

Pegaptanib Sodium for Neovascular Age-Related Macular Degeneration

Two-Year Safety Results of the Two Prospective, Multicenter, Controlled Clinical Trials

VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group*

Objective: To evaluate the safety of pegaptanib sodium injection, a specific vascular endothelial growth factor (VEGF) antagonist, in the treatment of neovascular age-related macular degeneration (AMD) during 2 years of therapy.

Design: Two concurrent, prospective, randomized, multicenter, double-masked, sham-controlled studies.

Methods: Patients with all angiographic choroidal neovascularization lesion compositions of AMD received either intravitreal pegaptanib sodium (0.3 mg, 1 mg, 3 mg) or sham injections every 6 weeks for 54 weeks. Those initially assigned to pegaptanib were re-randomized (1:1) to continue or discontinue therapy for 48 more weeks; sham-treated patients were re-randomized (1:1:1:1) to continue sham, discontinue, or receive one of the pegaptanib doses.

Main Outcome Measures: All reported adverse events, serious adverse events, and deaths.

Participants: In year 1, 1190 subjects received at least one study treatment (0.3 mg, n = 295; 1 mg, n = 301; 3 mg, n = 296; sham, n = 298); 7545 intravitreal injections of pegaptanib were administered. In year 2, 425 subjects (0.3 mg, n = 128; 1 mg, n = 126; 3 mg, n = 120; sham, n = 51) continued the same masked treatment as in year 1 and received at least one study treatment in year 2; 2663 intravitreal injections of pegaptanib were administered in these subjects.

Results: All doses of pegaptanib were well tolerated. The most common ocular adverse events were transient, mild to moderate in intensity, and attributed to the injection preparation and procedure. There was no evidence of an increase in deaths, in events associated with systemic VEGF inhibition (e.g., hypertension, thromboembolic events, serious hemorrhagic events), or in severe ocular inflammation, cataract progression, or glaucoma in pegaptanib-treated patients relative to sham-treated patients. In year 1, serious injection-related complications included endophthalmitis (12 events, 0.16%/injection), retinal detachment (RD) (6 events [4 rhegmatogenous, 2 exudative], 0.08%/injection), and traumatic cataract (5 events, 0.07%/injection). Most cases of endophthalmitis followed violations of the injection preparation protocol. In patients receiving pegaptanib for >1 year, there were no reports of endophthalmitis or traumatic cataract in year 2; RD was reported in 4 patients (all rhegmatogenous, 0.15%/injection).

Conclusion: The 2-year safety profile of pegaptanib sodium is favorable in patients with exudative AMD. *Ophthalmology* 2006;113:992–1001 © 2006 by the American Academy of Ophthalmology.



Extensive evidence has established a causal relationship between vascular endothelial growth factor (VEGF) and human eye diseases that feature neovascularization and increased vascular permeability.^{1–10} In humans, ocular VEGF levels have been shown to be directly related to the timing and extent of growth and leakage of new vessels.^{1–3} Animal models of corneal,⁴ iridic,⁵ retinal,⁶ and choroidal⁷ neovas-

cularization too have confirmed that neovascularization is intimately dependent upon VEGF. In supportive fashion, the introduction of VEGF into normal eyes recapitulates changes of pathological neovascularization that occur in these tissues during disease.^{8–10} The totality of these data

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provides a validated rationale for the targeting of VEGF in human disorders manifesting ocular neovascularization and increased vascular permeability.

Age-related macular degeneration (AMD) is the leading cause of irreversible severe vision loss in the developed world.¹¹ Although the neovascular form represents a minority of cases (approximately 10%), it is responsible for 90% of severe vision loss.^{12,13} The results of the V.I.S.I.O.N. (VEGF Inhibition Study in Ocular Neovascularization) trials¹⁴ have shown that pegaptanib sodium provides a statistically significant and clinically meaningful benefit to a broad spectrum of patients with neovascular AMD regardless of angiographic subtype, baseline vision, or lesion size. The safety profile of 1 and 2 years of continuous treatment with pegaptanib sodium is herein described in detail.

Materials and Methods

Study Design

The study designs of the V.I.S.I.O.N. trials have been reported.¹⁴ In brief, 2 concurrent, randomized, double-masked, multicenter, sham-controlled clinical trials were identically designed and implemented. The statistical plan prespecified that data would be combined for analysis. The studies met all national and institutional ethical requirements, and institutional review board/ethics committee approval was obtained. Signed informed consent was obtained from all study participants.

Patients age ≥ 50 years with subfoveal choroidal neovascularization secondary to AMD and best-corrected visual acuities (VAs) of 20/40 to 20/320 in the study eye and 20/800 or better in the fellow eye were eligible for inclusion. Patients with all angiographic subtypes of AMD were enrolled. Total lesion size could not exceed 12 total disc areas, in which at least 50% of the lesion was active choroidal neovascularization and no greater than 50% of the lesion was comprised of subretinal hemorrhage, with up to 25% scarring or atrophy outside of the subfovea. Eligible patients also were required to have an intraocular pressure (IOP) of ≤ 23 mmHg, sufficient pupillary dilation to allow good stereoscopic fundus photography, and clear ocular media. Patients with a history of no more than 1 prior administration of photodynamic therapy with verteporfin were eligible for enrollment. As well, subjects with predominantly classic lesions could receive photodynamic therapy at baseline and during the studies at the discretion of the investigator.

At baseline, patients were randomized to receive 0.3 mg, 1 mg, or 3 mg of pegaptanib sodium by intravitreal injection or sham injection every 6 weeks for 54 weeks for a total of 9 treatments. At 1 year (54 weeks), subjects were re-randomized for a second year to determine whether 54 weeks provided sufficient treatment. Subjects who were treated with pegaptanib sodium during the first year were re-randomized at week 54 in a ratio of 1:1 either to discontinue therapy (no further treatment but continued follow-up to week 102) or to continue therapy with the same dose and dosing regimen of pegaptanib sodium as in the first year. Subjects who were receiving sham injections during the first year were re-randomized at week 54 in a ratio of 1:1:1:1:1 (equal numbers of subjects in all 5 options) to stop therapy, to continue with sham injections, or to continue in the study, receiving 1 of the 3 pegaptanib sodium doses. Subjects who were randomized to continue treatment received intravitreal or sham injections once every 6 weeks for a total of 8 injections through week 96 with a follow-up period to week 102. For ethical reasons, subjects who were randomized to stop treatment were permitted to resume therapy (com-

passionate rescue therapy) if they had benefited from treatment in the first year, and subsequently lost at least 2 lines (10 letters) of vision after discontinuation.

Injection Protocol

All subjects underwent a protocol-specified ocular antisepsis procedure and received subconjunctival anesthetic. The antisepsis procedure as originally described in the study protocols was revised in a protocol amendment after approximately 60% of the injections were administered for the 2 years of these studies (Table 1 [available at <http://aaojournal.org>]). The amendment reinforced the aseptic nature of the procedure and mandated the use of (1) sterile preparation and drape similar to that used for routine intraocular surgery and (2) either preinjection topical ophthalmic antibiotic drops for 3 days before the injection or a 10-ml povidone-iodine flush immediately before injection. Active doses were injected into the vitreous, whereas subjects receiving sham had an identical but needleless syringe pressed against the conjunctiva. To maintain masking, the study ophthalmologist responsible for subject care and assessments did not administer the injection. Investigators were instructed not to permit subjects to leave the physicians' office until their IOP had returned to below 30 mmHg.

Independent Data Monitoring

An Independent Data Monitoring Committee consisting of experts independent from the sponsor and the investigators was established before the study's start. The committee reviewed the data and procedures of both trials on an ongoing basis to insure subject safety. The committee met every 4 months.

Safety Assessments

Safety assessments were made by ophthalmologists masked to study treatment. Safety end points included all reported adverse events (regardless of a perceived relationship to the study treatment), serious adverse events and deaths, discontinuations due to adverse events, clinical laboratory values, and vital signs. Baseline data for safety assessments were obtained within 7 days before the first treatment.

An adverse event was defined as any untoward medical occurrence, including unfavorable and unintended signs, symptoms, or disease temporally associated with the use of a study drug, that did not necessarily have a causal relationship to the study drug. All adverse events were coded according to the Medical Dictionary for Regulatory Activities 5.1. Adverse events continued to be recorded for subjects who discontinued study treatment but continued with their follow-up visits.

Severity of adverse events was graded by the investigator as mild, moderate, or severe. Adverse events also were assessed by investigators for their relationship to either the study drug or the injection procedure. Adverse events judged related to the study drug included only those events that investigators attributed to the actual drug. Adverse events judged related to the injection procedure included those events that investigators attributed to the concomitant procedures used in preparation of the study eye (eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush, and subconjunctival injection of anesthetic) as well as the actual intravitreal needle insertion.

A serious adverse event was defined as any untoward medical occurrence that was life threatening, resulted in death, required hospitalization or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, resulted in a congenital anomaly or birth defect, or was an important medical event

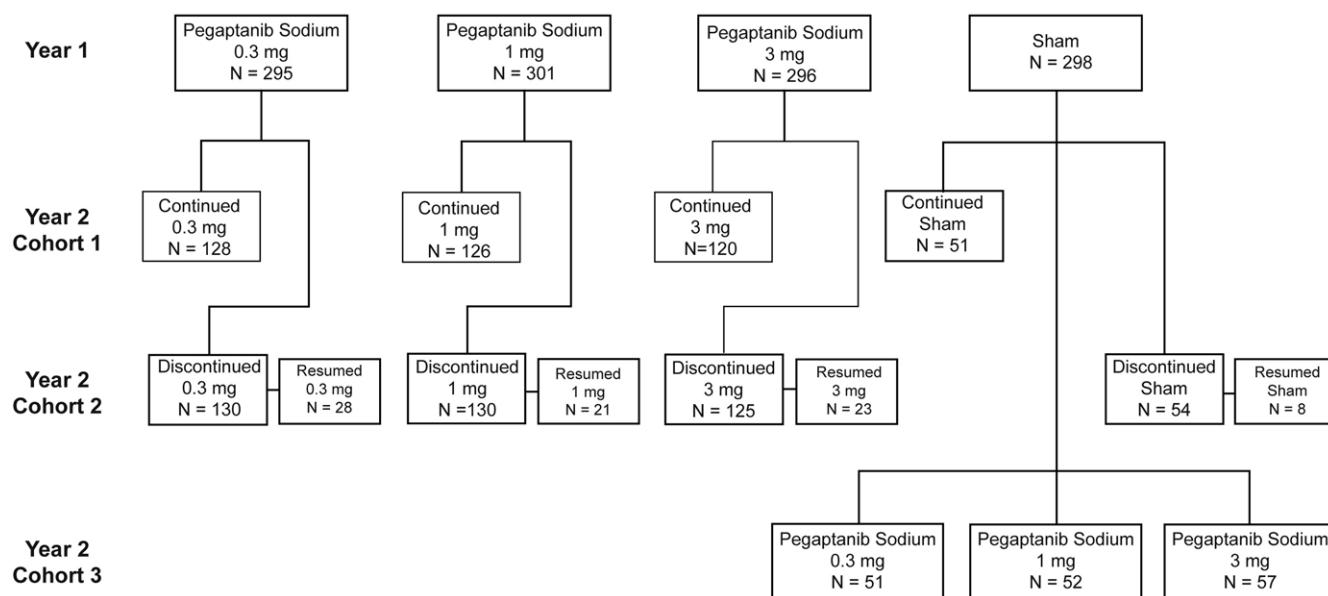


Figure 1. Number of patients in each analysis cohort.

that may have jeopardized the subject or required intervention to prevent one of these outcomes.

Clinical Monitoring

An ophthalmologic examination, including measurement of VA and IOP, inspection of the anterior chamber (AC) for inflammation or other abnormalities, inspection of the lens opacities rated using a modified Age-Related Eye Disease Study grading protocol, and inspection of the vitreous body and retina, was performed at baseline, every 6 weeks just before injection, and again at least 30 minutes and 1 week after injection. Color stereoscopic fundus photographs and fluorescein angiograms were taken at baseline and weeks 30, 54, 78, and 102 and were examined independently by the University of Wisconsin reading center for unexpected changes in retinal anatomy. Subjects were contacted by telephone 3 days after each study treatment to ensure that no signs or symptoms of endophthalmitis were present.

Vital signs, including blood pressure (BP), temperature, and pulse, were recorded routinely before the study treatment. Blood samples were collected at baseline and before every treatment throughout the study. Laboratory tests included hematology (complete blood counts) and chemistry (electrolytes, renal, and hepatic) assessments. A central laboratory conducted all analyses.

Data Analyses

Year 1 (week 54) data analyses were performed for the safety population using data collected between baseline and week 54. Year 2 (week 102) analyses were performed using data collected for the safety population between week 54 and week 102. Within the year 2 analysis, 3 cohorts were evaluated, consistent with the randomized withdrawal study design: cohort 1 included all subjects who were re-randomized to continue on the same treatment in the second year; cohort 2, all subjects who were re-randomized to discontinue treatment in the second year; and cohort 3, all sham-treated subjects who were re-randomized to active dose or sham in the second year. Figure 1 lists the number of patients in each cohort. For both periods analyzed, the safety population consisted

of all subjects who received at least 1 study treatment (pegaptanib sodium or sham) or, in the case of subjects randomized to discontinue therapy, subjects who had at least 1 study visit in the specified period.

Results

Year 1 (Baseline through Week 54)

Of the 1208 subjects randomized in the 2 studies, 1190 received at least 1 study treatment (0.3 mg, $n = 295$; 1 mg, $n = 301$; 3 mg, $n = 296$; sham, $n = 298$). Baseline demographic and ocular characteristics were similar across treatment groups (Table 2). The majority of subjects in each treatment group were at least 75 years old, female, and white, reflecting the general population of subjects with AMD. No clinically meaningful imbalances among treatment groups were noted with respect to baseline demographic or ocular characteristics. The percentage of patients with baseline risk factors for thromboembolic events (hypertension, elevated cholesterol, diabetes mellitus, history of stroke or transient ischemic attack, history of smoking) was somewhat higher in the pegaptanib sodium groups than in the sham group.

A total of 7545 intravitreal injections of pegaptanib sodium and 2557 sham injections were administered. Pegaptanib sodium was well tolerated at all 3 doses, and there were no notable differences among treatment groups, including sham, in overall adverse event or discontinuation rates (Table 3 [available at <http://aaojournal.org>]). Ocular adverse events were experienced by 820 of 892 (92%) subjects receiving pegaptanib sodium and 260 of 298 (87%) sham-treated subjects. Serious adverse events were experienced by 169 of 892 (19%) subjects treated with pegaptanib sodium and by 45 of 298 (15%) subjects in the sham group. Few subjects who received either active or sham treatment discontinued (90/892 [10%] and 23/298 [8%], respectively), and only 1% to 2% of those in pegaptanib sodium groups and 1% of sham-treated subjects discontinued due to adverse events.

Ocular adverse events reported for study eyes in $\geq 10\%$ of subjects in the pegaptanib sodium treatment group or the sham treatment group are summarized in Table 4 (available at <http://aaojournal.org>).

Table 2. Baseline Subject Characteristics and Study Completion Data (Year 1) [n (%)]

	Pegaptanib Sodium			Sham (n = 298)
	0.3 mg (n = 295)	1 mg (n = 301)	3 mg (n = 296)	
Gender				
Male	133 (45)	136 (45)	105 (36)	120 (40)
Female	162 (55)	165 (55)	191 (64)	178 (60)
Race				
White	283 (96)	291 (97)	286 (97)	284 (95)
Other	12 (4)	10 (3)	10 (3)	14 (5)
Age (yrs)				
50–64	19 (6)	21 (7)	18 (6)	21 (7)
65–74	86 (29)	105 (35)	90 (30)	94 (32)
75–84	155 (52)	147 (49)	153 (52)	160 (54)
≥85	35 (12)	28 (9)	35 (12)	23 (8)
Lesion type				
Predominantly classic	72 (24)	78 (26)	80 (27)	76 (26)
Minimally classic	111 (38)	108 (36)	105 (35)	102 (34)
Occult (no classic)	112 (38)	115 (38)	111 (38)	120 (40)
Subjects with at least 1 previous				
Photodynamic therapy with verteporfin	38 (13)	42 (14)	37 (13)	37 (12)
Systemic treatment for AMD*	15 (5)	16 (5)	17 (6)	19 (6)
Nonsurgical ocular disease, condition, or trauma	228 (77)	233 (77)	240 (81)	231 (78)
Ocular surgery or laser treatment	156 (53)	144 (48)	155 (52)	155 (52)
Ocular infection or inflammation within prior 4 wks	3 (1)	1 (0)	4 (1)	0 (0)
Baseline visual acuity scores (letters)				
Study eye				
Mean	52.8	50.7	51.1	52.7
Median; range	55; 11–75	52; 19–77	53; 14–76	53; 11–77
Fellow eye				
Mean	56.2	54.8	56	55.9
Median; range	68; 3–85	67; 3–85	65; 4–85	67; 2–85
Worse eye as study eye	187 (63)	180 (60)	188 (64)	181 (61)
No. of study treatments				
Mean	8.4	8.5	8.4	8.6
Median; range	9; 1–9	9; 1–9	9; 1–9	9; 1–9

AMD = age-related macular degeneration.

*Consisting mainly of vitamins, minerals, and antioxidants.

aaojournal.org). The most common ocular adverse events in pegaptanib sodium-treated eyes were eye pain (299/892 [34%]), vitreous floaters (294/892 [33%]), punctate keratitis (286/892 [32%]), and increased IOP (177/892 [20%]). The majority of the adverse events in the study eye were attributed by investigators to the injection procedure itself; few events were attributed to the study drug. The majority of these common ocular adverse events were transient and mild to moderate in severity.

No severe AC inflammation was seen, and moderate inflammation occurred in only 9 of 892 (1%) subjects treated with pegaptanib sodium. Sensitization to pegaptanib sodium did not appear to occur, because the incidence of AC inflammation declined slightly over time, from 8% of subjects during the first through third injections to 5% of subjects during the seventh through ninth injections. No subject was discontinued from the study due to AC inflammation.

Cataract was reported as an adverse event in a slightly higher proportion of phakic subjects in the active treatment groups compared with the sham group in the combined data analysis (Table 4 [available at <http://aaojournal.org>]). There was considerable variation in reporting, possibly due to multiple observers and the low-threshold definition of cataract progression: investigators were

instructed to report a 1-unit change in either nuclear, cortical, or posterior subcapsular Age-Related Eye Disease Study opacity grading as an adverse event. In a separate analysis, changes in the Age-Related Eye Disease Study lens opacity gradings from baseline to the last visit were evaluated (Table 5 [available at <http://aaojournal.org>]). There was little difference in proportions of subjects with any increased lens grade between the active treatment and sham groups, and almost all increases were of 1 grade only. Age-Related Eye Disease Study lens opacity gradings for fellow and study eyes were similar. There was no evident increase in posterior subcapsular cataracts, the type of cataract most likely associated with intravitreal injection. No consistent trends in cataract progression were identified. Only 3 patients underwent a cataract extraction during year 1 that could not be attributed to another cause (trauma, endophthalmitis, vitreous hemorrhage).

Twelve cases of endophthalmitis were reported, including 6 subjects in the 0.3-mg pegaptanib sodium group and 3 subjects each in the 1-mg and 3-mg groups (Table 6). Of these, only 1 subject (0.1% per subject year) experienced concomitant severe vision loss (≥ 30 letters), and 8 of 12 subjects (67%) lost ≤ 2 lines of vision (≤ 10 letters). Nine of these subjects had a positive culture result from a vitreous biopsy, with the most commonly isolated organism being coagulase-negative *Staphylococcus*. Nine

Table 6. Injection-Related Serious Adverse Events in Subjects Receiving Pegaptanib Sodium (Year 1; n = 892)

Condition	Rate		Severe Vision Loss*	
	Subjects	Percent per Injection	Subjects	Percent per Injection
Endophthalmitis	12 [†]	0.16	1	0.01
Traumatic cataract	5	0.07	1	0.01
Retinal detachment	6 [‡]	0.08	0 [§]	0

A total of 7545 intravitreal injections of pegaptanib sodium were administered.

*Defined as a loss of ≥ 30 letters.

[†]Three quarters of endophthalmitis subjects remained in the trial and received additional injections.

[‡]Four rhegmatogenous, 2 exudative detachments.

[§]Follow-up not available for 1 subject.

of the 12 subjects (75%) continued in the study after resolution of the endophthalmitis and received additional injections of pegaptanib sodium. The majority of endophthalmitis cases (9/12 [75%]) were associated with violations of the injection preparation protocol, such as failure to use an eyelid speculum.

Six cases of retinal detachment (RD) were reported in the study eye (Table 6). Two subjects (1 each in the 0.3-mg and 3-mg arms) had RDs that were exudative/hemorrhagic in nature and may have been secondary to the underlying disease process. The other 4 subjects (3 in the 1-mg arm and 1 in the 3-mg arm) had RDs with a rhegmatogenous component; risk factors included retinoschisis in the study eye of one of these subjects, and lattice degeneration in the study eye and a history of RD in the fellow eye in a second subject.

Five subjects developed traumatic cataracts during the first 54 weeks of the pivotal studies, all of which were iatrogenic in nature (Table 6). In 4 of these subjects (1 subject each in the 0.3-mg and 1-mg groups and 2 subjects in the 3-mg group), there was contact and/or penetration of the lens with the intravitreal injection needle; 2 of these events occurred on the same day at the same clinical site with the same investigator. In the fifth subject (1-mg group), an AC paracentesis was performed due to increased IOP after an intravitreal injection, and the paracentesis needle itself punctured the anterior lens capsule. All of these subjects subsequently had cataract extraction, and all but 1 continued in the study. Only 1 subject had severe vision loss (≥ 30 letters) after the event, most likely due to progression of the underlying AMD.

A transient decrease in central retinal artery perfusion in the study eye was seen in 4 subjects (1 receiving 0.3 mg of pegaptanib sodium and 3 receiving 1 mg). In all 4 cases, this was associated with increased IOP immediately after an injection, and all cases resolved after paracentesis. In all 4 cases, VA after the event improved, was unchanged, or remained within 1 line of the pre-event acuity. All 4 events resolved without sequelae, and all 4 subjects continued in the study. No retinal vein occlusion was reported in the study eye of any pegaptanib sodium-treated subjects. There were no recognizable sustained vascular occlusions in the study eye at any time during the first year of treatment.

Sixteen cases of vitreous hemorrhage in the study eye in pegaptanib sodium-treated subjects were noted in the first year, resulting in an incidence of 0.21% (16/7545) per injection. The hemorrhage was judged related to underlying choroidal neovascularization in 7 of 16 subjects (44%). The event was judged related to the injection procedure in 9 subjects; in all of these 9 cases, the hemorrhage was mild in nature, and VA after the event was within 2 lines of the pre-event measurement. Additionally, 2 subjects had

vitreous hemorrhages in the fellow eye; 1 was attributed to underlying choroidal neovascularization and 1 to complications from an AC intraocular lens. None of the vitreous hemorrhages was associated with retinal tears or detachments.

There was no evidence of a persistent increase in IOP associated with up to 1 year of treatment with pegaptanib sodium. The mean IOP measured immediately (30 minutes) after injection was 2 to 4 mmHg higher than preinjection IOP, with the highest mean increases seen in the 3-mg group. The mean IOP returned to preinjection levels at the next IOP measurement, 1 week after injection. Almost 90% of all pegaptanib sodium-treated subjects did not experience a postinjection IOP that was ≥ 35 mmHg (a monitoring threshold suggested by the Independent Data Monitoring Committee) at any time during the study. One sham-treated subject developed an IOP ≥ 35 mmHg, whereas 27 (9%), 28 (9%), and 44 (15%) subjects in the 0.3-mg, 1-mg, and 3-mg pegaptanib sodium groups, respectively, experienced values of ≥ 35 mmHg. In the cohort of patients (n = 68) with a history of ocular hypertension or glaucoma before randomization, a higher percentage of patients (32%) had an IOP value ≥ 35 mmHg on at least one injection day. The overall frequency of paracentesis after injection was low (3% per number of injections) and related to local site practice patterns; paracenteses performed at 10 of 117 (9%) sites accounted for almost three quarters of the procedures performed, and 1 site alone accounted for almost one quarter of all procedures. No subject required a trabeculectomy, and no subject was discontinued from the study due to increased IOP or signs of progressing glaucoma.

The University of Wisconsin reading center graded all fluorescein angiograms (baseline, week 30, and week 54). These examinations revealed no retinal vascular abnormalities in the study eye that were unexpected in the natural history of exudative AMD. There was no evidence of VEGF inhibitor-mediated toxicity to the retinal or choroidal vasculature in the study eye—that is, there were no notable delays in arteriovenous transit time, abnormalities in choroidal perfusion, or arteriolar occlusions identified.

No evidence of systemic toxicity was observed. Common non-ocular adverse events occurred with similar frequency across the treatment and sham groups, and no dose-response relationship was noted in pegaptanib sodium groups (Table 7 [available at <http://aaojournal.org>]). The most commonly occurring serious adverse events were cardiac disorders, yet the incidence of cardiac adverse events was higher in the sham arm (5%) than in the active treatment arms (3%). A 2% death rate was seen in the first year in both the pegaptanib sodium treatment and sham treatment groups (19/892 and 6/298 subjects, respectively), as expected given the age range of our subjects.¹⁵ Intravitreal pegaptanib sodium was not associated with the potential VEGF inhibition-related adverse events recognized with systemic administration of nonselective VEGF inhibitor agents—hypertension, thromboembolic events, or serious hemorrhagic events (Table 8) (J Clin Oncol 23[suppl]: 3019, 2005).^{16–20}

Data concerning laboratory test abnormalities were available for 885 subjects in the pegaptanib sodium group and for 296 of those receiving sham. There were no discontinuations from study treatment due to a laboratory abnormality. Incidences of pre-defined clinically significant laboratory test abnormalities appeared similar in the sham and active treatment groups. Median changes from baseline for all laboratory parameters were small, not judged to be clinically meaningful, and comparable across all treatment groups and sham. No clinically significant changes from baseline in median and/or mean measurements of vital signs, including BP, were noted in any treatment group.

Table 8. Potential Vascular Endothelial Growth Factor Inhibition-Related Adverse Events (Year 1) [n (%)]

	Pegaptanib Sodium (n = 892)	Sham (n = 298)
All thromboembolic adverse events	52 (6)	18 (6)
Arterial events	49 (5)	16 (5)
Venous events	5 (1)	2 (1)
All serious thromboembolic events	33 (4)	11 (4)
Serious arterial events	30 (3)	9 (3)
Serious venous events	3 (0)	2 (1)
Vascular hypertensive disorders	90 (10)	31 (10)
Serious hemorrhagic adverse events	7 (1)	3 (1)

Year 2 (Week 54 through Week 102)

The safety population in the second year consisted of a total of 1024 patients (425 in cohort 1, 439 in cohort 2, and 160 in cohort 3).

Cohort 1 (Subjects Re-randomized to Same Treatment in Year 2 as in Year 1). Demographic and ocular characteristics for re-randomized subjects were similar across all treatment groups. The safety population for cohort 1 consisted of 425 subjects (0.3 mg, n = 128; 1 mg, n = 126; 3 mg, n = 120; sham, n = 51) who received at least 1 dose of the study treatment. A total of 2663 intravitreal injections of pegaptanib sodium and 388 sham injections were administered to these subjects during year 2 of the study. Overall, the mean number of treatments for the 2 years for all subjects re-randomized to continue pegaptanib sodium therapy was 16 of 17 possible treatments.

The safety profile was similar in the second year of treatment with pegaptanib sodium to that already described for year 1; no new safety concerns were identified. Pegaptanib sodium was well tolerated at all 3 doses, and overall adverse event and discontinuation rates were similar across pegaptanib sodium doses and sham (Table 9 [available at <http://aaojournal.org>]). Few subjects receiving either active or sham treatment discontinued due to adverse events.

Ocular adverse events reported for study eyes in $\geq 10\%$ of subjects in the pegaptanib sodium or sham treatment groups are shown in Table 10 (available at <http://aaojournal.org>). The most common ocular adverse events in pegaptanib sodium-treated eyes were eye pain (93/374 [25%]), increased IOP (90/374 [24%]), punctate keratitis (86/374 [23%]), and vitreous floaters (83/374 [22%]). As in year 1, the majority of these events were transient, mild to moderate in severity, and attributed by the investigators to the injection procedure itself and not the study drug. The incidence of these common events was noted to be higher in the study eyes of sham patients than in fellow eyes for all active treatment groups, supporting the interpretation that many of these events may be related to the pre-intravitreal injection preparation procedure rather than to the intravitreal injection itself.

Pegaptanib sodium continued to have a favorable injection safety profile. There were no cases of endophthalmitis or traumatic cataract in this cohort of subjects (Table 11). Four cases of RD (all rhegmatogenous) were reported of the 2663 pegaptanib sodium injections administered in this cohort (0.15% per injection); RDs are discussed below for all second-year cohorts.

In this cohort of subjects who continued the same pegaptanib sodium dose in the second year as in the first, mean IOP elevation from before injection to 30 minutes after injection ranged from 2 to 6 mmHg. The highest mean increases were seen in the 3-mg group. Mean increases 30 minutes after sham injection ranged from 0.3 to 2.4 mmHg during the second year. Mean values for preinjection IOP for all subjects who continued the same treatment in the second year are illustrated in Figure 2. Preinjection IOP during the 2 years was similar to baseline levels, with a small but

clinically insignificant increase (≤ 1 mmHg) in preinjection mean IOP in the 3-mg group. As was seen in the first year, mean values for IOP returned to preinjection levels in all treatment groups by 1 week after injection. Mean values for IOP at all study time points—preinjection, postinjection, and 1 week after injection—are illustrated for subjects who received 0.3 mg of pegaptanib sodium in both the first and second years in Figure 3. The overall frequency of paracentesis per number of injections continued to be low (4.1%). No subject underwent a trabeculectomy, and no subject was discontinued due to increased IOP.

Fluorescein angiograms were obtained and graded at week 78 and week 102. These examinations revealed no retinal vascular abnormalities in the study eye that were unexpected in the natural history of exudative AMD. There was no evidence of VEGF inhibitor-mediated toxicity to the retinal or choroidal vasculature in the study eye—that is, there were no notable delays in arteriovenous transit time, abnormalities in choroidal perfusion, or retinal vascular occlusions identified.

Data from these subjects receiving up to 2 years of continuous treatment revealed no evidence of systemic toxicity. Systemic adverse events occurred with similar frequency across all treatment and sham groups (Table 12 [available at <http://aaojournal.org>]). In cohort 1, 2 deaths occurred in pegaptanib sodium-treated subjects ($<1\%$ death rate); no subject in the sham group died.

As in year 1, there was no evidence in year 2 that pegaptanib sodium was associated with the adverse events seen with systemically administered nonselective VEGF inhibitors—hypertension, thromboembolic events, or serious hemorrhagic events (Table 13) (J Clin Oncol 23[suppl]:3019, 2005).^{16–20} There were no findings in relation to vital signs, electrocardiograms, or laboratory test results that were suggestive of a relationship to treatment with pegaptanib sodium; specifically, there was no evidence of an increase in mean BP over the 2 years of treatment (Fig 4).

Cohort 2 (Subjects Re-randomized to Discontinue Treatment in Year 2). Of the 1190 subjects who participated in the first

Table 11. Injection-Related Serious Adverse Events in Subjects Receiving Pegaptanib Sodium (Year 2*)

Condition	Rate		Severe Vision Loss [†]	
	Subjects	Percent per Injection	Subjects	Percent per Injection
Cohort 1 [‡]				
Endophthalmitis	0	0	—	—
Traumatic cataract	0	0	—	—
Retinal detachment	4 [§]	0.15	1	0.04
All cohorts [¶]				
Endophthalmitis	4	0.10	0	0
Traumatic cataract	1	0.02	1 [#]	0.02
Retinal detachment	7 ^{**}	0.17	2	0.05

*Data for second year of treatment.

[†]Defined as a loss of ≥ 30 letters.

[‡]n = 374; a total of 2663 intravitreal injections of pegaptanib sodium were administered.

[§]All were rhegmatogenous.

^{||}Follow-up not available.

[¶]n = 374 for pegaptanib subjects re-randomized to pegaptanib; n = 160 for sham subjects re-randomized to pegaptanib; n = 72 for subjects re-randomized to discontinue, retreated with pegaptanib; a total of 4091 intravitreal injections of pegaptanib sodium were administered.

[#]Follow-up for only 1 mo after surgery.

^{**}Six were rhegmatogenous, 1 exudative.

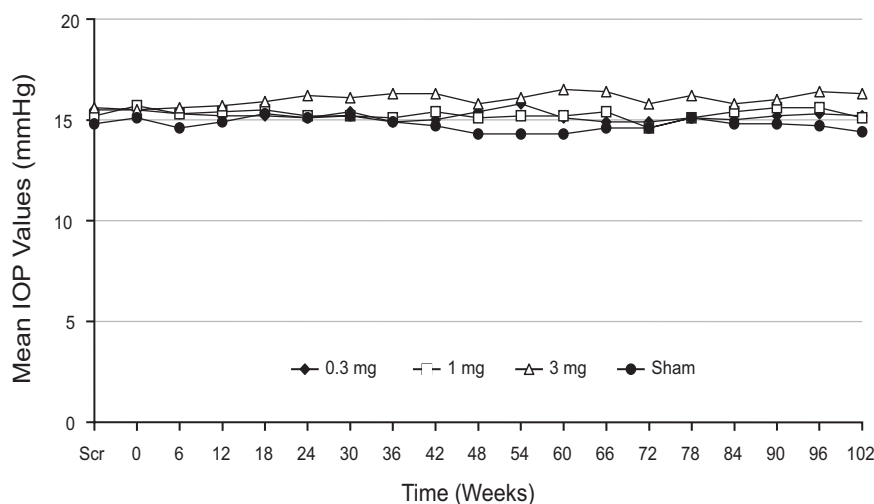


Figure 2. Mean values for preinjection intraocular pressure (IOP) for all subjects who continued the same treatment in the second year. Scr = screening.

year of the study, 439 (first-year treatment of 0.3 mg, $n = 130$; 1 mg, $n = 130$; 3 mg, $n = 125$; sham, $n = 54$) were re-randomized to discontinue their treatment at the end of the first year, though they were observed during the second year. Additionally, if a discontinued subject's vision declined by at least 2 lines in the second year but had improved in the first year, that subject was offered the option of resuming his or her first-year masked therapy (compassionate rescue therapy). Seventy-two pegaptanib-treated subjects (28, 21, and 23 subjects in the 0.3-mg, 1-mg, and 3-mg groups, respectively) and 8 sham-treated subjects resumed masked therapy during the second year, receiving a total of 334 injections (302 pegaptanib, 32 sham). No safety issues were identified in these subjects during the second year. There was 1 case of RD (rhegmatogenous; see below).

Cohort 3 (First-Year Sham Subjects Re-randomized to Pegaptanib Sodium in Year 2). Of the 298 subjects who had received sham during the first year, 160 were re-randomized to receive pegaptanib sodium at the end of the first year and continued into the second year (0.3 mg, $n = 51$; 1 mg, $n = 52$; 3 mg, $n = 57$). A total of 1126 pegaptanib sodium injections were ad-

ministered to these subjects in the second year. The safety profile of these subjects was consistent with that of those subjects initially treated with pegaptanib sodium during the first year of the study; no new safety issues were identified. Injection-related adverse events of endophthalmitis (4 cases), RD (2 cases [1 rhegmatogenous, 1 exudative]), and iatrogenic traumatic cataract (1 case) are discussed below.

All Cohorts. Pegaptanib sodium continued to have a favorable injection safety profile across all cohorts in the second year of the studies (Table 11). The incidence of endophthalmitis was 0.10% per injection (4/4091), that of traumatic cataract was 0.02% per injection (1/4091), and that of RD was 0.17% per injection (7/4091 [6 rhegmatogenous, 1 exudative]) across all cohorts within the second year. Of the 4 subjects who experienced endophthalmitis in the second year (cohort 3, 1 mg or 3 mg), none experienced severe vision loss (≥ 30 letters); 2 patients lost ≤ 1 line of vision (≤ 5 letters). Eleven cases of vitreous hemorrhage in the study eye in subjects receiving pegaptanib sodium were reported across all cohorts in the second year, resulting in an incidence of 0.27% (11/4091) per injection.

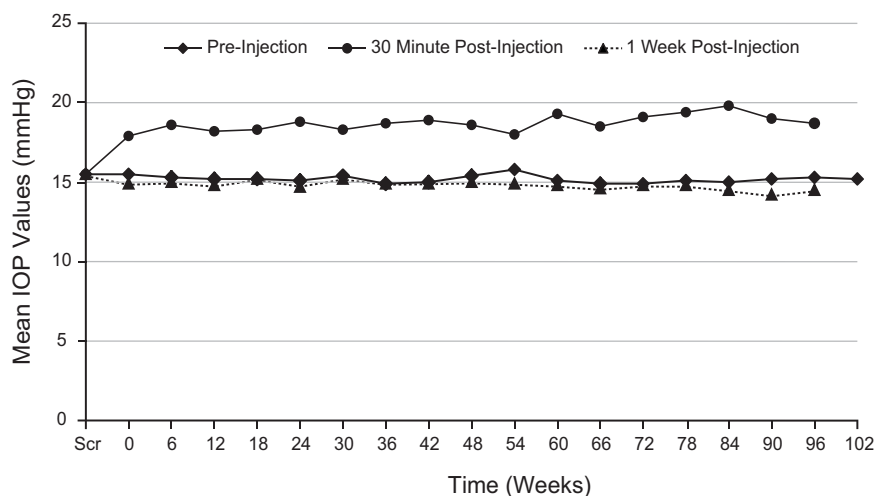


Figure 3. Mean values for intraocular pressure (IOP) at all study time points for subjects who received 0.3 mg of pegaptanib sodium in both the first and second years. Scr = screening.

Table 13. Potential Vascular Endothelial Growth Factor Inhibition–Related Adverse Events (Cohort 1; Year 2*) [n (%)]

	Pegaptanib Sodium (n = 374)	Sham (n = 51)
All thromboembolic adverse events	18 (5)	5 (10)
Arterial events	13 (3)	4 (8)
Venous events	5 (1)	1 (2)
All serious thromboembolic events	12 (3)	4 (8)
Serious arterial events	9 (2)	3 (6)
Serious venous events	3 (1)	1 (2)
Vascular hypertensive disorders	28 (7)	3 (6)
Serious hemorrhagic adverse events	2 (1)	1 (2)

*Data for second year of treatment.

Discussion

The data from these 2 prospective randomized studies demonstrate a favorable safety profile, both ophthalmologically and systemically, for pegaptanib sodium therapy. These studies were characterized by high compliance rates in both the first and the second year; patients continuing the same treatment in the second year received a mean of 16 of a possible 17 study treatments. All doses of pegaptanib sodium were well tolerated.

The common ocular adverse events were reported in a higher proportion of study eyes of sham patients, relative to the fellow eyes of each active treatment group. This suggests that many of these events may be related to the pre-intravitreal injection preparation procedure rather than to the intravitreal injection itself. As would be expected employing an aptamer for therapy, no significant activation of the immunological response was triggered, as illustrated by the lack of severe AC inflammation. Transient increases in IOP seen during this study were consistent with what is anticipated with intravitreal injections of any kind²¹; the expected increases in IOP were seen immediately after injection, and values returned to preinjection levels by the next visit. These increases were manageable and did not require intervention in the majority of cases; no

patient required surgical intervention for a sustained elevation of IOP that was ascribable to the study medication. Retinal detachment and traumatic cataract were infrequent, and there was no evidence of differences in cataract progression between treatment and sham groups. No retinal vascular abnormalities beyond those expected in the natural course of exudative AMD were identified on fluorescein angiography.

As is true for any agent injected into the vitreous, the most worrisome safety issue was the occurrence of endophthalmitis (16/11 636 injections, or 0.14% per injection) and its residual visual loss (1/16 cases [6%] had severe vision loss). Our protocol at study initiation was designed to maximize asepsis. During the initial period of these studies, the incidence of endophthalmitis was 0.18% per injection (13 cases of the 7171 injections administered from the beginning of the study through March 2003). Although this was consistent with the reported expectations for endophthalmitis after any intravitreal injection,²¹ we sought to determine if that rate could be modified and decreased by a revision of injection techniques with added vigilance to asepsis. Toward this end, we instituted an amendment to the protocol to include additional sterile preparation and drape similar to that used for routine intraocular surgery and additional preinjection antibiotic therapy or preinjection povidone-iodine flush. Following this protocol amendment, the rate of endophthalmitis decreased to an incidence of 0.07% per injection (3 cases of 4465 injections administered after March 2003 until the last subject completed the 2-year study). In 1 of these 3 cases, the site followed the original injection preparation procedure, and therefore, the incidence of endophthalmitis after the institution of the new injection procedure was actually 2 of 4465, or 0.04% per injection. This was a statistically significant reduction in the incidence of this event of infection and suggests that, though the risk of endophthalmitis with intravitreal pegaptanib sodium is low, that risk is modifiable and can be reduced with vigilance to aseptic technique. The precise impact of the protocol amendment cannot be determined, but attention to the injection procedure likely focused the attention of the investigators on specific elements of the injection protocol

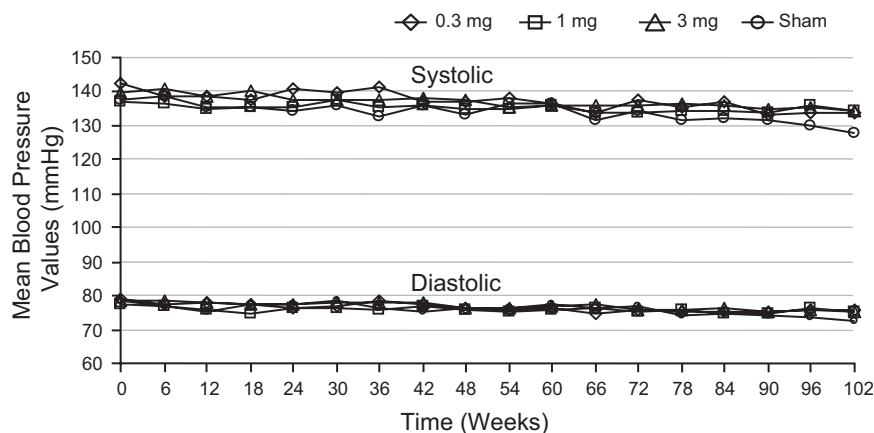


Figure 4. Blood pressure across time by treatment group.

and also may have increased compliance with measures that were common to both the original and revised injection procedures.

In the 2-year report of verteporfin therapy in AMD, 10 patients (total $n = 225$) were documented to have lost at least 20 letters of VA within 7 days of treatment with photodynamic therapy (4.4%).²² In a comparable analysis of subjects receiving pegaptanib sodium for 2 years, 7 of 374 subjects (1.9%) reported visual loss within 7 days of injection, with but 1 case of severe visual loss documented (0.27%). Most importantly, there was no evidence that pegaptanib sodium was associated with the pan-VEGF inhibition-related major systemic adverse events reported with the systemically administered nonselective VEGF inhibitor bevacizumab—hypertension, thromboembolic events, or serious hemorrhagic events (J Clin Oncol 23[suppl]:3019, 2005).^{16–20}

As the pharmacology of treatments for AMD progresses, successful agents will be measured by efficacy and safety. Given the relative risk for acute visual loss pursuant to pegaptanib sodium therapy compared with that reported for photodynamic therapy, even with the small but finite risk of endophthalmitis, pegaptanib sodium's safety profile seems superior. Given the lack of ocular inflammatory response generated by intravitreal pegaptanib sodium, selective blockade of the most pathologically driven isoform of VEGF (VEGF₁₆₅), and absence of evidence to suggest drug-related thromboembolic events in these pivotal trials, the 2-year safety profile of pegaptanib sodium remains compelling.

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Appendix I

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See “Appendix II” (available at <http://aaojournal.org>) for a list of the members of the Steering Committee, Data Management and Statistics Group, Eligibility and Classification Quality Assurance Team, Independent Fundus Photograph and Angiogram Reading Center, V.I.S.I.O.N. Clinical Trial Group, and Eyetech and Pfizer Staff who participated in the V.I.S.I.O.N. Clinical Trial.

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Table 1. Original and Amended Intravitreal Injection Antisepsis Procedures

Original injection antisepsis procedure	
Day of injection, before injection (in office)	<ul style="list-style-type: none"> • 2–3 drops of 5% povidone–iodine shortly before injection (or in the event of an allergy, a drop of topical antibiotic) • Placement of an eyelid speculum
After injection	<ul style="list-style-type: none"> • A broad-spectrum antibiotic ointment twice daily for 2 days
Amended injection antisepsis procedure	
Before day of injection	<ul style="list-style-type: none"> • Use of preinjection topical ophthalmic antibiotic drops (ofloxacin, levofloxacin, or an antibiotic with comparable antimicrobial coverage) 4 times a day for 3 days before injection • Eyelash washes with gentle soap and water twice daily for 3 days before injection
Day of injection, before injection (in the office)	<ul style="list-style-type: none"> • If a subject has been treated with 3 days of antibiotic drops <ul style="list-style-type: none"> ○ 3 consecutive drops of antibiotic at least 5 min apart ○ 2–3 drops of 5% povidone–iodine ○ Use of sterile gloves and cotton-tip applicators soaked in 5% povidone–iodine, scrubbing of eyelids and upper and lower eyelid margins and caruncle 3 times
	OR
	<ul style="list-style-type: none"> • If a subject has <i>not</i> been treated with 3 days of antibiotic drops <ul style="list-style-type: none"> ○ 3 consecutive drops of antibiotic at least 5 min apart ○ Use of sterile gloves, irrigation of fornices and caruncle with at least 10 ml of 5% povidone–iodine • Glove changing • Placement of sterile drape pinning eyelashes to lids • Placement of sterile eyelid speculum to hold back lashes under the drape • Placement of 1–2 drops of 5% povidone–iodine at the injection site and waiting for it to dry
Day of injection, after injection	<ul style="list-style-type: none"> • 2 drops of single-use antibiotic over injection site at the end of procedure • Antibiotic drops 4 times daily for 2 days after injection

The antisepsis procedure as originally described in the study protocols was revised in a protocol amendment after approximately 62% (7171/11 636) of the injections were administered during the 2 yrs of these studies.

Table 3. Adverse Event Summary (Year 1) [n (%)]

	Pegaptanib Sodium			Sham (n = 298)
	0.3 mg (n = 295)	1 mg (n = 301)	3 mg (n = 296)	
Subjects with an adverse event	286 (97)	286 (95)	288 (97)	283 (95)
Subjects with an ocular adverse event	272 (92)	276 (92)	272 (92)	260 (87)
Study eye	269 (91)	270 (90)	270 (91)	254 (85)
Fellow eye	119 (40)	125 (42)	133 (45)	132 (44)
Subjects with a serious adverse event	55 (19)	50 (17)	64 (22)	45 (15)
Subjects discontinuing due to an adverse event	3 (1)	4 (1)	6 (2)	4 (1)

Table 4. Adverse Events Reported in Study Eyes in $\geq 10\%$ of Subjects in the Pegaptanib Sodium Treatment Group or the Sham Treatment Group (Year 1) [n (%)]

Adverse Event	Pegaptanib Sodium			Sham (n = 298)
	0.3 mg (n = 295)	1 mg (n = 301)	3 mg (n = 296)	
Eye pain				
Study eye	97 (33)	97 (32)	105 (35)	83 (28)
Fellow eye	9 (3)	3 (1)	5 (2)	7 (2)
Vitreous floaters				
Study eye	88 (30)	103 (34)	103 (35)	23 (8)
Fellow eye	7 (2)	7 (2)	7 (2)	3 (1)
Punctate keratitis				
Study eye	97 (33)	91 (30)	98 (33)	79 (27)
Fellow eye	6 (2)	7 (2)	3 (1)	7 (2)
IOP increased*				
Study eye	42 (14)	58 (19)	77 (26)	8 (3)
Fellow eye	1 (0)	3 (1)	3 (1)	0 (0)
Visual acuity reduced				
Study eye	67 (23)	47 (16)	52 (18)	71 (24)
Fellow eye	22 (7)	15 (5)	12 (4)	18 (6)
Vitreous opacities				
Study eye	53 (18)	56 (19)	56 (19)	29 (10)
Fellow eye	6 (2)	3 (1)	2 (1)	2 (1)
Anterior chamber inflammation				
Study eye	47 (16)	42 (14)	39 (13)	17 (6)
Fellow eye	2 (1)	1 (0)	1 (0)	0 (0)
Visual disturbance NOS				
Study eye	38 (13)	39 (13)	40 (14)	33 (11)
Fellow eye	9 (3)	13 (4)	12 (4)	17 (6)
Corneal edema				
Study eye	25 (8)	23 (8)	37 (13)	21 (7)
Fellow eye	1 (0)	0 (0)	2 (1)	0 (0)
Abnormal sensation in eye				
Study eye	23 (8)	20 (7)	25 (8)	30 (10)
Fellow eye	1 (0)	2 (1)	2 (1)	3 (1)
No. of phakic study eyes	184	205	198	201
Cataract in study eye	50 (27)	60 (29)	67 (34)	53 (26)

IOP = intraocular pressure; NOS = not otherwise specified.

*The investigators were required to report an IOP of ≥ 30 mmHg at 30 min after injection as an adverse event.

Table 5. Increases in Age-Related Eye Disease Study Lens Grade: Last Visit Compared with Baseline (Year 1) [n (%)]

	Pegaptanib Sodium			Sham (n = 298; n _s = 201; n _f = 197)
	0.3 mg (n = 295; n _s = 183; n _f = 189)	1 mg (n = 301; n _s = 205; n _f = 205)	3 mg (n = 296; n _s = 197; n _f = 202)	
Nuclear				
Study eye	29 (16)	37 (18)	43 (22)	37 (18)
Fellow eye	30 (16)	36 (18)	31 (15)	24 (12)
Posterior subcapsular				
Study eye	16 (9)	26 (13)	20 (10)	23 (11)
Fellow eye	12 (6)	18 (9)	15 (7)	18 (9)
Cortical				
Study eye	31 (17)	33 (16)	41 (21)	30 (15)
Fellow eye	20 (11)	25 (12)	31 (15)	26 (13)

n_f = no. of phakic fellow eyes; n_s = no. of phakic study eyes.

Table 7. All-Causality Nonocular Adverse Events in ≥5% of Subjects Treated with Pegaptanib Sodium or Sham (Year 1) [n (%)]

Adverse Event (Preferred Term)	Pegaptanib Sodium			Sham (n = 298)
	0.3 mg (n = 295)	1 mg (n = 301)	3 mg (n = 296)	
Gastrointestinal disorders				
Nausea	13 (4)	7 (2)	16 (5)	13 (4)
Musculoskeletal and connective tissue disorders				
Arthralgia	13 (4)	12 (4)	11 (4)	17 (6)
Nervous system disorders				
Headache	19 (6)	23 (8)	20 (7)	11 (4)
Respiratory, thoracic, and mediastinal disorders				
Nasopharyngitis	19 (6)	23 (8)	27 (9)	19 (6)
Bronchitis NOS	16 (5)	12 (4)	11 (4)	10 (3)
Vascular disorders				
Hypertension NOS*	14 (5)	26 (9)	29 (10)	22 (7)

NOS = not otherwise specified.

*Incidences of systemic vascular hypertensive disorders (a Medical Dictionary for Regulatory Activities high-level term that includes the preferred terms *hypertension NOS*, *hypertension aggravated*, and *systolic hypertension*) were similar in the pegaptanib (10%) and sham (10%) subjects (Table 8).

Table 9. Adverse Event Summary (Cohort 1; Year 2*) [n (%)]

	Pegaptanib Sodium			Sham (n = 51)
	0.3 mg (n = 128)	1 mg (n = 126)	3 mg (n = 120)	
Subjects with an adverse event	122 (95)	118 (94)	109 (91)	46 (90)
Subjects with an ocular adverse event				
Study eye	92 (72)	98 (78)	92 (77)	39 (76)
Fellow eye	45 (35)	44 (35)	45 (38)	23 (45)
Subjects with a serious adverse event	22 (17)	23 (18)	18 (15)	14 (27)
Subjects discontinuing due to an adverse event	5 (4)	4 (3)	6 (5)	2 (4)

*Data for second year of treatment.

Table 10. Adverse Events Reported in Study Eyes in $\geq 10\%$ of Subjects in the Pegaptanib Sodium Treatment Group or the Sham Treatment Group (Cohort 1; Year 2*) [n (%)]

Adverse Event	Pegaptanib Sodium			Sham (n = 51)
	0.3 mg (n = 128)	1 mg (n = 126)	3 mg (n = 120)	
Eye pain				
Study eye	27 (21)	35 (28)	31 (26)	9 (18)
Fellow eye	0	1 (1)	5 (4)	0
IOP increased [†]				
Study eye	26 (20)	22 (17)	42 (35)	4 (8)
Fellow eye	2 (2)	2 (2)	1 (1)	0
Punctate keratitis				
Study eye	31 (24)	26 (21)	29 (24)	14 (27)
Fellow eye	2 (2)	1 (1)	0	1 (2)
Vitreous floaters				
Study eye	28 (22)	24 (19)	31 (26)	2 (4)
Fellow eye	3 (2)	2 (2)	2 (2)	3 (6)
Vitreous opacities				
Study eye	13 (10)	12 (10)	21 (18)	6 (12)
Fellow eye	3 (2)	2 (2)	0	1 (2)
Corneal edema				
Study eye	12 (9)	10 (8)	13 (11)	4 (8)
Fellow eye	0	0	0	0
Lacrimation increased				
Study eye	6 (5)	15 (12)	10 (8)	6 (12)
Fellow eye	1 (1)	3 (2)	0	2 (4)
Eye redness				
Study eye	9 (7)	6 (5)	10 (8)	6 (12)
Fellow eye	0	1 (1)	2 (2)	3 (6)
Vision blurred				
Study eye	4 (3)	3 (2)	4 (3)	5 (10)
Fellow eye	0	1 (1)	0	0
No. of phakic study eyes	78	79	87	34
Cataract in study eye	14 (18)	18 (23)	15 (17)	8 (24)

IOP = intraocular pressure.

*Data for second year of treatment.

[†]The investigators were required to report an IOP of ≥ 30 mmHg at 30 min after injection as an adverse event.

Table 12. All-Causality Nonocular Adverse Events in $\geq 5\%$ of Subjects Treated with Pegaptanib Sodium or Sham (Cohort 1; Year 2*) [n (%)]

Adverse Event (Preferred Term)	Pegaptanib Sodium			Sham (n = 51)
	0.3 mg (n = 128)	1 mg (n = 126)	3 mg (n = 120)	
Blood and lymphatic system disorders				
Anemia NOS	5 (4)	7 (6)	4 (3)	2 (4)
Cardiac disorders				
Cardiac failure congestive	2 (2)	1 (1)	1 (1)	4 (8)
Bradycardia NOS	0	1 (1)	0	4 (8)
Infections				
Upper respiratory tract infection NOS	4 (3)	9 (7)	2 (2)	2 (4)
Urinary tract infection NOS	8 (6)	2 (2)	3 (3)	3 (6)
Influenza	6 (5)	3 (2)	3 (3)	2 (4)
Musculoskeletal and connective tissue disorders				
Back pain	3 (2)	4 (3)	6 (5)	3 (6)
Nervous system disorders				
Headache	4 (3)	7 (6)	8 (7)	1 (2)
Dizziness	6 (5)	1 (1)	2 (2)	1 (2)
Respiratory, thoracic, and mediastinal disorders				
Nasopharyngitis	12 (9)	8 (6)	10 (8)	3 (6)
Vascular disorders				
Hypertension NOS [†]	8 (6)	5 (4)	8 (7)	3 (6)

NOS = not otherwise specified.

*Data for second year of treatment.

[†]Incidences of systemic vascular hypertensive disorders (a Medical Dictionary for Regulatory Activities high-level term that includes the preferred terms *hypertension* NOS and *hypertension aggravated*) were similar in the pegaptanib (7%) and sham (6%) subjects (Table 13).