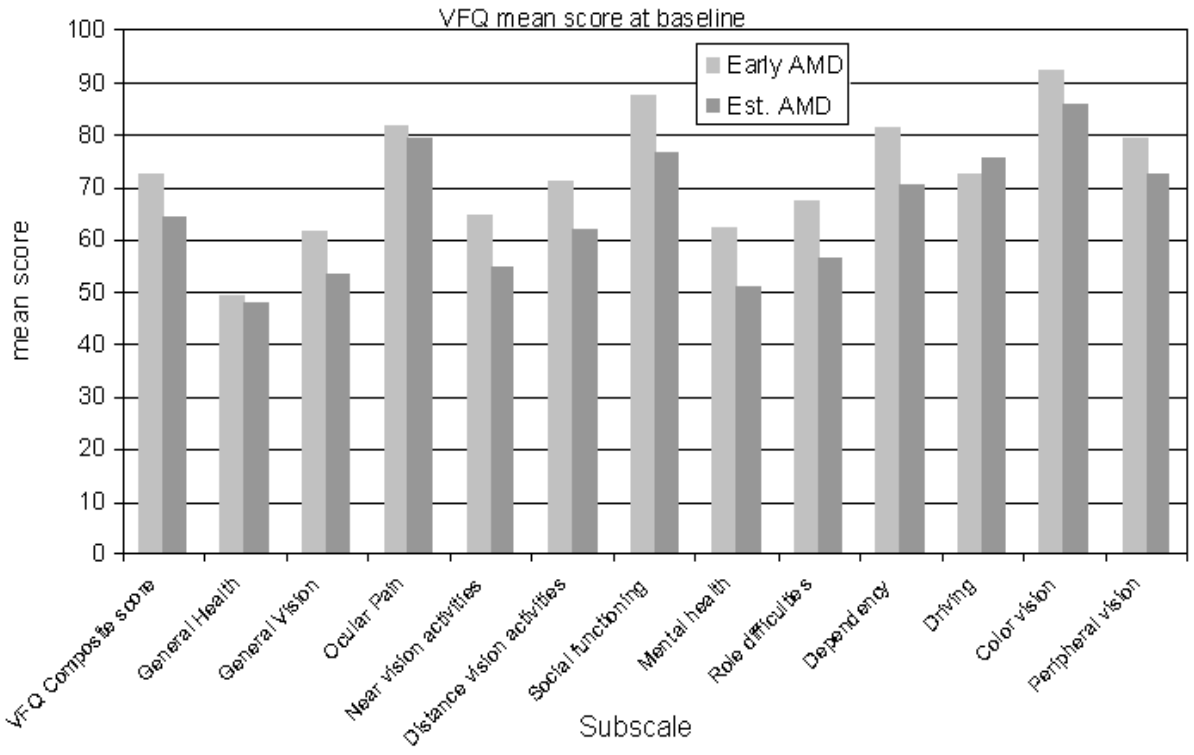
Only the data collected under pegaptanib exposure were used for the analysis (ie, the visual acuity assessments performed after the first salvage therapy administration were not included). For subjects requiring salvage therapy, the last available assessment preceding the first salvage therapy administration was carried over to all subsequent visits.
AMD = age-related macular degeneration; CI = confidence interval; LOCF = last observation carried forward; MITT = modified intent-to-treat; n = number of subjects with indicated observation; N = total number of subjects; SD = standard deviation.

Subjects self-reported visual functioning and visual related quality of life data are summarized in the 2 figures below. For the 3 visits with QoL data collection, study subjects had excellent questionnaire compliance rates, which ranged from 96.6% to 100%.

Figure 1 and Figure 2 summarize the findings for the NEI-VFQ-25. Figure 1 shows the baseline mean scores of the VFQ composite and its 12 subscales. The baseline mean VFQ composite scores were 72.5 and 64.5 for the early AMD and established AMD groups, respectively. When examining the baseline mean scores of the subscales, subjects in both AMD groups reported relatively poor general health, general vision, near vision activities, distance vision activities, mental health, and role difficulties; the subjects tended to have less

problem with ocular pain, social functioning, dependency, color, and peripheral visions. When comparing the baseline mean scores between the 2 AMD groups, subjects with early AMD had higher scores for the composite score and all vision-related subscales except the driving subscale (for which the established group had slightly higher score), though the between-group differences were small for the general health, ocular pain, and driving subscales. These data suggest that the 2 groups had similar general health at the start of the study, but subjects with early AMD tended to have better visual functioning (Figure 1).

Figure 1. NEI-VFQ-25 Baseline Mean Scores of the VFQ Composite and 12 Subscales

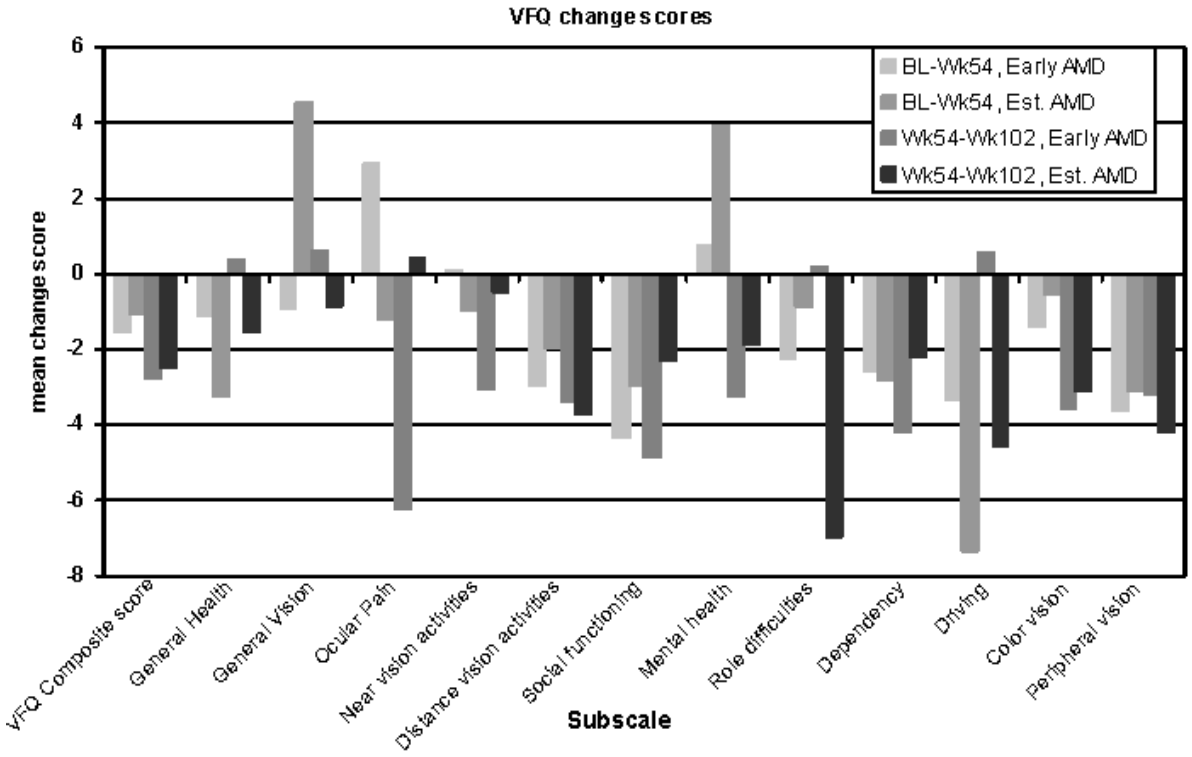


AMD = age-related macular degeneration; Est. = established; NEI-VFQ = National Eye Institute – Visual Functioning Questionnaire; VFQ = Visual Functioning Questionnaire.

Figure 2 displays the mean changes from baseline to Week 54 and from Week 54 to Week 102 for the 2 AMD groups. The mean changes of the VFQ composite score for both groups were less than 2 points decrease during the first year (ie, -1.54 and -1.03 from baseline to Week 54), less than 3 points decrease in the second year (ie, -2.74 and -2.48 from Week 54 to Week 102), and less than 5 points decrease through the study period (ie, -4.57 and -1.65 from Baseline to Week 102;), suggesting that the subjects' visual functioning was relatively stable during the 2 years of this study. This was also supported by the mean VFQ composite scores across at Baseline and Weeks 54 and 102; for these 3 time points, the mean VFQ composite scores were 72.5, 71.9, and 70.7 for the early AMD group, and 64.5, 63.7, and 62.1 for the established AMD group, respectively. However, the rate of deterioration in the visual functioning accelerated in the second year. When examining the mean change

scores of the subscales, the data showed that general health and general vision tended to be stable, and that visual functioning tended to get worse over time for most subscales for both groups of AMD.

Figure 2. NEI-VFQ-25 Mean Change Scores From Baseline to Week 54 and From Week 54 to Week 102



AMD = age-related macular degeneration; Est. = established; NEI-VFQ = National Eye Institute – Visual Functioning Questionnaire; Wk = Week.

The EQ-5D index is a health state utility measure with a score of 1.00 representing a perfect health state and a score of 0 representing the state of death. The mean scores and mean changes in EQ-5D index score from Baseline to Weeks 54 and 102 and from Weeks 54 to 102 showed that the EQ-5D index scores at baseline were similar in the 2 AMD groups (0.74 and 0.72 for the early AMD and established AMD groups, respectively), suggesting similar health status for both groups. The mean changes in the EQ-5D index scores were relatively small for the 2 AMD groups from baseline to Week 54 (0.00 and -0.01), from Week 54 to Week 102 (-0.01 and -0.03), and from baseline to Week 102 (-0.04 and -0.04), suggesting stable health status over the 2 years of this study for both the early and established AMD groups.

Safety Results: AEs were reported in 73 of 107 subjects with early AMD and in 124 of 179 subjects with established AMD; serious AEs (SAEs) were reported in 23 subjects with early AMD and in 32 subjects with established AMD. Overall, 4 subjects in the early AMD group discontinued due to treatment-emergent AEs (TEAEs) and 11 subjects in the established AMD group discontinued due to TEAEs. Eight of 107 subjects in the early AMD group and 14 of 179 subjects in the established AMD group had a temporary discontinuation

due to AEs; a dose reduction below the planned 0.3 mg of pegaptanib was not specified in the protocol. There were 5 subject deaths reported during the conduct of the study; none of the subject deaths were considered as treatment-related. An additional subject death was reported 7 days posttreatment. Five of the 6 subjects who died were in the established AMD group.

Overall, 73 of 107 subjects with early AMD had 331 AEs, of which 28 were considered to be related to treatment; 124 of 179 subjects with established AMD had 453 AEs, of which 46 were considered to be related to treatment. Twenty-three subjects with early AMD had SAEs, of which 2 had SAEs that were considered as related to treatment; 32 subjects with established AMD had SAEs, of which 6 subjects had SAEs that were considered as related to treatment. Five subjects in the early AMD group discontinued due to TEAEs, none of the AEs were considered to be related to treatment; 11 subjects in the established AMD group discontinued due to TEAEs, of which 4 subjects discontinued due to AEs considered as related to treatment (Table 9). Of the 331 AEs reported in subjects in the early AMD group, 214 were mild, 86 were moderate, and 31 were severe. Of the 453 AEs reported in subjects in the established AMD group, 257 were mild, 142 were moderate, and 54 were severe.

Table 9. Treatment-Emergent Adverse Events; All-Causality and Treatment-Related

No. (%) of Subjects	Early AMD		Established AMD	
	All Causality n (%)	Treatment Related n (%)	All Causality n (%)	Treatment Related n (%)
Subjects evaluable for AEs	107	107	179	179
Number of AEs	331	28	453	46
Subjects with AEs	73 (68.2)	18 (16.8)	124 (69.3)	32 (17.9)
Subjects with serious AEs	23 (21.5)	2 (1.9)	32 (17.9)	6 (3.4)
Subjects with severe AEs	21 (19.6)	2 (1.9)	33 (18.4)	7 (3.9)
Subjects discontinued due to AEs	5 (4.7)	0	11 (6.1)	4 (2.2)
Subjects with dose reduced or temporary discontinuation due to AEs	8 (7.5)	0	14 (7.8)	1 (0.6)

Subjects discontinued due to AEs represent subjects who discontinued study medication. Includes data up to 30 days after the last dose of study drug. Except for the number of AEs, subjects were counted only once per treatment in each row. Serious AEs were determined by the investigators.
AE = adverse event; AMD = age-related macular degeneration.

TEAEs (all causalities) are shown in Table 10. The most frequently reported treatment-related AEs by System Organ Class (SOC) for subjects in the established AMD group were eye disorders (21 [11.7%] of 179 subjects) and investigations (8 [4.5%] of 179 subjects) as shown in Table 10.

Table 10. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All-Causality)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD n (%)	Established AMD n (%)
No. (%) of Subjects:		
Evaluable for adverse events	107	179
With adverse events	68 (63.6)	120 (67.0)
Blood and lymphatic system disorders	1 (0.9)	4 (2.2)
Anaemia	0	4 (2.2)
Splenic lesion	1 (0.9)	0
Cardiac disorders	2 (1.9)	5 (2.8)
Aortic valve incompetence	0	1 (0.6)
Arrhythmia	1 (0.9)	1 (0.6)
Atrial fibrillation	1(0.9)	2 (1.1)
Cardiac failure	1 (0.9)	0
Palpitations	0	1 (0.6)
Congenital, familial and genetic disorders	1 (0.9)	0
Corneal dystrophy	1 (0.9)	0
Ear and labyrinth disorders	3 (2.8)	4 (2.2)
Deafness	0	2 (1.1)
Vertigo	3 (2.8)	2 (1.1)
Eye disorders	48 (44.9)	84 (46.9)
Anterior chamber cell	3 (2.8)	3 (1.7)
Anterior chamber flare	1 (0.9)	0
Anterior chamber pigmentation	2 (1.9)	0
Aphakia	1 (0.9)	0
Blepharitis	2 (1.9)	2 (1.1)
Blepharitis allergic	0	1 (0.6)
Blindness	2 (1.9)	2 (1.1)
Blindness transient	0	1 (0.6)
Blindness unilateral	3 (2.8)	0
Cataract	2 (1.9)	4 (2.2)
Cataract nuclear	1 (0.9)	1 (0.6)
Cataract subcapsular	0	1 (0.6)
Chalazion	1 (0.9)	2 (1.1)
Choroidal neovascularisation	1 (0.9)	6 (3.4)
Ciliary body haemorrhage	0	1 (0.6)
Conjunctival haemorrhage	17 (15.9)	16 (8.9)
Conjunctival hyperaemia	7 (6.5)	4 (2.2)
Conjunctival oedema	0	1 (0.6)
Conjunctivitis	7 (6.5)	8 (4.5)
Corneal deposits	0	1 (0.6)
Corneal disorder	2 (1.9)	2 (1.1)
Corneal epithelium defect	10 (9.3)	4 (2.2)
Corneal erosion	0	3 (1.7)
Corneal oedema	5 (4.7)	7 (3.9)
Corneal opacity	0	2 (1.1)
Detachment of retinal pigment epithelium	1 (0.9)	1 (0.6)
Dry eye	1 (0.9)	3 (1.7)
Episcleritis	1 (0.9)	0
Erythema of eyelid	1 (0.9)	0
Eye discharge	1 (0.9)	4 (2.2)

Table 10. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All-Causality)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD n (%)	Established AMD n (%)
Eye disorder	1 (0.9)	2 (1.1)
Eye haemorrhage	3 (2.8)	2 (1.1)
Eye irritation	1 (0.9)	5 (2.8)
Eye pain	9 (8.4)	9 (5.0)
Eye pruritus	1 (0.9)	0
Eyelid oedema	1 (0.9)	1 (0.6)
Foreign body sensation in eyes	4 (3.7)	0
Glaucoma	1 (0.9)	1 (0.6)
Hyalosis asteroid	0	1 (0.6)
Hyphaema	0	1 (0.6)
Iridocyclitis	0	3 (1.7)
Keratoconjunctivitis sicca	0	1 (0.6)
Lacrimation increased	6 (5.6)	2 (1.1)
Lens disorder	1 (0.9)	0
Macular degeneration	2 (1.9)	5 (2.8)
Maculopathy	0	1 (0.6)
Metamorphopsia	3 (2.8)	1 (0.6)
Myodesopsia	6 (5.6)	4 (2.2)
Ocular hyperaemia	3 (2.8)	3 (1.7)
Ocular hypertension	0	2 (1.1)
Photophobia	2 (1.9)	1 (0.6)
Photopsia	1 (0.9)	1 (0.6)
Posterior capsule opacification	1 (0.9)	3 (1.7)
Punctate keratitis	0	2 (1.1)
Retinal artery spasm	0	1 (0.6)
Retinal exudates	1 (0.9)	1 (0.6)
Retinal haemorrhage	3 (2.8)	9 (5.0)
Retinal oedema	1 (0.9)	0
Retinal pigment epithelial tear	1 (0.9)	1 (0.6)
Scleral haemorrhage	0	1 (0.6)
Vision blurred	3 (2.8)	1 (0.6)
Visual acuity reduced	2 (1.9)	9 (5.0)
Visual impairment	2 (1.9)	4 (2.2)
Vitreous detachment	3 (2.8)	1 (0.6)
Vitreous disorder	7 (6.5)	6 (3.4)
Vitreous haemorrhage	2 (1.9)	3 (1.7)
Vitreous opacities	1 (0.9)	1 (0.6)
Vitritis	0	1 (0.6)
Gastrointestinal disorders	10 (9.3)	17 (9.5)
Abdominal pain	0	1 (0.6)
Abdominal pain lower	0	1 (0.6)
Abdominal pain upper	1 (0.9)	1 (0.6)
Colitis	1 (0.9)	1 (0.6)
Constipation	0	4 (2.2)
Dental caries	1 (0.9)	1 (0.6)
Dental plaque	1 (0.9)	0
Diarrhoea	3 (2.8)	2 (1.1)
Duodenogastric reflux	1 (0.9)	0
Dyspepsia	0	1 (0.6)

Table 10. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All-Causality)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD n (%)	Established AMD n (%)
Food poisoning	0	1 (0.6)
Gastritis	0	2 (1.1)
Gastritis erosive	0	1 (0.6)
Gingivitis	1 (0.9)	0
Hiatus hernia	0	1 (0.6)
Irritable bowel syndrome	0	1 (0.6)
Mouth ulceration	0	1 (0.6)
Nausea	1 (0.9)	1 (0.6)
Pancreatitis chronic	0	1 (0.6)
Rectal prolapse	0	1 (0.6)
Salivary hypersecretion	1 (0.9)	0
Toothache	0	1 (0.6)
General disorders and administration site conditions	9 (8.4)	13 (7.3)
Asthenia	0	1 (0.6)
Chest pain	0	2 (1.1)
Fatigue	0	1 (0.6)
Influenza like illness	1 (0.9)	0
Injection site haemorrhage	1 (0.9)	4 (2.2)
Injection site irritation	0	2 (1.1)
Injection site pain	1 (0.9)	4 (2.2)
Injection site reaction	2 (1.9)	0
Pain	2 (1.9)	0
Polyp	0	1 (0.6)
Pyrexia	2 (1.9)	0
Therapeutic response unexpected	0	1 (0.6)
Hepatobiliary disorders	1 (0.9)	3 (1.7)
Hepatic cyst	1 (0.9)	1 (0.6)
Hepatic steatosis	0	1 (0.6)
Hyperbilirubinaemia	0	1 (0.6)
Liver disorder	1 (0.9)	0
Immune system disorders	1 (0.9)	3 (1.7)
Drug hypersensitivity	1 (0.9)	2 (1.1)
Hypersensitivity	0	1 (0.6)
Infections and infestations	27 (25.2)	43 (24.0)
Abscess	0	1 (0.6)
Bronchitis	2 (1.9)	8 (4.5)
Candidiasis	0	1 (0.6)
Conjunctivitis bacterial	1 (0.9)	0
Cystitis	1 (0.9)	2 (1.1)
Dacryocystitis	1 (0.9)	0
Erysipelas	1 (0.9)	0
Eye infection	1 (0.9)	0
Fungal skin infection	0	1 (0.6)
Gastroenteritis	1 (0.9)	2 (1.1)
Gastrointestinal fungal infection	1 (0.9)	0
Gingival infection	0	1 (0.6)
Herpes virus infection	0	1 (0.6)
Herpes zoster	1 (0.9)	1 (0.6)
Hordeolum	0	2 (1.1)

Table 10. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All-Causality)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD n (%)	Established AMD n (%)
Incision site infection	0	1 (0.6)
Infective exacerbation of chronic obstructive airways disease	0	1 (0.6)
Influenza	2 (1.9)	5 (2.8)
Keratitis herpetic	0	1 (0.6)
Laryngitis	0	2 (1.1)
Lower respiratory tract infection	1 (0.9)	4 (2.2)
Nasopharyngitis	9 (8.4)	10 (5.6)
Otitis media	0	2 (1.1)
Pharyngitis	0	1 (0.6)
Pneumonia	1 (0.9)	1 (0.6)
Pulpitis dental	0	1 (0.6)
Respiratory tract infection	1 (0.9)	0
Rhinitis	0	1 (0.6)
Sinusitis	0	3 (1.7)
Tooth abscess	1 (0.9)	1 (0.6)
Tooth infection	0	3 (1.7)
Upper respiratory tract infection	3 (2.8)	5 (2.8)
Urethritis	1 (0.9)	0
Urinary tract infection	3 (2.8)	1 (0.6)
Viral infection	1 (0.9)	0
Injury, poisoning and procedural complications	7 (6.5)	11 (6.1)
Accidental exposure	1 (0.9)	0
Cataract operation complication	0	1 (0.6)
Contusion	1 (0.9)	2 (1.1)
Corneal abrasion	0	1 (0.6)
Fall	2 (1.9)	3 (1.7)
Head injury	1 (0.9)	0
Hip fracture	1 (0.9)	0
Joint dislocation	1 (0.9)	2 (1.1)
Joint sprain	0	1 (0.6)
Ligament injury	1 (0.9)	0
Muscle strain	1 (0.9)	0
Periorbital haematoma	0	1 (0.6)
Post procedural discomfort	0	1 (0.6)
Procedural pain	0	2 (1.1)
Skeletal injury	1 (0.9)	0
Upper limb fracture	0	1 (0.6)
Investigations	12 (11.2)	19 (10.6)
Blood glucose increased	1 (0.9)	0
Blood pressure abnormal	0	1 (0.6)
Blood pressure increased	0	3 (1.7)
Blood uric acid increased	0	1 (0.6)
Gamma-glutamyltransferase increased	1 (0.9)	0
Haemoglobin decreased	0	1 (0.6)
Intraocular pressure decreased	1(0.9)	0
Intraocular pressure increased	8 (7.5)	15 (8.4)
Ultrasound doppler normal	1 (0.9)	0
Metabolism and nutrition disorders	3 (2.8)	6 (3.4)

Table 10. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All-Causality)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD n (%)	Established AMD n (%)
Anorexia	0	1 (0.6)
Dyslipidaemia	0	1 (0.6)
Hypercholesterolaemia	0	3 (1.7)
Hyperglycaemia	1 (0.9)	0
Hyperhomocysteinaemia	1 (0.9)	0
Hyperuricaemia	0	1 (0.6)
Hypoglycaemia	0	1 (0.6)
Type 2 diabetes mellitus	1 (0.9)	0
Musculoskeletal and connective tissue disorders	11 (10.3)	17 (9.5)
Arthralgia	2 (1.9)	2 (1.1)
Arthritis	2 (1.9)	3 (1.7)
Back pain	3 (2.8)	2 (1.1)
Bone pain	0	1 (0.6)
Exostosis	1 (0.9)	0
Jaw cyst	0	1 (0.6)
Musculoskeletal chest pain	1 (0.9)	0
Musculoskeletal pain	0	2 (1.1)
Neck pain	0	2 (1.1)
Osteoarthritis	1 (0.9)	4 (2.2)
Osteochondrosis	1 (0.9)	0
Pain in extremity	0	4 (2.2)
Tendonitis	1 (0.9)	0
Torticollis	1 (0.9)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1.9)	4 (2.2)
B-cell lymphoma	1 (0.9)	0
Basal cell carcinoma	1 (0.9)	0
Gastrointestinal tract adenoma	0	1 (0.6)
Neoplasm skin	0	1 (0.6)
Non-small cell lung cancer	0	1 (0.6)
Pancreatic carcinoma	0	1 (0.6)
Nervous system disorders	14 (13.1)	13 (7.3)
Aphasia	1 (0.9)	0
Balance disorder	1 (0.9)	0
Carpal tunnel syndrome	1 (0.9)	1 (0.6)
Dizziness	0	1 (0.6)
Headache	4 (3.7)	7 (3.9)
Hemicephalalgia	0	1 (0.6)
Hyperaesthesia	2 (1.9)	0
Hypertonia	1 (0.9)	0
Hypoaesthesia	1 (0.9)	0
Hyposmia	1 (0.9)	0
Neuralgia	1 (0.9)	0
Neuropathy peripheral	1 (0.9)	0
Post herpetic neuralgia	0	1 (0.6)
Presyncope	1 (0.9)	0
Sciatica	1 (0.9)	1 (0.6)
Transient ischaemic attack	0	1 (0.6)
Trigeminal neuralgia	0	1 (0.6)

Table 10. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All-Causality)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD n (%)	Established AMD n (%)
Visual field defect	1 (0.9)	1 (0.6)
Psychiatric disorders	7 (6.5)	5 (2.8)
Anxiety	1 (0.9)	2 (1.1)
Confusional state	1 (0.9)	0
Depressed mood	1 (0.9)	0
Depression	2 (1.9)	0
Insomnia	0	2 (1.1)
Nervousness	0	1 (0.6)
Reading disorder	1 (0.9)	0
Sleep disorder	1 (0.9)	0
Renal and urinary disorders	1 (0.9)	2 (1.1)
Micturition urgency	0	1 (0.6)
Nephrolithiasis	1 (0.9)	0
Renal cyst	0	1 (0.6)
Reproductive system and breast disorders	2 (1.9)	3 (1.7)
Breast cyst	1 (0.9)	0
Cystocele	0	1 (0.6)
Metrorrhagia	0	1 (0.6)
Prostatitis	1 (0.9)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	8 (7.5)	7 (3.9)
Asthma	0	1 (0.6)
Chronic obstructive pulmonary disease	2 (1.9)	0
Cough	1 (0.9)	4 (2.2)
Dyspnoea	1 (0.9)	0
Emphysema	1 (0.9)	1 (0.6)
Epistaxis	2 (1.9)	0
Oropharyngeal pain	2 (1.9)	0
Pleural effusion	0	1 (0.6)
Skin and subcutaneous tissue disorders	4 (3.7)	3 (1.7)
Acne	0	1 (0.6)
Dermal cyst	0	1 (0.6)
Dermatitis	1 (0.9)	1 (0.6)
Erythema	1 (0.9)	0
Pruritus	1 (0.9)	0
Rash	2 (1.9)	0
Surgical and medical procedures	3 (2.8)	3 (1.7)
Abscess drainage	0	1 (0.6)
Bladder neoplasm surgery	1 (0.9)	0
Carpal tunnel decompression	0	1 (0.6)
Curetting of chalazion	0	1 (0.6)
Gingival operation	1 (0.9)	0
Malignant tumour excision	1 (0.9)	0
Tooth extraction	1 (0.9)	0
Vascular disorders	8 (7.5)	12 (6.7)
Deep vein thrombosis	1 (0.9)	0
Haematoma	0	3 (1.7)
Hypertension	5 (4.7)	10 (5.6)
Orthostatic hypotension	1 (0.9)	0
Phlebitis	1 (0.9)	0

Table 10. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All-Causality)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD n (%)	Established AMD n (%)
Varicose vein	0	1 (0.6)

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (v12.0) coding dictionary applied.
AE = adverse event; AMD = age-related macular degeneration; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events; v = version.

The most frequently reported treatment-emergent ocular AEs (all causalities) by MedDRA preferred term for subjects in the early AMD group were conjunctival hemorrhage (17 [15.9%] of 107 subjects), corneal epithelium defect (10 [9.3%] of 107 subjects), and eye pain (9 [8.4%] of 107 subjects). The most frequently reported treatment-emergent ocular AEs (all causalities) by MedDRA preferred term for subjects in the established AMD group were conjunctival hemorrhage (16 [18.9%] of 179 subjects), VA reduced (10 [5.6%] of 179 subjects, and eye pain and retinal hemorrhage (each reported in 9 [5.0%] of 179 subjects) (Table 10). Treatment-related TEAEs are shown in Table 11.

Table 11. Treatment-Emergent Adverse Events (Treatment-Related)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD (N=107)	Established AMD (N=179)
	n (%)	n (%)
Cardiac disorders	1 (0.9)	0
Atrial fibrillation	1 (0.9)	0
Ear and labyrinth disorders	1 (0.9)	0
Vertigo	1 (0.9)	0
Eye disorders	11 (10.3)	21 (11.7)
Anterior chamber cell	3 (2.8)	2 (1.1)
Anterior chamber flare	1 (0.9)	0
Blepharitis	0	1 (0.6)
Blindness unilateral	1 (0.9)	0
Cataract	0	1 (0.6)
Choroidal neovascularisation	0	2 (1.1)
Conjunctival haemorrhage	0	1 (0.6)
Corneal deposits	0	1 (0.6)
Corneal oedema	1 (0.9)	1 (0.6)
Corneal opacity	0	2 (1.1)
Eye discharge	0	2 (1.1)
Eye disorder	0	1 (0.6)
Eye haemorrhage	1 (0.9)	0
Eye pain	0	1 (0.6)
Iridocyclitis	0	2 (1.1)
Lacrimation increased	0	1 (0.6)
Myodesopsia	3 (2.8)	2 (1.1)
Ocular hyperaemia	0	1 (0.6)
Open angle glaucoma	0	1 (0.6)
Photophobia	1 (0.9)	0
Retinal haemorrhage	1 (0.9)	0
Retinal oedema	1 (0.9)	0
Retinal pigment epithelial tear	1 (0.9)	1 (0.6)
Uveitis	0	2 (1.1)
Vision blurred	0	1 (0.6)
Visual impairment	0	2 (1.1)
Vitreous disorder	0	1 (0.6)
Vitreous opacities	1 (0.9)	0
Vitritis	0	1 (0.6)
Gastrointestinal disorders	1 (0.9)	1 (0.6)
Abdominal pain upper	1 (0.9)	1 (0.6)
Nausea	1 (0.9)	0
Injury, poisoning and procedural complications	0	2 (1.1)
Fall	0	1 (0.6)
Procedural pain	0	1 (0.6)
Investigations	5 (4.7)	8 (4.5)
Intraocular pressure increased	5 (4.7)	8 (4.5)
Nervous system disorders	1 (0.9)	5 (2.8)
Balance disorder	1 (0.9)	0
Cerebrovascular accident	0	3 (1.7)
Headache	0	2 (1.1)
Psychiatric disorders	2 (1.9)	0
Depression	1 (0.9)	0
Reading disorder	1 (0.9)	0
Vascular disorders	1 (0.9)	0

Table 11. Treatment-Emergent Adverse Events (Treatment-Related)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD (N=107)	Established AMD (N=179)
	n (%)	n (%)
Hypertension	1 (0.9)	0

If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is taken. Subjects are counted only once per treatment in each row.
For the TESS algorithm any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline severities are imputed as mild.
Includes data up to 30 days after last dose of study drug.
MedDRA (v12.0) coding dictionary applied
AE = adverse event; AMD = age-related macular degeneration; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events; N = total number of subjects.

SAEs (all causalities) are shown in Table 12. Treatment-related SAEs are summarized in Table 13. Overall, 9 SAEs were considered by the reporting investigator as related to study treatment.

Table 12. Serious Adverse Events by System Organ Class and Preferred Term (All Causality)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD n (%)	Established AMD n (%)
Number (%) of Subjects:		
Evaluable for adverse events	107	179
With adverse events	23 (21.5)	32 (17.9)
Blood and lymphatic system disorders	1 (0.9)	0
Hypochromic anaemia	1 (0.9)	0
Cardiac disorders	6 (5.6)	6 (3.4)
Angina pectoris	3 (2.8)	0
Angina unstable	1 (0.9)	1 (0.6)
Atrial fibrillation	1 (0.9)	2 (1.1)
Bradycardia	1 (0.9)	0
Myocardial infarction	0	1 (0.6)
Myocardial ischaemia	0	1 (0.6)
Palpitations	0	1 (0.6)
Ear and labyrinth disorders	1 (0.9)	0
Vertigo	1 (0.9)	0
Eye disorders	1 (0.9)	7 (3.9)
Cataract	1 (0.9)	1 (0.6)
Eye haemorrhage	0	2 (1.1)
Iridocyclitis	0	1 (0.6)
Open angle glaucoma	0	1 (0.6)
Retinal detachment	0	1 (0.6)
Uveitis	0	2 (1.1)
Visual acuity reduced	0	1 (0.6)
Vitritis	0	1 (0.6)
Gastrointestinal disorders	3 (2.8)	1 (0.6)
Abdominal adhesions	1 (0.9)	0
Duodenal ulcer haemorrhage	0	1 (0.6)
Inguinal hernia	1 (0.9)	0
Intestinal ischaemia	1 (0.9)	0
General disorders and administration site conditions	0	2 (1.1)
Injection site injury	0	1 (0.6)
Oedema peripheral	0	1 (0.6)
Hepatobiliary disorders	0	2 (1.1)
Cholecystitis	0	1 (0.6)
Cholelithiasis	0	1 (0.6)
Infections and infestations	2 (1.9)	6 (3.4)
Cellulitis	0	1 (0.6)
Endophthalmitis	2 (1.9)	2 (1.1)
Gastroenteritis	0	1 (0.6)
Herpes zoster	0	1 (0.6)
Urinary tract infection	0	1 (0.6)
Injury, poisoning and procedural complications	4 (3.7)	1 (0.6)
Fall	1 (0.9)	0
Femur fracture	1 (0.9)	0
Hip fracture	1 (0.9)	0
Lower limb fracture	1 (0.9)	1 (0.6)
Road traffic accident	1 (0.9)	0

Table 12. Serious Adverse Events by System Organ Class and Preferred Term (All Causality)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v12.0) Preferred Term	Early AMD n (%)	Established AMD n (%)
Musculoskeletal and connective tissue disorders	2 (1.9)	2 (1.1)
Back pain	1 (0.9)	0
Intervertebral disc protrusion	1 (0.9)	0
Pain in extremity	0	2 (1.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (4.7)	2 (1.1)
Bladder cancer	0	1 (0.6)
Bladder neoplasm	1 (0.9)	0
Lymphoma	1 (0.9)	0
Non-Hodgkin's lymphoma	1 (0.9)	0
Prostate cancer	2 (1.9)	0
Skin cancer	0	1 (0.6)
Nervous system disorders	1 (0.9)	5 (2.8)
Cerebrovascular accident	0	3 (1.7)
Loss of consciousness	0	1 (0.6)
Neuropathy peripheral	1 (0.9)	0
Transient ischaemic attack	0	1 (0.6)
Reproductive system and breast disorders	0	1 (0.6)
Benign prostatic hyperplasia	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (0.9)	2 (1.1)
Asthma	0	1 (0.6)
Dyspnoea	0	1 (0.6)
Pulmonary embolism	1 (0.9)	0
Skin and subcutaneous tissue disorders	0	1 (0.6)
Dermatitis	0	1 (0.6)
Surgical and medical procedures	1 (0.9)	1 (0.6)
Eye operation	1 (0.9)	0
Meniscus operation	0	1 (0.6)
Vascular disorders	3 (2.8)	1 (0.6)
Arterial thrombosis limb	1 (0.9)	0
Peripheral arterial occlusive disease	1 (0.9)	0
Peripheral ischaemia	0	1 (0.6)
Phlebitis	1 (0.9)	0

Includes data up to 30 days after last dose of study drug.
Subjects are only counted once per treatment for each row'.
MedDRA (v12.0) coding dictionary applied.
AE = adverse event; AMD = age-related macular degeneration; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events; N = total number of subjects.

Table 13. Serious Adverse Events (Treatment-Related)

SAE	AMD Stratum	Event Onset Day[a]	Therapy Stop Day[a]	Study Drug Action Taken	Outcome/ Causality[b]
Uveitis	Est	3	1	Temporarily withdrawn	Recovered/ related
Uveitis	Est	58	NA	Dose not changed	Recovered/ related
Vitritis	Est	58	NA	Dose not changed	Recovered/ related
Cerebrovascular accident	Est	172	167	Permanently withdrawn	Recovered/ related
Vertigo	Early	13	NA	Dose not changed	Recovered/ related
Atrial fibrillation	Early	603	NA	Dose not changed	Recovered/ related
Iridocyclitis	Est	89	NA	Dose not changed	Recovered/ related
Open angle glaucoma	Est	89	NA	Dose not changed	Recovered/ related
Endophthalmitis	Early	134	NA	Dose not changed	Recovered/ related
Cerebrovascular accident	Est	58	46	Permanently withdrawn	Recovering/ related
Cerebrovascular accident	Est	105	86	Permanently withdrawn	Recovered/ related
Retinal disorder	Early	47	1	Permanently withdrawn	Recovered/ related
Retinal hemorrhage	Early	47	1	Permanently withdrawn	Recovered/ related
Retinal detachment	Early	47	1	Permanently withdrawn	Recovered/ related

All subjects were treated in the study eye with pegaptanib 0.3 mg.
AMD = age-related macular degeneration; Est = established; F = female; M = male; NA = not applicable; SAE = serious adverse event.
a. Days relative to the day of starting active therapy (Day 1).
b. Causality as determined by the investigator.

Overall, 4 subjects in the early AMD group discontinued the study (ie, active treatment) due to AEs; none of these AEs was considered related to study drug. Overall, 11 subjects in the established AMD group discontinued the study due to AEs, of which 4 subjects discontinued due to AEs considered as related to study treatment. A summary of subjects who discontinued the study during active treatment or posttreatment is provided in Table 14.

Table 14. Discontinuations Due to Adverse Events

Serial No.	System Organ Class[a]	Preferred Term[a]	Treatment Phase[b]	Adverse Event		
				Study Start Day[c]/ Study Stop Day[c]	Severity/ Outcome	Causality
Early AMD Group						
1	Eye disorders	Retinal hemorrhage	Post	40/ [>40][d]	Moderate/ still present	Disease under study
2	Nervous system disorders	Cerebrovascular accident[e]	Post	407/ [>407] [d]	Severe/ still present	Other illness – high blood pressure and high cholesterol
3	Infections and infestations	Endophthalmitis[e, f]	Active	254/ 260	Severe/ resolved	Injection/procedure related
4	Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Lymphoma[e, f]	Active	329/ [>336] [d]	Severe/ still present	Other illness – lymphoma
5	Eye disorders	Visual acuity reduced[f]	Active	43/ [>43] [d]	Severe/ still present	Other – deterioration due to progression of AMD and loss of 15 lines of vision = 73 letters
6	Cardiac disorders	Myocardial infarction[e]	Post	463/ [>463] [d]	Severe/ still present	Other – cardiac problem
7	Injury, poisoning, and procedural complications	Lower limb fracture[e, f]	Active	258/ 366	Severe/ resolved	Other - unknown
		Lower limb fracture[e, f]	Post	258/ 356	Severe/ resolved	Other - unknown
8	Psychiatric disorders	Depression	Post	420 [>420] [d]	Severe/ still present	Other illness – depression
9	Eye disorders	Detachment of retinal pigment epithelium[e]	Post	47/ [>47] [d]	Moderate/ still present	Study drug
		Retinal disorder[e]	Post	47/ 51	Severe/ resolved	Study drug
		Retinal disorder[e]	Post	51/ [>51] [d]	Moderate/ still present	Study drug
		Retinal hemorrhage[e]	Post	47/ [>47] [d]	Moderate/ still present	Study drug
Established AMD Group						
1	Eye disorders	Visual impairment[f]	Active	47 [>47] [d]	Moderate/ still present	Other illness – worsening AMD
2	Eye disorders	Macular hole[e]	Post	89/ 193	Mild/ resolved	Disease under study
3	Eye disorders	Eye hemorrhage[e, f]	Active	254/ [>254] [d]	Severe/ still present	Injection/procedure related
4	Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Non-small cell lung cancer recurrent[e]	Post	555/ [>555] [d]	Severe/ still present	Other – non-small cell lung cancer
5	Blood and lymphatic system disorders	Anemia[f]	Active	332 [>386] [d]	Mild/ still present	Other illness – anemia
		Anemia[f]	Post	332 [>386] [d]	Mild/ still present	Other illness – anemia
6	Eye disorders	Choroidal neovascularization	Post	561/ [>561] [d]	Severe/ still present	Disease under study

Table 14. Discontinuations Due to Adverse Events

Serial No.	System Organ Class[a]	Preferred Term[a]	Treatment Phase[b]	Adverse Event		
				Study Start Day[c]/ Study Stop Day[c]	Severity/ Outcome	Causality
7	Nervous system disorders	Cerebrovascular accident[e, f]	Active	172/ 210	Severe/ resolved	Study drug
		Cerebrovascular accident[e, f]	Post	172/ 210	Severe/ resolved	Study drug
8	Eye disorders	Eye hemorrhage[e, f]	Active	311/ 345	Severe/ resolved	Other illness – macular degeneration
		Eye hemorrhage[e, f]	Post	311/ 345	Severe/ resolved	Other illness – macular degeneration
9	Injury, poisoning, and procedural complications	Lower limb fracture[e, f]	Active	326/ [>326] [d]	Severe/ still present	Other – traffic accident
10	Nervous system disorders	Cerebrovascular accident[e, f]	Active	58/ [>58] [d]	Severe/ still present	Study drug
11	Cardiac disorders	Palpitationse[f]	Active	21 [>21] [d]	Moderate/ still present	Other – considered as psychogenic by the cardiologist
	Respiratory, thoracic, and mediastinal disorders	Dyspneae[f]	Active	21 [>21] [d]	Severe/ still present	Other – considered as psychogenic by the cardiologist
12	Eye disorders	Vitreous hemorrhage[f]	Active	353/ [>353] [d]	Severe/ still present	Other – disease under study
13	Nervous system disorders	Cerebrovascular accidente[f]	Active	105/ 345	Moderate/ resolved	Study drug
		Cerebrovascular accidente[f]	Post	105/ 345	Moderate/ resolved	Study drug
14	Eye disorders	Choroidal neovascularization[f]	Active	`187 [>187] [d]	Mild/ still present	Study drug

AE = adverse event, AMD = age-related macular degeneration, MedDRA = Medical Dictionary for Regulatory Activities;v = version.

a. MedDRA (v12.0) coding dictionary applied.
b. Treatment at onset relative to treatment at time of AE.
c. Day relative to start of study treatment; first day of treatment = Day 1.
d. Days in brackets were imputed days derived from incomplete data.
e. Considered by the investigator to be a serious adverse event.
f. Treatment-emergent event.

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Eight (7.5%) of 107 subjects in the early AMD group had a temporary discontinuation due to AEs; a dose reduction below the planned 0.3 mg of pegaptanib was not specified in the protocol. None of the AEs were considered as related to study treatment. Fourteen (7.8%) of 179 subjects in the established AMD group had a dose reduction or temporary discontinuation due to AEs, of which 1 AE was considered as related to study treatment.

There were 5 subject deaths reported during the conduct of the study (ie, active treatment); none of the subject deaths were considered as treatment-related. An additional subject death was reported during the post-treatment phase of the study. Overall, 5 of the 6 subjects who died were in the established AMD group.

CONCLUSION: Mean baseline VA by ETDRS was 68.19 letters in the early AMD group and 55.50 letters in the established AMD group. Using the LOCF method, at 1 year, the early group lost 4.30 letters (slightly < 1 line of VA) and the established group lost 5.51 letters (slightly > 1 line of VA). The number of letters lost between the groups was similar despite a difference in measured baseline VA. Subjects with early lesions began the study with better vision than the established lesion group and ended the study with better vision as well. Hence it can be concluded that the efficacy of pegaptanib to preserve vision and visual functioning does not differ numerically between subjects with early CNV lesions and established CNV lesions in this study.

Pegaptanib was shown to be safe in subjects with early and established CNV lesions who received this study treatment.