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

PROTOCOL NO.: A5751009/EOP1009

PROTOCOL TITLE: A Phase II Prospective, Randomized, Double-Masked, Sham-Controlled, Dose-Ranging, Multi-Center Trial to Assess the Effect of Pegaptanib Sodium on Foveal Thickening in Patients With Exudative Subfoveal Age-Related Macular Degeneration (AMD)

Study Centers: Twenty (20) centers took part in the study and randomized subjects: 10 in the United States of America (USA); 2 each in France and Germany, and 1 each in Denmark, Belgium, Italy, Spain, Austria and the United Kingdom (UK).

Study Initiation Date and Final Completion Date: 14 May 2004 to 23 May 2006

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To investigate the effect of pegaptanib sodium (0.3 mg, 1.0 mg) or sham on foveal thickening in subjects with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Secondary Objectives:

- To investigate the relationship between foveal thickening and visual acuity,
- To assess the behavior over time of foveal thickening after administration of pegaptanib.

METHODS

Study Design: This was a prospective, randomized, double-masked, dose-ranging, sham-controlled, multicenter trial in subjects with AMD. Subjects were randomized 1:1:1 to pegaptanib 0.3 mg/eye, 1.0 mg/eye, or sham. Randomization was stratified by center and baseline foveal thickness. Treatment was administered every 6 weeks for the first 12 weeks and subjects were followed without treatment, but with frequent visits through 24 weeks. Foveal thickening was measured by optical coherence tomography (OCT) using center point thickness at designated visits.

At Week 24, subjects resumed treatment every 6 weeks through 1 year. Subjects previously randomized to the 0.3 mg/eye or 1.0 mg/eye continued on the same dose for the remainder of the study. Subjects previously randomized to sham were re-randomized at 24 weeks 1:1 to 0.3 mg/eye or 1.0 mg/eye, stratified by center. A follow-up visit occurred 6 weeks after the last injection at Week 60. A summary of study procedures and evaluations is provided in Table 1, Table 2 and Table 3.

Table 1. Schedule of Activities (Baseline to Week 10)

Visit	Baseline[a]	Day 0	Day 0 +3 Days	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 6 +3 Days	Week 7	Week 8	Week 10
Enrollment/randomization		X											
Pegaptanib sodium injection		X							X				
Informed consent	X												
Medical history	X												
Ophthalmologic history	X												
Physical exam/vital signs[b]	X								X				
Telephone safety check			X							X			
Protocol refraction and visual acuity using ETDRS chart[c]	X			X	X		X		X		X	X	X
Tonometry[c,d]	X	X		X					X		X		
Ophthalmologic examination[c,d]	X	X		X					X		X		
Color fundus photographs (OU)	X												
Fluorescein angiogram (OU)	X												
Optical coherence tomography[c]	X	X		X	X	X	X	X	X		X	X	X
Assessment of adverse events		X	X	X					X	X	X		
12-lead ECG	X												
Serum pregnancy test[e]	X												
Laboratory tests[f]	X												

ALT = alanine amino transferase; AST = aspartame amino transferase; BUN = blood urea nitrogen; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; GGT = gamma glutamyl transferase; OU = both eyes; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cells.

a. Baseline assessments were performed within 1 week prior to the first study drug injection - except pregnancy test, which was performed within 48 hours.
b. Physical examination was performed at Baseline and vital signs were collected at all other time points indicated. Additional physical examinations performed at the Investigator's discretion.
c. Performed OU at Baseline, Week 24, Week 54, and early withdrawal; performed in the study eye at all other time points.
d. Performed prior to each injection and again 30 minutes after the injection for all injection visits; performed only once at all 1-week follow-up visits.
e. Only in females who were not postmenopausal for at least 12 months or surgically sterile.
f. Laboratory tests included hematology (hemoglobin, platelet count, WBC, and differential), renal function (serum creatinine and BUN), hepatic function (serum bilirubin, alkaline phosphatase, GGT, SGOT/AST, and SGPT/ALT), and electrolytes (sodium, potassium, chloride, bicarbonate, calcium, and phosphate).

Table 2. Schedule of Activities (Week 12 to Week 30+3 Days)

Visit	Week 12	Week 12 +3 Days	Week 13	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 24 +3 Days	Week 25	Week 30	Week 30 +3 Days
Enrollment/randomization									X[a]				
Pegaptanib sodium injection	X								X			X	
Physical exam/vital signs[b]	X					X			X			X	
Telephone safety check		X								X			X
Protocol refraction and visual acuity using ETDRS chart[c]	X		X	X	X	X	X	X	X			X	
Tonometry[d c]	X		X			X			X		X	X	
Ophthalmologic examination[d,c]	X		X			X			X		X	X	
Color fundus photographs (OU)									X				
Fluorescein angiogram (OU)									X			X	
Optical coherence tomography[c]	X		X	X	X	X	X	X	X			X	
Assessment of AEs	X	X	X			X			X	X	X	X	X
12-lead ECG													
Laboratory tests[e]						X							

AE = adverse events; ALT = alanine amino transferase; AST = aspartame amino transferase; BUN = blood urea nitrogen; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; GGT = gamma glutamyl transferase; OU = both eyes; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cells.

a. Prior to the injection, all subjects were re-randomized.
b. Physical examination was performed at Baseline and vital signs were to be collected at all other time points indicated. Additional physical examinations performed at the Investigator's discretion.
c. Performed OU at Baseline, Week 24, Week 54, and early withdrawal; performed in the study eye at all other time points.
d. Performed prior to each injection and again 30 minutes after the injection for all injection visits; performed only once at all 1-week follow-up visits.
e. Laboratory tests included hematology (hemoglobin, platelet count, WBC, and differential), renal function (serum creatinine and BUN), hepatic function (serum bilirubin, alkaline phosphatase, GGT, SGOT/AST, and SGPT/ALT), and electrolytes (sodium, potassium, chloride, bicarbonate, calcium, and phosphate).

Table 3. Schedule of Activities (Week 31 to Early Withdrawal)

Visit	Week 31	Week 36	Week 36+3 Days	Week 37	Week 42	Week 42+3 Days	Week 43	Week 48	Week 48+3 Days	Week 49	Week 54	Early Withdrawal
Pegaptanib sodium injection		X			X			X				
Physical exam/vital signs[a]		X			X			X			X	X
Telephone safety check		X	X			X			X			
Protocol refraction and visual acuity using ETDRS chart[b]		X			X			X			X	X
Tonometry[b,c]	X	X		X	X		X	X		X	X	X
Ophthalmologic examination[b,c]	X	X		X	X		X	X		X	X	X
Color fundus photographs (OU)											X	X
Fluorescein angiogram (OU)											X	X
Optical coherence tomography[b]		X			X			X			X	X
Assessment of AEs	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG											X	X
Laboratory tests[d]		X									X	X

AE = adverse events; ALT = alanine amino transferase; AST = aspartame amino transferase; BUN = blood urea nitrogen; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; GGT = gamma glutamyl transferase; OU = both eyes; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cells.

a. Physical examination was performed at Baseline and vital signs were to be collected at all other time points indicated. Additional physical examinations could have been performed at the Investigator's discretion.
b. Performed OU at Baseline, Week 24, Week 54, and early withdrawal; performed in the study eye at all other time points.
c. Must have been performed prior to each injection and again 30 minutes after the injection for all injection visits; performed only once at all 1 week follow-up visits.
d. Laboratory tests included hematology (hemoglobin, platelet count, WBC, and differential), renal function (serum creatinine and BUN), hepatic function (serum bilirubin, alkaline phosphatase, GGT, SGOT/AST, and SGPT/ALT), and electrolytes (sodium, potassium, chloride, bicarbonate, calcium, and phosphate).

Number of Subjects (Planned and Analyzed): Approximately 135 subjects were planned for the study (45 subjects per treatment group). A total of 138 subjects; 20 in USA, 3 in Denmark, 35 in France, 5 in Italy, 10 in Belgium, 8 in the UK, 12 in Spain, 9 in Austria and 36 in Germany were randomized and analyzed (44 subjects in the 0.3 mg cohort, 46 in the 1.0 mg cohort and 48 to sham).

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged ≥50 years with foveal thickness ≥300 μm (measured by OCT center point thickness), best corrected visual acuity in the study eye between 20/40 and 20/320 and better or equal to 20/800 in the fellow eye and subfoveal choroidal neovascularization secondary to AMD, with a total lesion size (including blood, scar/atrophy and neovascularization) of ≤12 disc areas, of which at least 50% must be active CNV.

Exclusion Criteria: Subjects with previous thermal laser therapy, with any subfoveal atrophy or scarring, blood over the fovea, or fibrosis; additionally, no more than 25% of the total lesion size could be made up of scarring or atrophy or previous photodynamic therapy with Visudyne (PDT) in the study eye were excluded from the study. Eyes with predominantly classic lesions (as classified by fluorescein angiographic appearance) may have been enrolled in the trial if, in the clinical judgment of the Investigator, PDT could be deferred for at least 54 weeks after the first study treatment.

Study Treatment: Subjects received an intravitreous injection of 0.3 mg or 1.0 mg pegaptanib or sham administered once every 6 weeks during the first 12 weeks and, following re-randomization, 0.3 mg or 1.0 mg pegaptanib from Weeks 24 to 48. Subjects were randomized 1:1:1 to pegaptanib 0.3 mg, 1.0 mg, or sham. Randomization was stratified by center and baseline foveal thickness (300–399, 400–499, >500 μm or more).

Efficacy and Safety Endpoints:

Primary Efficacy Endpoint: The average effect of treatment on foveal thickening (measured with OCT) during the period between Baseline and 6 weeks post-treatment.

Secondary Efficacy Endpoints:

- Average effect of treatment on foveal thickening (measured by OCT center point thickness) during the period between second and third treatments (6 and 12 weeks),
- Average effect of treatment on foveal thickening at 1, 2, and 3 weeks postbaseline treatment,
- Predictive value of the average effect of treatment on foveal thickening (measured by OCT center point thickness) during the period between Baseline and 6 weeks post-treatment on mean visual acuity at Weeks 24 and 54.

Safety Endpoints:

- All adverse events (AEs) reported, whether deemed related to treatment or not,

- All serious AEs (SAEs), whether deemed related to treatment or not,
- All laboratory abnormalities, whether deemed clinically relevant or not.

Safety Evaluations: Safety was assessed by AE reporting, ophthalmic examination, tonometry, laboratory assessments, and electrocardiograms (ECG) and vital signs.

Statistical Methods:

Intent-to-Treat (ITT) Population: All randomized subjects were included in the ITT, regardless of eligibility status. As far as statistical inferences were concerned, subjects were analyzed in the treatment group and in the stratum to which they were assigned by the randomization.

Safety Population: The safety population consisted of all treated subjects, ie, all subjects who received at least 1 injection of the study drug, regardless of their eligibility for the study. Due to Week 24 re-randomization, treatment groups were considered separately for the 2 study periods: Day 0 to the day before Week 24 and Weeks 24 to 54.

Efficacy analyses were performed on the ITT population. Safety analyses were conducted on the safety population. All summary tables were displayed by treatment groups.

A step-down procedure was used to control the experiment-wise type I error rate of the primary analysis, which consisted of comparing changes in the mean area under the curve (AUC) of retinal thickening over the first 6-week period between treatment groups. The first test compared the dose of 0.3 mg of pegaptanib to sham, using the required nominal significance level (0.001 for the interim analysis, 0.049 for the final analysis). If this test reached statistical significance ($P \leq$ nominal significance level), then the dose of 1.0 mg of pegaptanib was compared with sham at the same nominal significance level.

Secondary analyses consisted of a comparison of changes in the mean AUC of retinal thickening over the second 6-week period (Weeks 6 to 12) between treatment groups; a comparison of changes in retinal thickening at Weeks 1, 2, and 3 between treatment groups; and an estimation of the correlation between changes in mean AUC of retinal thickening over the first 6-week period and visual acuity at 24 and 54 weeks. The change in mean AUC of retinal thickening and changes in retinal thickening were analyzed using an analysis of covariance (ANCOVA) model, which included main effects of treatments and stratification factors, ie, retinal thickening at Baseline.

Clinical AEs were analyzed in terms of their type, incidence, severity, and relationship. The incidence of clinically significant abnormalities for each of the laboratory parameters was presented by treatment group and by baseline assessment (normal or abnormal) in accordance with predetermined criteria for clinically significant laboratory abnormalities. The median was used as the summary statistic of central tendency for presentation of baseline values and changes from Baseline to last assessment.

RESULTS

Subject Disposition and Demography: A total of 138 subjects were enrolled in the study. During the first randomization, 44 subjects were assigned to the 0.3 mg cohort, 46 were assigned to the 1.0 mg cohort, and 48 were assigned to the sham cohort. During the second randomization at Week 24, 62 subjects were assigned to the 0.3 mg cohort and 66 subjects were assigned to the 1.0 mg cohort. Ten (10) subjects who enrolled during the Day 0 to Week 24 period (including 1 subject in the 1.0 mg cohort who never received treatment) did not participate in the Week 24 to Week 54 period.

Table 4 shows the evaluation groups by treatment arm. One (1) subject did not receive any study treatment and was excluded from the safety population. Two (2) subjects in the 0.3 mg cohort and 4 subjects in the 1.0 mg cohort did not participate in the second randomization. Forty-four (44) of the 48 subjects who received sham during the first randomization were re-randomized to receive 0.3 mg (20 subjects) or 1.0 mg (24 subjects).

Table 4. Number of Subjects in Each Evaluation Group

	0.3 mg	1 mg	Sham	All
First Randomization	**(N=44)**	**(N=46)**	**(N=48)**	**(N=138)**
Randomized population	44 (100%)	46 (100%)	48 (100%)	138 (100%)
Intent-to-treat population[a]	44 (100%)	46 (100%)	48 (100%)	138 (100%)
Safety population[b]	44 (100%)	45 (98%)	48 (100%)	137 (99%)
Second Randomization	**(N=62)**	**(N=66)**	**NA**	**(N=128)**
Continued 0.3 mg and 1 mg	42 (68%)	42 (64%)	NA	84 (66%)
Re-randomized sham subjects[a]	20 (32%)	24 (36%)	NA	44 (34%)
Safety population[b]	62 (100%)	66 (100%)	NA	128 (100%)

N = number of subjects per treatment group; NA = not applicable.
a. All randomized subjects.
b. All subjects who received at least 1 study treatment.

Six (6) subjects withdrew from the study during the Day 0 to Week 24 period and 3 subjects withdrew during the Weeks 24 to 54 period. Table 5 shows the reasons for study discontinuation for all subjects. Discontinuations were uncommon. Four (4) subjects in the Day 0 to Week 24 sham cohort discontinued due to AEs, as did 2 subjects in the 0.3 mg cohort during Weeks 24 to 54. Two (2) subjects in the 0.3 mg cohort requested to be withdrawn from the study during the first 24-week period. The majority of subjects (96% from Day 0 to Week 24 and 98% from Weeks 24 to 54) remained on study.

Table 5. Reasons for Discontinuations From Treatment

	0.3 mg	1 mg	Sham	All
Day 0 to Week 24	**N=44**	**N=45**	**N=48**	**N=137**
Adverse event	0	0	4	4
Subject request	2	0	0	2
Total	2 (5%)	0 (0%)	4 (8%)	6 (4%)
Week 24 to Week 54	**N=62**	**N=66[a]**	**NA**	**N=128**
Adverse event	2	0	NA	2
Other	1	0	NA	1
Total	3 (5%)	0 (0%)	NA	3 (2%)

N = number of subjects per treatment group; NA = not applicable.
a. Four (4) subjects in the 1.0 mg dose cohort did not participate in the Week 24 to 54 study period.

Demographic characteristics by treatment cohort for the ITT population are shown in Table 6.

Table 6. Demographic Data (ITT Population)

		0.3 mg N=44	1 mg N=46	Sham N=48	All N=138
Sex	Male	23 (52%)	19 (41%)	20 (42%)	62 (45%)
	Female	21 (48%)	27 (59%)	28 (58%)	76 (55%)
Age	Mean	75.9	74.7	75.1	75.2
	SD	5.5	8.0	5.6	6.5
	Median	76.0	76.0	76.5	76.0
	Range	61 to 84	56 to 91	64 to 87	56 to 91

ITT = intent-to-treat, N = number of subjects per treatment group; SD = standard deviation.

Efficacy Results: The changes in standardized AUC of foveal thickness (center point of grid) from Baseline to Week 6 are shown in Table 7 and for Week 6 to Week 12 are shown in Table 8.

The mean change in retinal thickening from Baseline to Week 6 in the 0.3 mg cohort was not significantly different from the change observed in the sham cohort (-12.7 µm versus -6.75 µm, p=0.6417). The mean change in retinal thickening from Baseline to Week 6 was greater in the 1.0 mg cohort (-40.3 µm) than in the 0.3 mg cohort. There was considerable variability in the retinal thickness measurements, with an overall range of 87 µm to 1002 µm for the baseline measurements and changes from Baseline to Week 6 ranging from -301 µm to 208 µm.

There continued to be changes in retinal thickness from Week 6 to Week 12. The mean change in retinal thickness in the 0.3 mg cohort was -19.9 up to Week 12. There was no statistically significant difference in mean change of retinal thickness from Week 6 to Week 12 between the 0.3 mg cohort and the sham cohort.

Table 7. Changes in Standardized AUC of Foveal Thickness (Center Point of Grid) From Baseline to Week 6 (ITT Population)

Number of Subjects		0.3 mg (N=44)	1 mg (N=46)	Sham (N=48)	All (N=138)
Retinal thickness (center point) at Baseline[a]	Mean	407.8	435.9	420.3	421.5
	SD	118.2	158.6	142.0	140.3
	Median	416.0	378.0	394.0	398.0
	Range	156;717	228;1002	87;833	87;1002
	N	44	46	48	138
Change at Week 6	Mean	-12.7	-40.3	-6.7	-19.5
	SD	73.4	92.2	85.6	84.7
	Median	-2.1	-18.5	3.0	-4.7
	Range	-255;202	-301;208	-290;169	-301;208
	N	44	43	46	133

Upto	Treatment Group	N	Change From Baseline (ANCOVA Model)[b] Mean	LS Mean (SE)	Difference[c]	95% CI	p-Value[d]
Week 6	0.3 mg	44	-12.67	-22.59 (13.63)	-8.24	(-43.18, 26.70)	0.6417
	Sham	46	-6.75	-14.36 (12.98)			

ANCOVA = analysis of covariance; AUC = area under the curve; CI = confidence interval; ITT = intention-to-treat; LS = least square; N = number of subjects per treatment group; SD = standard deviation; SE = standard error.

a. Day 0 data was used as Baseline. If missing, Screening data was used.
b. Adjusted for retinal thickening at Baseline (stratification factor) as a covariate.
c. Difference in LS means between each dose group and sham.
d. The p-values of pairwise comparisons, unadjusted for multiplicity.

Table 8. Changes in Standardized AUC of Foveal Thickness (Center Point of Grid) From Week 6 to Week 12 (ITT Population)

Number of Subjects		0.3 mg (N=44)	1 mg (N=46)	Sham (N=48)	All (N=138)
Retinal thickness (center point) at Week 6	Mean	395.0	391.9	413.3	400.3
	SD	143.2	177.3	140.2	153.2
	Median	396.0	344.0	375.5	370.0
	Range	118;969	98;927	158;798	98;969
	N	44	43	46	133
Change at Week 12	Mean	-19.9	-19.1	-4.8	-14.5
	SD	65.7	81.3	59.6	69.1
	Median	-15.3	-18.3	2.0	-13.0
	Range	-183;167	-393;187	-170;160	-393;187
	N	43	42	44	129

Upto	Treatment Group	N	Change From Week 6 (ANCOVA Model[a])				
			Mean	LS Mean (SE)	Difference[b]	95% CI	p-Value[c]
Week 12	0.3 mg	43	-19.90	-23.10 (11.46)	-15.93	(-45.60, 13.75)	0.2902
	1 mg	42	-19.14	-21.95 (11.40)	-14.78	(-44.59, 15.03)	0.3283
	Sham	44	-4.76	-7.17 (11.12)			

ANCOVA = analysis of covariance; AUC = area under the curve; CI = confidence interval; ITT =intention-to-treat; LS = least square; N = number of subjects per treatment group; SD = standard deviation; SE = standard error.

a. Adjusted for retinal thickening at Baseline (stratification factor) as a covariate.
b. Difference in LS means between each dose group and sham.
c. The p-values of pairwise comparisons, unadjusted for multiplicity.

The changes in standardized AUC of foveal thickness (center point of grid) from Baseline to Week 1, Week 2 and Week 3 are shown in Table 9.

Table 9. Changes in Standardized AUC of Foveal Thickness From Baseline to Weeks 1, 2, and 3 (ITT Population)

	0.3 mg N=44	1 mg N=46	Sham N=48	
Baseline Retinal Thickness				
Mean	407.8	435.9	420.3	
SD	118.2	158.6	142.0	
Median	416.0	378.0	394.0	
Range	156 to 717	228 to 1002	87 to 833	
Change at Week 1				
Mean	-8.2	-16.5	-8.0	Mean change 0.3 mg vs sham: p=0.9465[a]
SD	28.6	39.6	35.9	Mean change 1.0 mg vs sham: p=0.2461[b]
Median	-4.0	-16.0	-1.8	
Range	-75 to 71	-136 to 91	141 to 47	
Change at Week 2				
Mean	-13.1	-20.6	-10.0	0.3 mg vs sham: p=0.7232[a]
SD	37.7	82.3	53.9	1.0 mg vs sham: p=0.3745[b]
Median	-9.8	-16.0	-1.9	
Range	-103 to 80	-214 to 335	-214 to 79	
Change at Week 3				
Mean	-15.0	-34.9	-8.8	0.3 mg vs sham: p=0.5449[a]
SD	44.1	72.5	64.5	1.0 mg vs sham: p=0.0389[b]
Median	-1.2	-13.2	-4.6	
Range	-124 to 77	-257 to 89	-251 to 120	

AUC = area under the curve; ITT = intention-to-treat; N = number of subjects per treatment group; SD = standard deviation; vs = versus.

a. The p-values of pair-wise comparisons.

b. The p-values of pair-wise comparisons, not adjusted for multiplicity.

Changes in visual acuity from Baseline over time for the study eye from Day 0 to Week 24 are presented in Table 10 and from Weeks 24 to 54 in Table 11. No clear correlation was demonstrated between central retinal thickening at Week 6 and visual acuity at Weeks 24 and 54.

Table 10. Summary of Changes in Visual Acuity From Baseline Over Time (Observed Data) - Study Eye (Day 0 to Week 24, ITT Population)

Number of Subjects		0.3 mg N=44	1 mg N=46	Sham N=48	All N=138
Baseline Vision (in letters)	Mean	50.3	52.8	49.1	50.7
	SD	12.0	14.0	13.9	13.4
	Median	52.0	54.0	47.5	53.0
	Range	23;73	25;74	16;71	16;74
	N	44	45	48	137
Change at Week 6	Mean	-0.8	-1.3	-3.4	-1.9
	SD	9.0	9.6	10.6	9.8
	Median	1.0	-0.5	-2.0	-1.0
	Range	-37;15	-44;14	-37;13	-44;15
Change at Week 12	N	44	44	46	134
	Mean	-1.8	-3.9	-3.8	-3.2
	SD	10.8	14.9	12.0	12.6
	Median	0.0	-3.0	-2.0	-2.0
	Range	-31;19	-59;37	-38;21	-59;37
Change at Week 18	N	44	43	46	133
	Mean	-3.1	-5.0	-3.0	-3.7
	SD	12.7	15.5	11.3	13.2
	Median	-2.0	-2.0	-1.0	-2.0
	Range	-37;21	-59;18	-39;17	-59;21
	N	42	42	44	128
Change at Week 24	Mean	-4.5	-6.6	-3.8	-4.9
	SD	15.3	16.2	11.6	14.4
	Median	-1.0	-3.0	-3.0	-2.0
	Range	-60;20	-59;17	-31;21	-60;21
	N	42	41	44	127

ITT = intention-to-treat; N = number of subjects per treatment group; SD = standard deviation.

Table 11. Summary of Changes in Visual Acuity From Baseline Over Time (Observed Data) - Study Eye (Week 24 to Week 54, ITT Population)

Number of Subjects		0.3 mg N=62	1 mg N=66	All Doses N=128
Baseline Vision (in letters)	Mean	50.7	52.5	51.6
	SD	12.3	13.3	12.8
	Median	52.0	53.0	53.0
	Range	23;73	25;74	23;74
	N	62	65	127
Change at Week 24	Mean	-4.2	-5.7	-4.9
	SD	14.1	14.7	14.4
	Median	-1.0	-4.0	-2.0
	Range	-60;20	-59;21	-60;21
	N	62	65	127
Change at Week 30	Mean	-5.5	-7.5	-6.5
	SD	14.7	15.0	14.9
	Median	-3.5	-7.0	-4.0
	Range	-62;26	-59;15	-62;26
	N	62	65	127
Change at Week 36	Mean	-5.8	-9.3	-7.6
	SD	14.3	16.0	15.2
	Median	-3.0	-9.0	-5.0
	Range	-62;21	-59;17	-62;21
	N	62	65	127
Change at Week 42	Mean	-6.5	-9.3	-7.9
	SD	15.3	16.3	15.8
	Median	-2.0	-8.0	-4.0
	Range	-60;19	-59;15	-60;19
	N	60	65	125
Change at Week 48	Mean	-6.6	-8.8	-7.7
	SD	16.3	15.7	16.0
	Median	-2.0	-8.0	-6.0
	Range	-57;22	-59;20	-59;22
	N	60	65	125
Change at Week 54	Mean	-8.3	-9.4	-8.9
	SD	16.4	17.3	16.8
	Median	-2.0	-6.0	-5.5
	Range	-57;16	-59;22	-59;22
	N	59	63	122

ITT = intention-to-treat; N = number of subjects per treatment group; SD = standard deviation.

Safety Results:

Eighty-two percent (82%) of the 44 subjects who received 0.3 mg pegaptanib from Day 0 to Week 24 experienced at least 1 AE, as did 87% of the 45 subjects who received 1.0 mg. Similar incidences of AEs occurred during Weeks 24 to 54 (81% of the 62 subjects in the 0.3 mg cohort and 88% of the 66 subjects in the 1.0 mg cohort). The incidence of AEs in the sham cohort was similar to that observed in the 1.0 mg cohort; 88% of 48 subjects experienced at least 1 AE from Day 0 to Week 24. Table 12 and Table 13 presents the AEs by system organ class (SOC) and preferred term (PT) (all causalities) from Day 0 to Week 24 and Week 24 to Week 54 respectively.

Table 12. Adverse Events by System Organ Class and Preferred Term (All-Causalities) (Day 0 to Week 24) - Safety Population

Number (%) of Subjects With AEs	Pegaptanib Sodium			Sham
System Organ Class and Preferred Term	0.3 mg N=44	1.0 mg N=45	All Doses N=89	N=48
Subjects with at least 1 AE	36 (82%)	39 (87%)	75 (84%)	42 (88%)
Blood and lymphatic system disorders	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Iron deficiency anaemia	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Cardiac disorders	2 (5%)	1 (2%)	3 (3%)	4 (8%)
Arrhythmia NOS	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Atrial fibrillation	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Myocardial infarction	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Palpitations	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Pulmonary oedema NOS	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Angina pectoris	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Atrioventricular block second degree	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Myocardial ischaemia	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Palpitations aggravated	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Sinus tachycardia	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Ear and labyrinth disorders	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Ear pain	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Eye disorders	32 (73%)	34 (76%)	66 (74%)	39 (81%)
Eye pain	9 (20%)	10 (22%)	19 (21%)	10 (21%)
Punctate keratitis	10 (23%)	9 (20%)	19 (21%)	8 (17%)
Vitreous floaters	7 (16%)	6 (13%)	13 (15%)	1 (2%)
Visual acuity reduced	5 (11%)	7 (16%)	12 (13%)	7 (15%)
Eye discharge	3 (7%)	7 (16%)	10 (11%)	1 (2%)
Abnormal sensation in eye	4 (9%)	5 (11%)	9 (10%)	3 (6%)
Macular degeneration	2 (5%)	7 (16%)	9 (10%)	4 (8%)
Blepharitis	5 (11%)	2 (4%)	7 (8%)	0 (0%)
Corneal oedema	4 (9%)	3 (7%)	7 (8%)	3 (6%)
Conjunctival haemorrhage	3 (7%)	3 (7%)	6 (7%)	1 (2%)
Eye redness	3 (7%)	2 (4%)	5 (6%)	4 (8%)
Corneal dystrophy	1 (2%)	3 (7%)	4 (4%)	0 (0%)
Photophobia	2 (5%)	2 (4%)	4 (4%)	1 (2%)
Retinal haemorrhage	2 (5%)	1 (2%)	3 (3%)	3 (6%)
Visual disturbance NOS	0 (0%)	3 (7%)	3 (3%)	1 (2%)
Vitreous opacities	1 (2%)	2 (4%)	3 (3%)	0 (0%)
Anterior chamber inflammation	0 (0%)	2 (4%)	2 (2%)	0 (0%)
Conjunctival oedema	1 (2%)	1 (2%)	2 (2%)	1 (2%)
Eye irritation	1 (2%)	1 (2%)	2 (2%)	2 (4%)
Eyelid ptosis	2 (5%)	0 (0%)	2 (2%)	0 (0%)
Keratopathy NOS	1 (2%)	1 (2%)	2 (2%)	1 (2%)
Lacrimation increased	0 (0%)	2 (4%)	2 (2%)	1 (2%)
Ocular discomfort	1 (2%)	1 (2%)	2 (2%)	0 (0%)
Photopsia	1 (2%)	1 (2%)	2 (2%)	0 (0%)
Retinal scar	0 (0%)	2 (4%)	2 (2%)	3 (6%)
Conjunctival hyperaemia	0 (0%)	1 (2%)	1 (1%)	1 (2%)
Conjunctivitis	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Corneal deposits	0 (0%)	1 (2%)	1 (1%)	1 (2%)
Corneal epithelium defect	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Dry eye NOS	1 (2%)	0 (0%)	1 (1%)	2 (4%)
Eye pruritus	0 (0%)	1 (2%)	1 (1%)	1 (2%)
Glaucoma NOS	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Meibomianitis	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Ocular hypertension	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Retinal oedema	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Retinal pigment epitheliopathy	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Vision blurred	0 (0%)	1 (2%)	1 (1%)	1 (2%)
Vitreous disorder NOS	0 (0%)	1 (2%)	1 (1%)	0 (0%)

Table 12. Adverse Events by System Organ Class and Preferred Term (All-Causalities) (Day 0 to Week 24) - Safety Population

Number (%) of Subjects With AEs	Pegaptanib Sodium			Sham
System Organ Class and Preferred Term	0.3 mg N=44	1.0 mg N=45	All Doses N=89	N=48
Vitreous haemorrhage	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Corneal scar	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Eyelid oedema	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Posterior capsule opacification	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Retinal exudates	0 (0%)	0 (0%)	0 (0%)	2 (4%)
Vitreous detachment	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Gastrointestinal disorders	2 (5%)	0 (0%)	2 (2%)	5 (10%)
Diverticulum NOS	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Intestinal obstruction NOS	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Nausea	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Diverticulitis NOS	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Gastritis NOS	0 (0%)	0 (0%)	0 (0%)	2 (4%)
Hyperacidity	0 (0%)	0 (0%)	0 (0%)	1 (2%)
General disorders and administration site conditions	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Asthenia	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Chest pain	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Fatigue	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Immune system disorders	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Hypersensitivity NOS	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Infections and infestations	4 (9%)	4 (9%)	8 (9%)	5 (10%)
Influenza	2 (5%)	2 (4%)	4 (4%)	1 (2%)
Upper respiratory tract infection NOS	1 (2%)	1 (2%)	2 (2%)	0 (0%)
Keratitis herpetic	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Lower respiratory tract infection NOS	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Urinary tract infection NOS	0 (0%)	1 (2%)	1 (1%)	1 (2%)
Tooth abscess	0 (0%)	0 (0%)	0 (0%)	2 (4%)
Tracheitis NOS	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Injury, poisoning and procedural complications	1 (2%)	1 (2%)	2 (2%)	3 (6%)
Corneal erosion	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Humerus fracture	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Post procedural pain	1 (2%)	0 (0%)	1 (1%)	1 (2%)
Ankle fracture	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Femoral neck fracture	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Ulna fracture	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Investigations	2 (5%)	3 (7%)	5 (6%)	2 (4%)
Intraocular pressure increased	0 (0%)	2 (4%)	2 (2%)	1 (2%)
Blood creatine increased	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Blood urea increased	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Gamma-glutamyltransferase increased	1 (2%)	0 (0%)	1 (1%)	1 (2%)
Heart rate increased	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Metabolism and nutrition disorders	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Diabetes mellitus non-insulin-dependent	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Hyperkalaemia	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Musculoskeletal and connective tissue disorders	0 (0%)	4 (9%)	4 (4%)	1 (2%)
Osteoporosis NOS	0 (0%)	2 (4%)	2 (2%)	0 (0%)
Back pain	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Myalgia	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Neck pain	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Spinal osteoarthritis	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Rheumatoid arthritis	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Squamous cell carcinoma	0 (0%)	0 (0%)	0 (0%)	1 (2%)

Table 12. Adverse Events by System Organ Class and Preferred Term (All-Causalities) (Day 0 to Week 24) - Safety Population

Number (%) of Subjects With AEs	Pegaptanib Sodium			Sham
System Organ Class and Preferred Term	0.3 mg N=44	1.0 mg N=45	All Doses N=89	N=48
Nervous system disorders	0 (0%)	3 (7%)	3 (3%)	2 (4%)
Headache	0 (0%)	2 (4%)	2 (2%)	0 (0%)
Dizziness	0 (0%)	1 (2%)	1 (1%)	1 (2%)
Dystonia	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Psychiatric disorders	1 (2%)	2 (4%)	3 (3%)	2 (4%)
Anxiety	0 (0%)	2 (4%)	2 (2%)	1 (2%)
Nightmare	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Insomnia	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Renal and urinary disorders	2 (5%)	0 (0%)	2 (2%)	1 (2%)
Cystitis NOS	1 (2%)	0 (0%)	1 (1%)	1 (2%)
Renal artery stenosis	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	1 (2%)	4 (9%)	5 (6%)	2 (4%)
Bronchitis NOS	0 (0%)	3 (7%)	3 (3%)	2 (4%)
Cough	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Cough aggravated	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Acute respiratory distress syndrome	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Skin and subcutaneous tissue disorders	2 (5%)	2 (4%)	4 (4%)	1 (2%)
Contusion	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Cutis laxa	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Dry skin	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Eczema	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Rash NOS	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Pruritus	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Surgical and medical procedures	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Cataract extraction	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Vascular disorders	2 (5%)	5 (11%)	7 (8%)	0 (0%)
Hypertension NOS	1 (2%)	2 (4%)	3 (3%)	0 (0%)
Hypertension aggravated	1 (2%)	1 (2%)	2 (2%)	0 (0%)
Deep vein thrombosis	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Thrombosis	0 (0%)	1 (2%)	1 (1%)	0 (0%)

AEs summarized using MedDRA (Version 5.1) terms.
Non SAE and SAE results are not separated out.
AE = adverse events; MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects per treatment group; NOS = not otherwise specified, SAE = serious adverse event.

Table 13. Adverse Events by System Organ Class and Preferred Term (All Causalities) (Week 24 to Week 54, Safety Population)

Number of Subjects (%) With AEs	Pegaptanib Sodium		
System Organ Class and Preferred Term	0.3 mg N=62	1.0 mg N=66	All Doses N=128
Subjects with at least 1 AE	50 (81%)	58 (88%)	108 (84%)
Blood and lymphatic system disorders	1 (2%)	1 (2%)	2 (2%)
Thrombocytopenia	1 (2%)	1 (2%)	2 (2%)
Cardiac disorders	2 (3%)	3 (5%)	5 (4%)
Arrhythmia NOS	0 (0%)	1 (2%)	1 (1%)
Atrial fibrillation	0 (0%)	1 (2%)	1 (1%)
Cardiomyopathy NOS	1 (2%)	0 (0%)	1 (1%)
Coronary artery disease aggravated	1 (2%)	0 (0%)	1 (1%)
Sinus bradycardia	0 (0%)	1 (2%)	1 (1%)
Endocrine disorders	1 (2%)	0 (0%)	1 (1%)
Thyroid disorder NOS	1 (2%)	0 (0%)	1 (1%)
Eye disorders	48 (77%)	54 (82%)	102 (80%)
Punctate keratitis	18 (29%)	20 (30%)	38 (30%)
Eye pain	14 (23%)	15 (23%)	29 (23%)
Vitreous floaters	14 (23%)	9 (14%)	23 (18%)
Visual acuity reduced	4 (6%)	12 (18%)	16 (13%)
Corneal oedema	4 (6%)	9 (14%)	13 (10%)
Eye redness	5 (8%)	8 (12%)	13 (10%)
Conjunctival haemorrhage	7 (11%)	5 (8%)	12 (9%)
Eye discharge	4 (6%)	6 (9%)	10 (8%)
Vitreous disorder NOS	6 (10%)	4 (6%)	10 (8%)
Abnormal sensation in eye	4 (6%)	5 (8%)	9 (7%)
Blepharitis	4 (6%)	5 (8%)	9 (7%)
Macular degeneration	3 (5%)	6 (9%)	9 (7%)
Corneal dystrophy	2 (3%)	6 (9%)	8 (6%)
Retinal haemorrhage	5 (8%)	3 (5%)	8 (6%)
Photophobia	4 (6%)	3 (5%)	7 (5%)
Photopsia	2 (3%)	4 (6%)	6 (5%)
Vitreous opacities	3 (5%)	3 (5%)	6 (5%)
Ocular hypertension	1 (2%)	4 (6%)	5 (4%)
Retinal pigment epitheliopathy	2 (3%)	3 (5%)	5 (4%)
Retinal scar	2 (3%)	3 (5%)	5 (4%)
Anterior chamber inflammation	3 (5%)	1 (2%)	4 (3%)
Eye pruritus	1 (2%)	3 (5%)	4 (3%)
Vision blurred	2 (3%)	2 (3%)	4 (3%)
Cataract	1 (2%)	2 (3%)	3 (2%)
Retinal depigmentation	1 (2%)	2 (3%)	3 (2%)
Conjunctival hyperaemia	0 (0%)	2 (3%)	2 (2%)
Conjunctival oedema	0 (0%)	2 (3%)	2 (2%)
Corneal deposits	1 (2%)	1 (2%)	2 (2%)
Dermatitis eyelid	1 (2%)	1 (2%)	2 (2%)
Erythema of eyelid	1 (2%)	1 (2%)	2 (2%)
Keratitis	1 (2%)	1 (2%)	2 (2%)
Lacrimation increased	1 (2%)	1 (2%)	2 (2%)
Visual disturbance NOS	1 (2%)	1 (2%)	2 (2%)
Arcus lipoides	1 (2%)	0 (0%)	1 (1%)
Chorioretinal scar	0 (0%)	1 (2%)	1 (1%)
Conjunctivitis allergic	0 (0%)	1 (2%)	1 (1%)
Corneal disorder NOS	1 (2%)	0 (0%)	1 (1%)
Corneal opacity	1 (2%)	0 (0%)	1 (1%)
Diplopia	0 (0%)	1 (2%)	1 (1%)
Endophthalmitis	1 (2%)	0 (0%)	1 (1%)
Eye irritation	0 (0%)	1 (2%)	1 (1%)
Eye swelling	1 (2%)	0 (0%)	1 (1%)
Eyelid disorder NOS	0 (0%)	1 (2%)	1 (1%)

Table 13. Adverse Events by System Organ Class and Preferred Term (All Causalities) (Week 24 to Week 54, Safety Population)

Number of Subjects (%) With AEs	Pegaptanib Sodium		
System Organ Class and Preferred Term	**0.3 mg N=62**	**1.0 mg N=66**	**All Doses N=128**
Eyelid oedema	0 (0%)	1 (2%)	1 (1%)
Eyelids pruritus	0 (0%)	1 (2%)	1 (1%)
Keratoconjunctivitis sicca	1 (2%)	0 (0%)	1 (1%)
Maculopathy	0 (0%)	1 (2%)	1 (1%)
Ocular discomfort	0 (0%)	1 (2%)	1 (1%)
Pupillary deformity	1 (2%)	0 (0%)	1 (1%)
Retinal degeneration	0 (0%)	1 (2%)	1 (1%)
Retinal neovascularisation	1 (2%)	0 (0%)	1 (1%)
Retinal tear	0 (0%)	1 (2%)	1 (1%)
Retinoschisis NOS	1 (2%)	0 (0%)	1 (1%)
Vitreous haemorrhage	0 (0%)	1 (2%)	1 (1%)
Gastrointestinal disorders	3 (5%)	2 (3%)	5 (4%)
Gastric ulcer	1 (2%)	0 (0%)	1 (1%)
Gastrooesophageal reflux disease	0 (0%)	1 (2%)	1 (1%)
Haemorrhoids	1 (2%)	0 (0%)	1 (1%)
Hyperacidity	1 (2%)	0 (0%)	1 (1%)
Nausea	0 (0%)	1 (2%)	1 (1%)
General disorders and administration site conditions	1 (2%)	2 (3%)	3 (2%)
Chest pain	1 (2%)	0 (0%)	1 (1%)
Fatigue	0 (0%)	1 (2%)	1 (1%)
Oedema peripheral	0 (0%)	1 (2%)	1 (1%)
Immune system disorders	2 (3%)	0 (0%)	2 (2%)
Seasonal allergy	2 (3%)	0 (0%)	2 (2%)
Infections and infestations	4 (6%)	3 (5%)	7 (5%)
Pneumonia NOS	0 (0%)	2 (3%)	2 (2%)
Herpes simplex	1 (2%)	0 (0%)	1 (1%)
Herpes zoster	1 (2%)	0 (0%)	1 (1%)
Hordeolum	1 (2%)	0 (0%)	1 (1%)
Sinusitis NOS	0 (0%)	1 (2%)	1 (1%)
Upper respiratory tract infection NOS	1 (2%)	0 (0%)	1 (1%)
Injury, poisoning and procedural complications	3 (5%)	0 (0%)	3 (2%)
Corneal erosion	1 (2%)	0 (0%)	1 (1%)
Ear injury	1 (2%)	0 (0%)	1 (1%)
Limb hyperextension	1 (2%)	0 (0%)	1 (1%)
Investigations	9 (15%)	3 (5%)	12 (9%)
Intraocular pressure increased	5 (8%)	3 (5%)	8 (6%)
Blood urea increased	2 (3%)	0 (0%)	2 (2%)
QRS axis abnormal	1 (2%)	0 (0%)	1 (1%)
Transaminases increased	1 (2%)	0 (0%)	1 (1%)
Metabolism and nutrition disorders	3 (5%)	3 (5%)	6 (5%)
Diabetes mellitus non-insulin-dependent	0 (0%)	2 (3%)	2 (2%)
Anorexia	1 (2%)	0 (0%)	1 (1%)
Hypercholesterolaemia aggravated	0 (0%)	1 (2%)	1 (1%)
Iron deficiency	1 (2%)	0 (0%)	1 (1%)
Lactose intolerance	1 (2%)	0 (0%)	1 (1%)
Musculoskeletal and connective tissue disorders	4 (6%)	3 (5%)	7 (5%)
Arthralgia	1 (2%)	1 (2%)	2 (2%)
Arthritis NOS	0 (0%)	1 (2%)	1 (1%)
Back pain	1 (2%)	0 (0%)	1 (1%)
Osteoarthritis NOS	1 (2%)	0 (0%)	1 (1%)
Pain in limb	0 (0%)	1 (2%)	1 (1%)
Polymyalgia	1 (2%)	0 (0%)	1 (1%)
Nervous system disorders	4 (6%)	2 (3%)	6 (5%)
Headache	1 (2%)	2 (3%)	3 (2%)
Sciatica	2 (3%)	0 (0%)	2 (2%)

Table 13. Adverse Events by System Organ Class and Preferred Term (All Causalities) (Week 24 to Week 54, Safety Population)

Number of Subjects (%) With AEs	Pegaptanib Sodium		
System Organ Class and Preferred Term	**0.3 mg N=62**	**1.0 mg N=66**	**All Doses N=128**
Cerebral infarction	1 (2%)	0 (0%)	1 (1%)
Psychiatric disorders	2 (3%)	1 (2%)	3 (2%)
Anxiety	0 (0%)	1 (2%)	1 (1%)
Depression	1 (2%)	0 (0%)	1 (1%)
Depression aggravated	1 (2%)	0 (0%)	1 (1%)
Renal and urinary disorders	0 (0%)	1 (2%)	1 (1%)
Cystitis NOS	0 (0%)	1 (2%)	1 (1%)
Respiratory, thoracic and mediastinal disorders	6 (10%)	4 (6%)	10 (8%)
Nasopharyngitis	3 (5%)	2 (3%)	5 (4%)
Bronchitis NOS	0 (0%)	2 (3%)	2 (2%)
Cough	1 (2%)	0 (0%)	1 (1%)
Laryngitis NOS	1 (2%)	0 (0%)	1 (1%)
Pharyngitis	1 (2%)	0 (0%)	1 (1%)
Skin and subcutaneous tissue disorders	0 (0%)	2 (3%)	2 (2%)
Alopecia	0 (0%)	1 (2%)	1 (1%)
Contusion	0 (0%)	1 (2%)	1 (1%)
Surgical and medical procedures	1 (2%)	0 (0%)	1 (1%)
Coronary revascularisation	1 (2%)	0 (0%)	1 (1%)
Vascular disorders	0 (0%)	3 (5%)	3 (2%)
Hypertension NOS	0 (0%)	2 (3%)	2 (2%)
Hypotension NOS	0 (0%)	1 (2%)	1 (1%)

AEs summarized using MedDRA (Version 5.1) terms.
Non SAE and SAE results are not separated out.
AE = adverse event; MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects per treatment group; NOS = not otherwise specified, SAE = serious adverse event.

The AEs by SOC and PT related to injection/procedure from Day 0 to Week 24 and Week 24 to Week 54 are presented in Table 14 and Table 15 respectively. Table 16 and Table 17 presents the AEs related to drug therapy from Day 0 to Week 24 and Week 24 to Week 54 respectively.

Table 14. Adverse Events by System Organ Class and Preferred Term (Injection/Procedure Related) (Day 0 to Week 24, Safety Population)

Number (%) of Subjects With AEs: System Organ Class and Preferred Term	Pegaptanib Sodium			Sham
	0.3 mg N=44	1.0 mg N=45	All Doses N=89	N=48
Subjects with at least 1 AE	26 (59%)	27 (60%)	53 (60%)	24 (50%)
Eye disorders	26 (59%)	25 (56%)	51 (57%)	24 (50%)
Eye pain	9 (20%)	10 (22%)	19 (21%)	10 (21%)
Punctate keratitis	9 (20%)	9 (20%)	18 (20%)	8 (17%)
Eye discharge	3 (7%)	7 (16%)	10 (11%)	1 (2%)
Abnormal sensation in eye	3 (7%)	5 (11%)	8 (9%)	3 (6%)
Corneal oedema	4 (9%)	3 (7%)	7 (8%)	3 (6%)
Conjunctival haemorrhage	3 (7%)	3 (7%)	6 (7%)	1 (2%)
Vitreous floaters	4 (9%)	2 (4%)	6 (7%)	0 (0%)
Eye redness	3 (7%)	2 (4%)	5 (6%)	3 (6%)
Photophobia	2 (5%)	2 (4%)	4 (4%)	1 (2%)
Anterior chamber inflammation	0 (0%)	2 (4%)	2 (2%)	0 (0%)
Conjunctival oedema	1 (2%)	1 (2%)	2 (2%)	1 (2%)
Eye irritation	1 (2%)	1 (2%)	2 (2%)	1 (2%)
Lacrimation increased	0 (0%)	2 (4%)	2 (2%)	1 (2%)
Ocular discomfort	1 (2%)	1 (2%)	2 (2%)	0 (0%)
Vitreous opacities	1 (2%)	1 (2%)	2 (2%)	0 (0%)
Blepharitis	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Conjunctival hyperaemia	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Dry eye NOS	1 (2%)	0 (0%)	1 (1%)	1 (2%)
Eye pruritus	0 (0%)	1 (2%)	1 (1%)	1 (2%)
Macular degeneration	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Ocular hypertension	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Vision blurred	0 (0%)	1 (2%)	1 (1%)	1 (2%)
Visual disturbance NOS	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Vitreous disorder NOS	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Immune system disorders	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Hypersensitivity NOS	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Investigations	0 (0%)	2 (4%)	2 (2%)	0 (0%)
Intraocular pressure increased	0 (0%)	2 (4%)	2 (2%)	0 (0%)
Nervous system disorders	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Headache	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Psychiatric disorders	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Nightmare	1 (2%)	0 (0%)	1 (1%)	0 (0%)

AEs summarized using MedDRA (Version 5.1) terms.
Non SAE and SAE results are not separated out.
AE = adverse event; MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects per treatment group; NOS = not otherwise specified, SAE = serious adverse event.

Table 15. Adverse Events by System Organ Class and Preferred Term (Injection/Procedure Related) (Week 24 to Week 54, Safety Population)

Number (%) of Subjects With AEs	Pegaptanib Sodium		
System Organ Class and Preferred Term	0.3 mg N=62	1.0 mg N=66	All Doses N=128
Subjects with at least 1 AE	42 (68%)	43 (65%)	85 (66%)
Eye disorders	40 (65%)	41 (62%)	81 (63%)
Punctate keratitis	17 (27%)	18 (27%)	35 (27%)
Eye pain	14 (23%)	15 (23%)	29 (23%)
Eye redness	5 (8%)	8 (12%)	13 (10%)
Conjunctival haemorrhage	7 (11%)	5 (8%)	12 (9%)
Corneal oedema	3 (5%)	8 (12%)	11 (9%)
Vitreous floaters	8 (13%)	3 (5%)	11 (9%)
Eye discharge	4 (6%)	6 (9%)	10 (8%)
Abnormal sensation in eye	4 (6%)	5 (8%)	9 (7%)
Vitreous disorder NOS	5 (8%)	4 (6%)	9 (7%)
Photophobia	3 (5%)	3 (5%)	6 (5%)
Vitreous opacities	2 (3%)	2 (3%)	4 (3%)
Vision blurred	2 (3%)	1 (2%)	3 (2%)
Anterior chamber inflammation	2 (3%)	0 (0%)	2 (2%)
Eye pruritus	1 (2%)	1 (2%)	2 (2%)
Keratitis	1 (2%)	1 (2%)	2 (2%)
Ocular hypertension	0 (0%)	2 (3%)	2 (2%)
Blepharitis	1 (2%)	0 (0%)	1 (1%)
Conjunctival oedema	0 (0%)	1 (2%)	1 (1%)
Corneal disorder NOS	1 (2%)	0 (0%)	1 (1%)
Corneal dystrophy	1 (2%)	0 (0%)	1 (1%)
Diplopia	0 (0%)	1 (2%)	1 (1%)
Endophthalmitis	1 (2%)	0 (0%)	1 (1%)
Erythema of eyelid	1 (2%)	0 (0%)	1 (1%)
Eye irritation	0 (0%)	1 (2%)	1 (1%)
Eye swelling	1 (2%)	0 (0%)	1 (1%)
Lacrimation increased	1 (2%)	0 (0%)	1 (1%)
Ocular discomfort	0 (0%)	1 (2%)	1 (1%)
Photopsia	0 (0%)	1 (2%)	1 (1%)
Retinal haemorrhage	1 (2%)	0 (0%)	1 (1%)
Retinoschisis NOS	1 (2%)	0 (0%)	1 (1%)
Visual acuity reduced	1 (2%)	0 (0%)	1 (1%)
Vitreous haemorrhage	0 (0%)	1 (2%)	1 (1%)
General disorders and administration site conditions	0 (0%)	1 (2%)	1 (1%)
Fatigue	0 (0%)	1 (2%)	1 (1%)
Investigations	3 (5%)	2 (3%)	5 (4%)
Intraocular pressure increased	3 (5%)	2 (3%)	5 (4%)
Nervous system disorders	0 (0%)	1 (2%)	1 (1%)
Headache	0 (0%)	1 (2%)	1 (1%)

AEs were summarized using MedDRA (Version 5.1) terms.
Non SAE and SAE results are not separated out.
AE = adverse events, MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects per treatment group; NOS = not otherwise specified; SAE = serious adverse event.

Table 16. Adverse Events by System Organ Class and Preferred Term (Study Therapy Related) (Day 0 to Week 24, Safety Population)

Number (%) of Subjects With AEs System Organ Class and Preferred Term	Pegaptanib Sodium 0.3 mg N=44	Pegaptanib Sodium 1.0 mg N=45	Pegaptanib Sodium All doses N=89	Sham N=48
Subjects with at least 1 AE	2 (5%)	3 (7%)	5 (6%)	0 (0%)
Eye disorders	1 (2%)	3 (7%)	4 (4%)	0 (0%)
Vitreous floaters	1 (2%)	2 (4%)	3 (3%)	0 (0%)
Corneal dystrophy	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Retinal scar	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Gastrointestinal disorders	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Nausea	1 (2%)	0 (0%)	1 (1%)	0 (0%)

AEs summarized using MedDRA (Version 5.1) terms.
Non SAE and SAE results are not separated out.
AE = adverse events, MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects per treatment group, SAE = serious adverse event.

Table 17. Adverse Events by System Organ Class and Preferred Term (Study Therapy Related) (Week 24 to Week 54, Safety Population)

Number (%) of Subjects With AEs System Organ Class and Preferred Term	Pegaptanib Sodium 0.3 mg N=62	Pegaptanib Sodium 1.0 mg N=66	Pegaptanib Sodium All Doses N=128
Subjects with at least 1 AE	9 (15%)	6 (9%)	15 (12%)
Eye disorders	8 (13%)	5 (8%)	13 (10%)
Vitreous floaters	4 (6%)	3 (5%)	7 (5%)
Vitreous opacities	2 (3%)	1 (2%)	3 (2%)
Punctate keratitis	1 (2%)	1 (2%)	2 (2%)
Retinal scar	2 (3%)	0 (0%)	2 (2%)
Photophobia	1 (2%)	0 (0%)	1 (1%)
Vitreous disorder NOS	1 (2%)	0 (0%)	1 (1%)
Investigations	1 (2%)	1 (2%)	2 (2%)
Intraocular pressure increased	1 (2%)	1 (2%)	2 (2%)

AEs were summarized using MedDRA (Version 5.1) terms.
Non SAE and SAE results are not separated out.
AEs = adverse events, MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects per treatment group; NOS = not otherwise specified, SAE = serious adverse event.

Summaries of SAEs are shown in Table 18 for Day 0 to Week 24 and Table 19 Weeks 24 to Week 54.

Table 18. Summary of Serious Adverse Events by SOC and Preferred Term (All Causalities) – Day 0 to Week 24 (Safety Population)

System Organ Class Preferred Term	Pegaptanib Sodium			Sham
	0.3 mg N=44	1.0 mg N=45	All Doses N=89	N=48
Subjects with at least 1 adverse event	3 (7%)	3 (7%)	6 (7%)	6 (13%)
Cardiac disorders	0 (0%)	1 (2%)	1 (1%)	3 (6%)
Atrial fibrillation	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Angina pectoris	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Myocardial ischaemia	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Palpitations aggravated	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Infections and infestations	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Lower respiratory tract infection NOS	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Injury, poisoning and procedural complications	1 (2%)	0 (0%)	1 (1%)	2 (4%)
Humerus fracture	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Ankle fracture	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Femoral neck fracture	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Nervous system disorders	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Dizziness	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Renal and urinary disorders	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Renal artery stenosis	1 (2%)	0 (0%)	1 (1%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Acute respiratory distress syndrome	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Vascular disorders	1 (2%)	1 (2%)	2 (2%)	0 (0%)
Deep vein thrombosis	0 (0%)	1 (2%)	1 (1%)	0 (0%)
Hypertension NOS	1 (2%)	0 (0%)	1 (1%)	0 (0%)

Adverse events were summarized using MedDRA (Version 5.1) terms.
MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects per treatment group;
NOS = not otherwise specified; SOC = system organ class.

Table 19. Summary of Serious Adverse Events by SOC and Preferred Term (All Causalities) Week 24 to Week 54

System Organ Class and Preferred Term	Pegaptanib Sodium		
	0.3 mg N=62	1.0 mg N=66	All Doses N=128
Subjects with at least one adverse event	8 (13%)	2 (3%)	10 (8%)
Cardiac disorders	1 (2%)	1 (2%)	2 (2%)
Atrial fibrillation	0 (0%)	1 (2%)	1 (1%)
Cardiomyopathy NOS	1 (2%)	0 (0%)	1 (1%)
Endocrine disorders	1 (2%)	0 (0%)	1 (1%)
Thyroid disorder NOS	1 (2%)	0 (0%)	1 (1%)
Eye disorders	1 (2%)	0 (0%)	1 (1%)
Endophthalmitis	1 (2%)	0 (0%)	1 (1%)
Gastrointestinal disorders	0 (0%)	1 (2%)	1 (1%)
Nausea	0 (0%)	1 (2%)	1 (1%)
General disorders/administration site conditions	1 (2%)	0 (0%)	1 (1%)
Chest pain	1 (2%)	0 (0%)	1 (1%)
Infections and infestations	0 (0%)	1 (2%)	1 (1%)
Pneumonia NOS	0 (0%)	1 (2%)	1 (1%)
Metabolism and nutrition disorders	2 (3%)	0 (0%)	2 (2%)
Anorexia	1 (2%)	0 (0%)	1 (1%)
Lactose intolerance	1 (2%)	0 (0%)	1 (1%)
Musculoskeletal/connective tissue disorders	2 (3%)	0 (0%)	2 (2%)
Osteoarthritis NOS	1 (2%)	0 (0%)	1 (1%)
Polymyalgia	1 (2%)	0 (0%)	1 (1%)
Nervous system disorders	1 (2%)	0 (0%)	1 (1%)
Cerebral infarction	1 (2%)	0 (0%)	1 (1%)
Psychiatric disorders	1 (2%)	0 (0%)	1 (1%)
Depression	1 (2%)	0 (0%)	1 (1%)
Surgical and medical procedures	1 (2%)	0 (0%)	1 (1%)
Coronary revascularisation	1 (2%)	0 (0%)	1 (1%)

Adverse events were summarized using MedDRA (Version 5.1) terms.
MedDRA = Medical Dictionary of Regulatory Activities; N = number of subjects per treatment group; NOS = not otherwise specified; SOC = system organ class.

No SAE that occurred during the Day 0 to Week 24 period was considered related to the injection/procedure. Only 1 SAE during the Weeks 24 to 54 period (endophthalmitis in 1 subject) was considered related to the injection/procedure; the subject recovered without sequelae and her subsequent visual acuity was within 1 line of the acuity before the event occurred. No SAE was considered related to study therapy.

During the study, 6 subjects discontinued due to AEs: 4 subjects during the Day 0 to Week 24 period (all in the sham cohort) and 2 subjects during the Weeks 24 to 54 period (both in the 0.3 mg cohort). Only 1 subject discontinued due an AE considered related to the injection/procedure (endophthalmitis). No subject discontinued due to an AE considered related to study therapy (Table 20).

Table 20. Adverse Events Leading to Study Discontinuation

Subject Serial Number	Dose group	Adverse Event	Severity	Relationship
Day 0 to Week 24[a]				
1	Sham	Visual acuity reduced	Moderate	Not related
2	Sham	Acute respiratory distress syndrome	Severe	Not related
3	Sham	Myocardial ischaemia	Severe	Not related
Week 24 to Week 54				
4	0.3 mg	Endophthalmitis	Moderate	Related to injection/procedure
5	0.3 mg	Thyroid disorder NOS	Severe	Not related
		Anorexia	Severe	Not related
		Depression	Severe	Not related

IOP = intra-ocular pressure, NOS = not otherwise specified.

a. One (1) additional subject, in the sham cohort discontinued due to an adverse event (IOP increased) but, because the event for which the subject was discontinued was not treatment-emergent (the onset of the event was prior to the first study treatment), therefore, it was not included.

Four (4) subjects died during the study: 2 died during the Day 0 to Week 24 period (both in the sham cohort), 1 due to acute respiratory distress and the other due to myocardial ischemia; and 2 died during the Weeks 24 to 54 period (both in the 0.3 mg cohort), 1 due to anorexia and the other due to cardiomyopathy. None of the events leading to death were considered related to the injection/procedure or to the study therapy.

There were no findings in relation to laboratory tests or ECG results that were suggestive of a relationship to treatment with pegaptanib. Assessment of cataract in phakic subjects did not suggest pegaptanib injections were associated with cataract progression.

Small increases in mean intraocular pressure (IOP) were noted immediately after intravitreous injections. Increases in mean IOP were transient, and returns to baseline levels were seen within 1 week of injection. There was no dose relationship observed, and no evidence of a persistent increase in IOP. No subject experienced increases in IOP to ≥35 mmHg during the Day 0 to Week 24 period, and only 1 pegaptanib-treated subject (1%) experienced such an increase during Weeks 24 to 54. No subject underwent paracentesis or received concomitant treatment for increased IOP starting on an injection day in either portion of the study. There were no discontinuations due to increased IOP.

CONCLUSIONS:

- There was no significant difference in the mean central retinal thickening between the 0.3 mg and sham cohorts between Baseline and Week 6 (-12.7 μm versus -6.75 μm, P=0.6417).

- The difference from Baseline to Week 6 in the mean central retinal thickening was greater in the 1.0 mg cohort (-40.3 μm) than in the 0.3 mg cohort.

- There was considerable variability in retinal thickness measurements.

- No clear correlation existed between central retinal thickening at Week 6 and visual acuity at Weeks 24 and 54.

- There was no evidence of specific systemic safety concerns.

- AEs were primarily ocular in nature, mild, and predictable, with the most common being eye pain and punctate keratitis.

- Throughout either study period, no single type of SAE occurred in >1 subject and only 1 SAE (endophthalmitis) was considered related to the injection/procedure and resulted in discontinuation.

- There were no findings in relation to laboratory test or ECG results that were suggestive of a relationship to treatment with pegaptanib.

- Assessment of cataract in phakic subjects did not suggest pegaptanib injections were associated with cataract progression.

- Small increases in mean IOP noted immediately after intravitreous injections were transient, not dose related, and returned to baseline levels within 1 week of injection.