

Pegaptanib 1-Year Systemic Safety Results from a Safety–Pharmacokinetic Trial in Patients with Neovascular Age-Related Macular Degeneration

Macugen AMD Study Group*

Objective: To characterize the safety, tolerability, and pharmacokinetics of the pegylated anti-vascular endothelial growth factor (VEGF) aptamer pegaptanib sodium in subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD).

Design: Prospective 2-cohort study: (1) open-label cohort and (2) randomized, double-masked, uncontrolled multicenter trial.

Participants: In the combined cohorts, 147 subjects with any angiographic subtype of subfoveal choroidal neovascularization secondary to AMD and best-corrected visual acuities (VAs) in the study eye of 20/40 to 20/320 and in the fellow eye of 20/800 or better received pegaptanib sodium.

Intervention: Subjects were randomized to receive intravitreal pegaptanib sodium (1 mg or 3 mg [3- and 10-fold higher than the 0.3-mg approved dose]) every 6 weeks for 54 weeks.

Main Outcome Measures: Safety assessments included blood chemistries, urinalyses, vital signs, electrocardiograms, serum antipegaptanib antibody assays, adverse events, VAs, and intraocular pressures. After the first, fourth, and eighth injections, serial blood samples were obtained for quantification of pegaptanib plasma concentrations.

Results: No antipegaptanib immunoglobulin G (IgG) or IgM antibodies were detected. Few systemic adverse events were noted. Mild or moderate ocular adverse events related to the injection procedure were reported in most patients. Pegaptanib did not accumulate in plasma after multiple doses; systemic exposures were similar after the first, fourth, and eighth doses. The mean apparent terminal half-life was 10 days. Evaluation of blood pressure (BP) and urine protein, both of which are known to be affected by systemic VEGF inhibition, indicated no evidence of a pegaptanib treatment effect on these parameters. Mean BP at the end of year 1 remained below 140 mmHg (systolic) and 90 mmHg (diastolic), levels considered hypertension by the American College of Cardiology.

Conclusions: At doses up to 10-fold higher than the 0.3-mg dose approved for the treatment of AMD, pegaptanib sodium was well tolerated, with no detectable clinical evidence of systemic VEGF inhibition (i.e., no clinically meaningful changes in proteinuria or mean BP) and no clinically relevant ocular inflammation. Most ocular adverse events were related to the injection procedure itself and were mild or moderate in severity. *Ophthalmology* 2007;114:1702–1712 © 2007 by the American Academy of Ophthalmology.



Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in older individuals in the industrialized world.¹ While there are a number of factors

contributing to the development of AMD, the principal cause of vision loss is choroidal neovascularization.^{2,3} Although a combination of endogenous molecular regulators has been identified as facilitating this complex process, a large body of evidence has validated the major role of vascular endothelial growth factor (VEGF).^{4–10} The 165

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isoform (VEGF₁₆₅), in particular, is specifically operative in the pathogenesis of ocular neovascularization¹¹ and has been found to be present in all angiographic subtypes of choroidal neovascularization associated with neovascular AMD.^{12–14} Pegaptanib sodium injection [Macugen, (OSI) Eyetech Inc., New York, New York), a VEGF₁₆₅ inhibitor, is the first anti-VEGF agent proven to be efficacious for its management.¹⁵

Pegaptanib is a pegylated (i.e., conjugated to polyethylene glycol) neutralizing RNA aptamer that targets VEGF₁₆₅.¹⁵ Aptamers are chemically synthesized modified oligonucleotides composed of single-stranded nucleic acids that adopt a specific 3-dimensional conformation allowing them to bind with high specificity and affinity to molecular targets in a manner similar to that of monoclonal antibodies.¹⁶ An important feature of aptamers is that they are essentially nonimmunogenic, thereby avoiding issues of immunogenicity associated with a number of recombinant human proteins.^{16,17} Pegaptanib's lack of immunogenicity also might be due to its pegylation, which has been shown to suppress the immunogenicity of proteins.^{18–20}

Pegaptanib was designed to be a locally acting drug with the polyethylene glycol moiety serving to increase the residence time of the drug in the eye. After intravitreal administration in rabbits and monkeys, pegaptanib is slowly cleared from the eye via the systemic circulation, with an estimated vitreal half-life of 94 hours. Plasma concentrations were shown in young healthy monkeys to be approximately 800- to several thousand-fold lower than those seen in the vitreal throughout the dosing interval.²¹

The present study was initiated concurrently with the phase III studies of pegaptanib sodium (VEGF Inhibition Study in Ocular Neovascularization trials) to provide an early indicator of safety and tolerability and to profile the pharmacokinetics of pegaptanib sodium when given as intravitreal injections every 6 weeks for 54 weeks to patients with subfoveal choroidal neovascularization secondary to AMD. Extensive evaluation of early indicators of systemic VEGF inhibition (i.e., blood pressure [BP] elevation and proteinuria) was performed in this study at doses 3- to 10-fold higher than the dose now approved for treating patients with AMD (i.e., 0.3-mg pegaptanib sodium every 6 weeks).^{15,22}

Materials and Methods

Study Design

This study was a prospective, 2-cohort, multicenter trial of the safety, tolerability, and pharmacokinetics of pegaptanib sodium administered by intravitreal injection every 6 weeks for 54 weeks in patients with AMD. Patients were recruited from 20 centers in the United States. Using an open-label run-in design, the first cohort received single intravitreal injections of 3-mg pegaptanib sodium in the study eye every 6 weeks for 54 weeks. Because the recommended dose for pegaptanib sodium had not been established at the time this study was initiated, the highest of the 3 doses tested in the phase III trials (0.3, 1, and 3 mg) was used. When data obtained from the first cohort demonstrated no systemic safety concerns, enrollment for this cohort was discontinued and enrollment of the second cohort began. The second cohort was random-

ized (1:1) in a double-masked parallel-group fashion to receive either 1- or 3-mg pegaptanib sodium per study eye every 6 weeks for 54 weeks. No sham or placebo group was enrolled in this study. In the randomized double-masked cohort, treatment was allocated centrally by a dynamic minimization procedure stratified by center, angiographic lesion subtype, and previous treatment with photodynamic therapy with verteporfin. To maintain masking, the study ophthalmologist responsible for patient care and safety assessments did not administer the injection, and visual acuity (VA) was evaluated by a separate certified examiner masked to treatment assignment and to previous VA measurements. Patients from both cohorts were observed for up to 60 weeks or for at least 6 weeks after their last injection.

Except where noted, patient inclusion and exclusion criteria were the same as those in the phase III VEGF Inhibition Study in Ocular Neovascularization trials.¹⁵ In brief, ≥ 50 -year-old patients with subfoveal choroidal neovascularization secondary to AMD and best-corrected VAs in the study eye of 20/40 to 20/320 and in the fellow eye of 20/800 or better were eligible. Patients with all angiographic subtypes of AMD were enrolled. The 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. Eligible patients also were required to have an intraocular pressure (IOP) of ≤ 21 mmHg (≤ 23 mmHg in the VEGF Inhibition Study in Ocular Neovascularization), 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. Also, patients with predominantly classic lesions could receive photodynamic therapy with verteporfin as defined in the product label approved by the U.S. Food and Drug Administration at baseline and during the study at the discretion of the investigator. Patients were also required to have a serum creatinine value ≤ 2.5 mg/dl; blood urea nitrogen levels within 2.5 times the upper limit of normal; urine protein $\leq +1$; serum bilirubin ≤ 1.5 mg/dl; and γ -glutamyl transferase, serum glutamic-oxaloacetic transaminase/aspartate aminotransferase, serum glutamic-pyruvate transaminase/alanine aminotransferase, and alkaline phosphatase within 2 times the upper limit of normal. Patients with clinically significant concomitant diseases were excluded (e.g., diabetic retinopathy; New York Heart Association functional class III or IV cardiac disease; myocardial infarction within the last 6 months; unstable angina; peripheral vascular disease; clinically significant impaired renal or hepatic function; stroke within 12 months; previous therapeutic radiation to eye, head, or neck).

The study was conducted in full accordance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, South Africa, and Scotland) and with the International Conference on Harmonization Guideline for Good Clinical Practice. Institutional review board or ethics committee approval was obtained from each clinical center, and signed informed consent was obtained from all study participants.

Treatment

Pegaptanib sodium, formulated for intravitreal injection at 1 mg/90 μ l and 3 mg/90 μ l concentrations in preservative-free phosphate-buffered saline (pH, 5–7), was packaged in a sterile, single-use, United States Pharmacopeia type 1 graduated glass 1-ml syringe with a preattached 27-gauge needle. As described previously,^{15,23} all study eyes underwent a protocol-specified ocular antisepsis procedure and received subconjunctival anesthetic before intravitreal injection of pegaptanib sodium.

Patients in the open-label cohort were to receive 3 mg per study eye of pegaptanib sodium by intravitreal injection once every 6

weeks for 54 weeks. Patients in the randomized cohort were to receive either 1 or 3 mg per study eye of pegaptanib sodium by intravitreal injection once every 6 weeks for 54 weeks. At week 60, patients could be randomized to another year of treatment. The dose received in the randomized cohort was to remain masked throughout the study to both patients and centers.

Safety Assessments

Safety end points included all reported adverse events regardless of perceived relationship to study treatment, serious adverse events and deaths, discontinuations due to adverse events, vision loss, clinical laboratory values, determination of the presence or absence of serum immunoglobulin G (IgG) and IgM antibodies against pegaptanib, electrocardiograms (ECGs), and vital signs. Baseline safety assessments were obtained within 7 days before the first treatment. Patients withdrawn due to an adverse event were observed until the event resolved or the patient's condition was stable.

All adverse events were coded according to the Medical Dictionary for Regulatory Activities 5.1.²⁴ Adverse events that investigators felt were caused by the actual drug were classified as being related to the study drug. Events judged related to the injection procedure included those related to the intravitreal needle insertion as well as events resulting from concomitant procedures used to prepare the study eye (eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush, and subconjunctival injection of anesthetic).

An ophthalmologic examination including measurement of IOP; inspection of the anterior chamber (AC) for inflammation; and inspection of the lens, vitreous body, eyelids, pupils, iris, cornea, and retina was performed in the study eye at baseline, every 6 weeks just before injection, and again at least 30 minutes and 1 week after injection. The site phoned the patient at 3 days after injection to query for adverse events, unless the patient was in the office for a pharmacokinetic evaluation. Refraction testing and vision testing were performed at baseline and every injection day (predose) using retroilluminated modified Ferris-Bailey Early Treatment Diabetic Retinopathy Study charts. Color fundus photography and fluorescein angiography were performed at baseline, weeks 30 and 60, and early withdrawal, if applicable; photographs were sent to the Fundus Photograph Reading Center at the University of Wisconsin to determine enrollment eligibility retrospectively and to evaluate changes from baseline.

Laboratory assessments (hematology, renal function, hepatic function, electrolytes, and urinalysis), vital signs determinations (BP, pulse rate, temperature, and respiration rate), and body weight measurements were performed at baseline, before dose at each injection visit, and upon early withdrawal, if applicable. Two sitting BP measurements taken 2 to 5 minutes apart were required for each BP assessment. Additional urine samples were collected and BP measurements were made just before the blood pharmacokinetic sampling times after the first, fourth, and eighth injections (predose and at approximately 4 hours, 24 hours, 3 days, 1 week, 3 weeks, and 6 weeks). An ECG reading interpreted by the patients' internist was obtained at baseline, week 60, and early withdrawal, if applicable.

The presence or absence of IgG and IgM antibodies against pegaptanib was assessed in serum samples collected at baseline and before injections at weeks 6, 12, 18, 30, and 54 or early withdrawal using a screening qualitative sandwich enzyme-linked immunosorbent assay. Briefly, polystyrene microtiter plates (Maxisorp 96-well enzyme-linked immunosorbent assay plates, Nalgen Nunc International, Rochester, NY) were coated with pegaptanib at 4° C overnight (for approximately 16–18 hours), blocked with a 20% solution of human serum albumin in phosphate-

buffered saline, and washed with buffer (phosphate-buffered saline/0.05% polyoxyethylene 20 [Tween 20, Sigma-Aldrich, St. Louis, MO]). Microtiter wells were then incubated with diluted patient sera (1:100) in Superchemiblock blocking buffer (Chemicon International, Temecula, CA) at room temperature for approximately 1 hour, washed as before, then incubated with a mixture of horseradish peroxidase-conjugated anti-IgG+IgM (Sigma-Aldrich). Peroxidase activity was quantified by incubation with tetramethyl benzidine (Bio FX, Owings Mills, MD). The reaction was stopped at 30 minutes, and optical densities at 450 nm with a 630-nm reference wavelength were determined. A ≥ 2 increase in absorbance between pretreatment and posttreatment samples was considered positive for an antibody response. The enzyme-linked immunosorbent assay was not considered to be validated according to good laboratory practice due to the absence of a positive control antibody (efforts to make an antibody against pegaptanib and to validate the assay have been unsuccessful). Therefore, the detection limits for the assay are not known.

Pharmacokinetics

Serial blood samples were collected predose and after the first, fourth, and eighth intravitreal injections of 1- or 3-mg pegaptanib sodium. Scheduled blood draws were predose and at 4 $\pm$ 2 hours, 24 $\pm$ 4 hours, 3 $\pm$ 1 days, 1 week (7 $\pm$ 2 days), 3 weeks (21 $\pm$ 3 days), and 6 weeks (42 $\pm$ 3 days) after dose and before the next scheduled injection. Additional trough samples were obtained before dosing at weeks 12, 36, and 54. Pegaptanib plasma concentrations were measured using a validated (according to good laboratory practice) dual hybridization assay. All patients in this study received pegaptanib sodium and donated blood samples for the analysis of pharmacokinetics. Mean plasma concentrations for the 2 cohorts by dose were depicted graphically. The results of a population pharmacokinetic and pharmacodynamic analysis are to be reported in a separate publication.

Data Analyses

The safety population included all patients who received at least 1 dose of study medication. Hematology, liver function, renal function, and electrolyte laboratory parameters were evaluated for the incidence of predefined clinically significant abnormalities and for median and mean changes from baseline to last observation up to week 60. Urine samples were analyzed for urine protein, urine blood, and urinary albumin-to-creatinine ratio; categorical changes from baseline were evaluated at each time point. Although the accuracy of the random collections for urine albumin-to-creatinine ratio estimations is inferior to that of the first-morning urine sample and abnormal values vary with age and gender, an abnormal value was considered to be >30 mg/g for this study based on previous reports.²⁵ Adverse events were coded according to the Medical Dictionary for Regulatory Activities 5.1.²⁴ Adverse events also were summarized according to the investigator-determined relationship to the injection procedure or the study drug.

The study was neither powered nor designed to analyze efficacy, and no hypothesis testing was planned. Data were analyzed using SAS (version 8.2, SAS Institute, Cary, NC). It was planned to include 125 patients to yield 100 evaluable patients for the safety and pharmacokinetic analyses; due to rapid recruitment, the study enrolled 147 patients.

Table 1. Baseline Patient Characteristics and Study Treatments

	Open-Label Cohort (3 mg)* (N = 37)	Randomized Cohort			All Patients (N = 147)
		1 mg (N = 54)	3 mg (N = 56)	All Randomized (N = 110)	
Gender [n (%)]					
Male	13 (35)	15 (28)	24 (43)	39 (35)	52 (35)
Female	24 (65)	39 (72)	32 (57)	71 (65)	95 (65)
Race [n (%)]					
White	37 (100)	52 (96)	54 (96)	106 (96)	143 (97)
Age (yrs)					
Mean (SD)	75.6 (8.2)	78.2 (6.2)	77.6 (6.5)	77.9 (6.3)	77.3 (6.9)
Range	53–88	61–90	64–90	61–90	53–90
Lesion type [n (%)]					
Predominantly classic	13 (35)	8 (15)	11 (20)	19 (17)	32 (22)
Minimally classic	11 (30)	26 (48)	25 (45)	51 (46)	62 (42)
Occult (no classic)	13 (35)	20 (37)	20 (36)	40 (36)	53 (36)
≥1 previous, study eye [n (%)]					
PDT [†]	13 (35)	9 (17)	8 (14)	17 (15)	30 (20)
AMD treatment	8 (22)	15 (28)	9 (16)	24 (22)	32 (22)
Baseline visual acuity (letters)					
Study eye					
Mean (SD)	51.1 (13.9)	49.7 (15)	53 (11.1)	51.4 (13.2)	51.3 (13.3)
Median; range	53; 23–73	52; 21–75	53; 33–72	52.5; 21–75	53; 21–75
Fellow eye					
Mean (SD)	57 (28.9)	53.2 (24.7)	54.4 (29.2)	53.8 (27.0)	54.6 (27.4)
Median; range	70; 7–85	59; 7–85	67.5; 4–85	61; 4–85	64; 4–85
Worse eye as study eye [n (%)]	21 (57)	31 (57)	34 (61)	65 (59)	86 (59)
No. of study treatments					
Mean	9.8	9.6	9.4	9.5	9.6
Median; range	10; 4–10	10; 5–10	10; 5–10	10; 5–10	10; 4–10

AMD = age-related macular degeneration; PDT = photodynamic therapy; SD = standard deviation.

*Due to a labeling error, 31 of the 37 patients received 0.3 mg instead of 3 mg on ≥1 occasions between weeks 24 and 48.

[†]Prior or baseline with verteporfin.

Results

Patient Disposition and Demographics

Of the 147 patients enrolled, 37 patients were assigned to the open-label cohort (3 mg per study eye every 6 weeks for 54 weeks), and 110 patients were assigned to the double-masked randomized cohort (54 patients to 1 mg per study eye and 56 patients to 3 mg per study eye every 6 weeks for 54 weeks). All patients received at least one treatment. A total of 1407 intravitreal injections of pegaptanib sodium were administered up to week 60. Overall, the mean number of injections received was 9.6 of a possible 10 treatments (Table 1). The mean duration of treatment was 52.2 weeks. No patients were lost to follow-up during the reporting period up to week 60.

Baseline demographics and ocular characteristics were similar across treatment groups (Table 1). The patient population in both cohorts was predominantly female and white and had a mean age of 75 years, reflecting the general population with AMD. There were no clinically meaningful imbalances among treatment groups. The most frequently reported concomitant diseases at baseline were hypertension (63%), arthritis (29%), hypercholesterolemia (29%), osteoporosis (24%), and gastroesophageal reflux disease (22%). The study eye was the worse eye in 86 of 147 (59%) patients.

Clinical Laboratory Results

Hematology, liver function, renal function, and electrolyte laboratory parameters were evaluated for predefined clinically significant

abnormalities and median and mean change from baseline to last observation up to week 60. No clinically meaningful pattern of change from baseline was identified for any of the analytes evaluated. There were no findings to suggest a relationship between laboratory abnormalities and treatment with pegaptanib sodium. No patient discontinued from study treatment due to a laboratory abnormality.

The majority of patients' urinalyses were negative for urine protein throughout the study (Fig 1). Twenty-eight percent (41/147) of patients had urine protein of ≥+1 on ≥1 of the 47 occasions on which it was measured (Table 2); however, more than half of these abnormalities were isolated single elevations, and all subsequent values were negative. Three patients with a preenrollment history of hypertension experienced proteinuria (+3) on at least 1 occasion during the study. Values returned to pretreatment levels by week 60 for 2 patients. The third patient (in the 1-mg randomized group) had +3 values for both urine protein and blood at week 60 and had a history of hypertension, interstitial nephritis, nephrolithiasis, prostate hypertrophy, and prostate cancer. Hematuria (≥+1) was detected in 26 of 147 (18%) patients (Table 2) and occurred on only 1 occasion in 11 patients, with all subsequent values negative. As with proteinuria, by week 60 almost all patients had values consistent with pretreatment levels.

Overall, 74 of 147 (50%) patients had an abnormal albumin-to-creatinine ratio on one or more occasions. At baseline and week 60, respectively, 36 of 147 (24%) and 26 of 147 (19%) patients had an abnormal ratio. The frequency of patients with ratios above the normal limit in this study was likely the result of multiple measure-

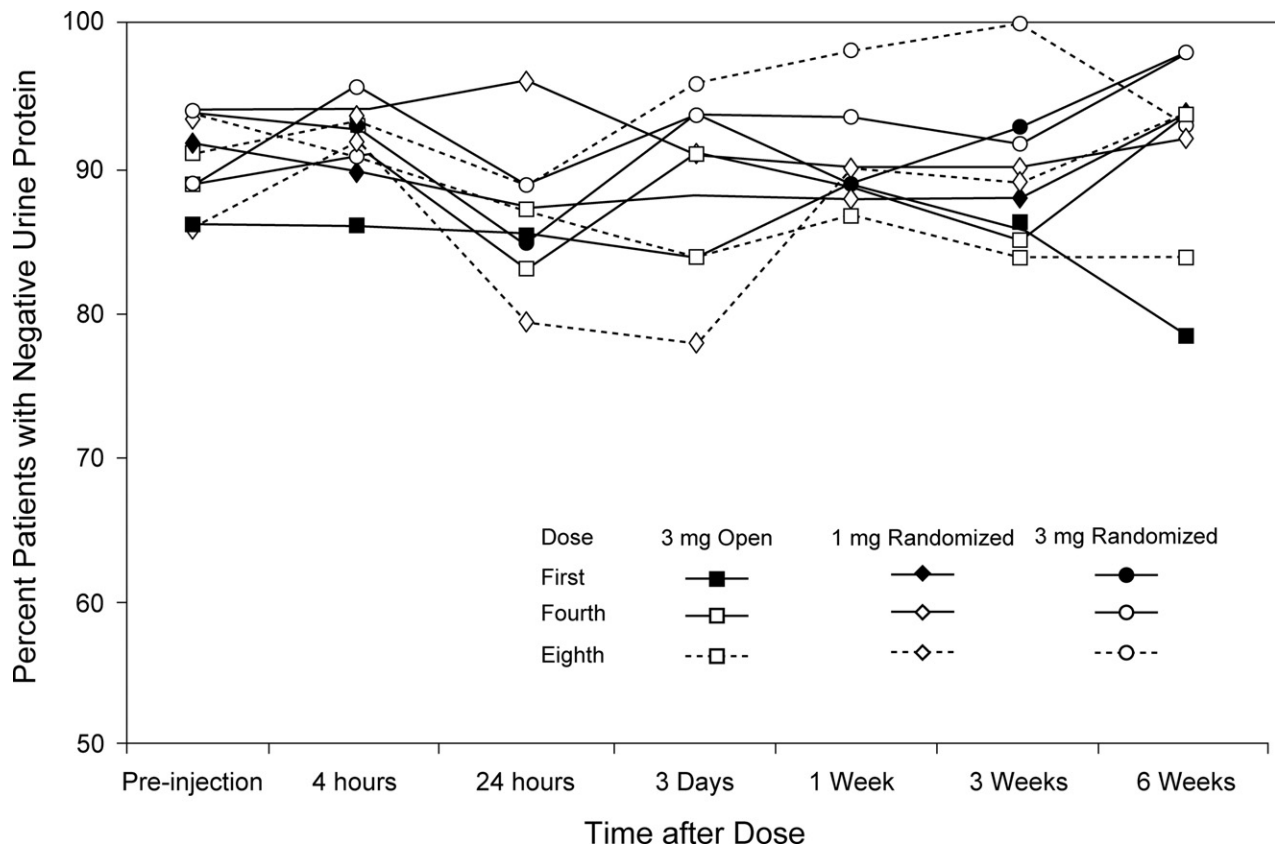


Figure 1. Percent of patients with negative urine protein after the first, fourth, and eighth doses throughout the dosing interval. Open = open-label.

ments (47 times after the first dose) of a parameter that is highly variable and commonly abnormal in this population. No relationship between treatment with pegaptanib sodium and urine abnormalities was identified; in particular, no dose-related change was noted.

Vital Signs and Electrocardiograms

No clinically meaningful changes from baseline mean or median measurements of vital signs, including BP, were noted in any

treatment group. There was little change from baseline values in sitting systolic and diastolic BPs at 4 hours, 24 hours, 3 days, 1 week, and 3 weeks after the first, fourth, and eighth doses in any of the groups (see Fig 2 for a depiction of data from the 3-mg randomized group; data for the other treatment groups are not shown). There also were no clinically meaningful changes in mean systolic and diastolic BPs during the 1-year study period for any treatment group (Fig 3). Mean BP at the end of year 1 remained below 140 mmHg systolic and 90 mmHg diastolic, levels consid-

Table 2. Summary of Patients with Urine Laboratory Abnormalities [n (%)]

Laboratory Abnormality	Open-Label Cohort (3 mg) (N = 37)	Randomized Cohort			All Patients (N = 147)
		1 mg (N = 54)	3 mg (N = 56)	All Randomized (N = 110)	
Urine protein $\geq$ 1+					
Baseline	1 (3)	2 (4)	2 (4)	4 (4)	5 (3)
At least one occasion after first dose	7 (19)	20 (37)	14 (25)	34 (31)	41 (28)
Week 60	0 (0)	3 (6)	2 (4)	5 (5)	5 (3)
Urine blood $\geq$ 1+					
Baseline	1 (3)	2 (4)	3 (5)	5 (5)	6 (4)
At least one occasion after first dose	8 (22)	12 (22)	6 (11)	18 (16)	26 (18)
Week 60	1 (3)	3 (6)	0 (0)	3 (3)	4 (3)
Urine albumin-to-creatinine ratio $>$ 30 mg/g					
Baseline	8 (22)	14 (26)	14 (25)	28 (25)	36 (24)
At least one occasion after first dose	20 (54)	29 (54)	25 (45)	54 (49)	74 (50)
Week 60	4 (11)	14 (28)	8 (16)	22 (22)	26 (19)

The number of patients contributing samples may vary at baseline and week 60; percentages are based on the number of patients donating samples at each time point.

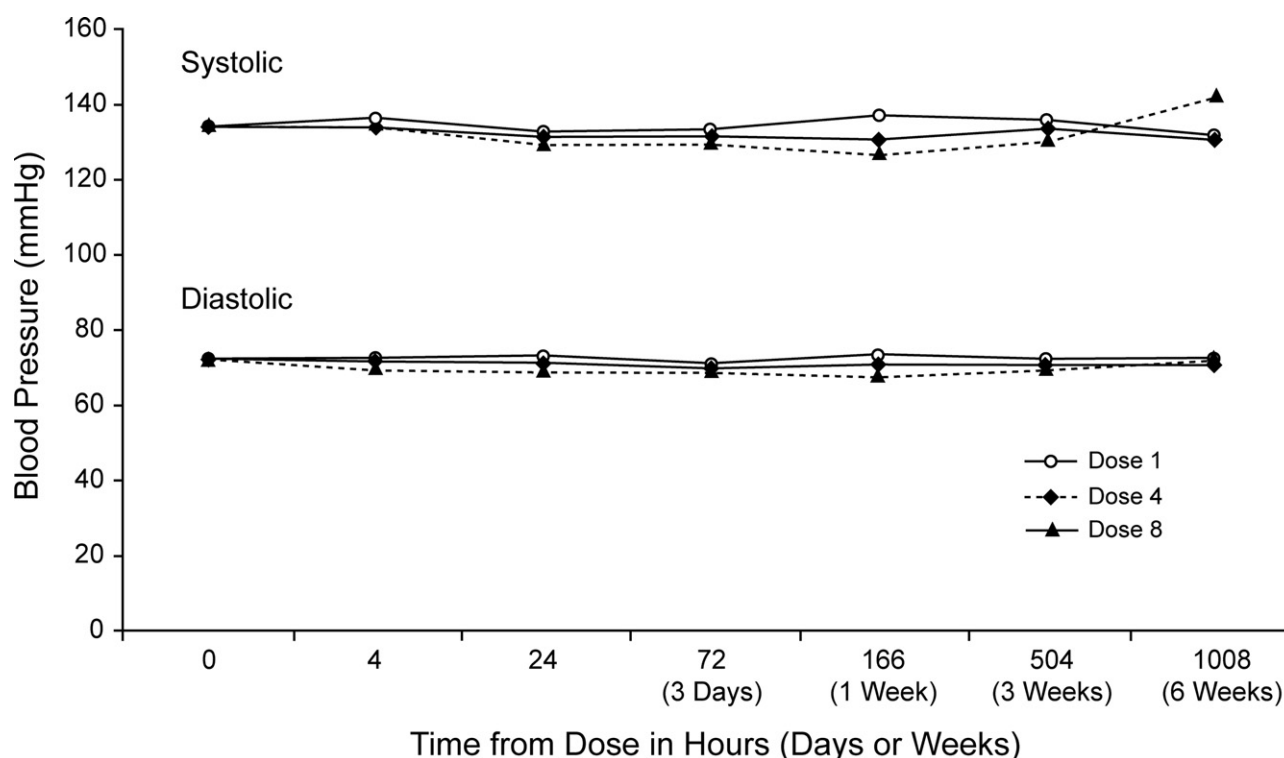


Figure 2. Mean systolic and diastolic blood pressures after the first, fourth, and eighth doses, 3-mg randomized group.

ered a threshold for institution of antihypertensive therapy by the American College of Cardiology.²⁶ There was no suggestion of a difference in ECG findings among treatment groups, and there did not appear to be a relationship between long-term treatment with pegaptanib sodium and ECG findings.

Pharmacokinetic and Antibody Assessments

In patients receiving 1-mg pegaptanib sodium, mean pegaptanib plasma concentrations were measurable (>8 ng/ml) for up to 1 week after injection (Fig 4). Mean maximal pegaptanib plasma concentrations after the first, fourth, and eighth injections were similar and ranged from 20 to 24 ng/ml.

In patients receiving 3-mg pegaptanib sodium (in either the randomized or the open-label cohort), mean plasma concentrations were maximal during the first week after injection, ranging from 65 to 98 ng/ml (Fig 4). Thereafter, mean pegaptanib plasma concentrations for the 3-mg groups declined with measurable levels (>8 ng/ml) for up to 3 to 4 weeks after dosing, reflecting the slow clearance of pegaptanib from the eye into the systemic circulation. The mean pegaptanib plasma concentration–time profiles after the fourth and eighth 3-mg injections were similar to those observed after the first dose, suggesting that there was no accumulation of pegaptanib in plasma after multiple dosing. In the majority of patients, pegaptanib plasma concentrations were not measurable 6 weeks after dosing for the 3-mg groups.

Sera for evaluation of IgG and IgM antibodies against pegaptanib were available from a majority of patients, generally 85% of patients at all time points; one patient did not provide a baseline sample and was excluded from further evaluation. No patient had detectable antipegaptanib antibodies at any assessment, although interpretation of these results is limited by the inability to validate the assay due to the lack of a positive control serum.

Adverse Events

All but 2 patients experienced at least one adverse event (Table 3). Serious adverse events were experienced by 28 of 147 (19%) patients and were most frequently classified as cardiac disorders (Table 3). No patient discontinued the study due to adverse events, and there were no notable differences among treatment groups in overall adverse event rates (Table 3). Nonocular adverse events were uncommon (Table 4), and there was no evidence of systemic toxicity. Five patients (2 receiving 1 mg and 3 receiving 3 mg in the randomized cohort) died before the week 60 cutoff and within 60 days of the last dose (causes of death were arteriosclerosis, aortic disorder, cardiac arrest, dementia, and pneumonia). None of the events that resulted in death was considered to be related to study treatment.

Ocular adverse events in the study eye were experienced by 138 of 147 (94%) patients. Most ocular events were mild to moderate in severity. Only one ocular adverse event was reported as serious—retinal hemorrhage, moderate in severity, was reported on day 245 in one patient (3 mg randomized) and was considered to be unrelated to the study treatment by the investigator; the patient continued study treatment. There were no reports of endophthalmitis, retinal detachment (RD), or traumatic cataract in the study eye.

The most common ocular adverse events in the study eye for both the open-label cohort and the randomized cohort were eye pain (69/147 [47%]), vitreous floaters (63/147 [43%]), punctate keratitis (60/147 [41%]), visual disturbance (37/147 [25%]), eye irritation (33/147 [22%]), and increased IOP (31/147 [21%]). Eleven patients (11/147 [7%]) were noted to have mild AC inflammation; moderate or severe inflammation was not noted. Most events occurred with similar frequency across treatment groups. The incidence of increased IOP appeared to be greater in the 3-mg

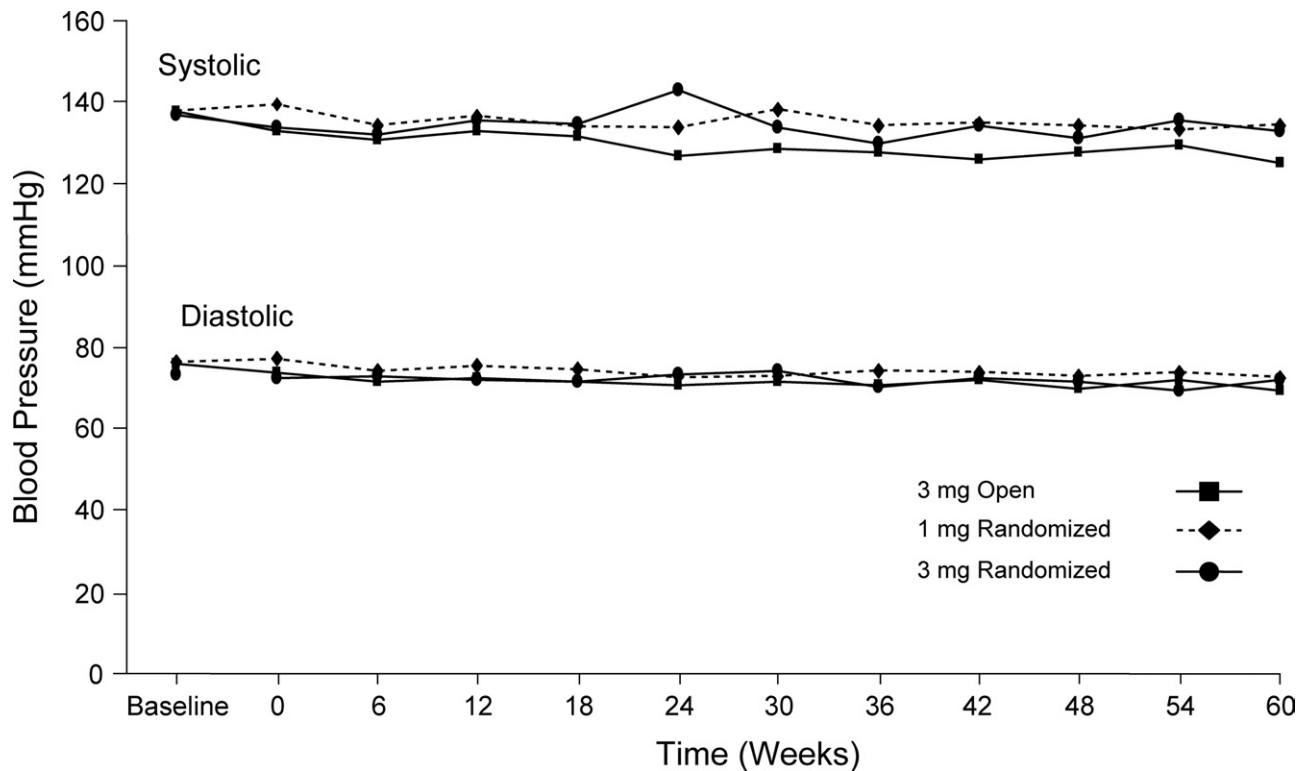


Figure 3. Mean systolic and diastolic blood pressures during the 60-week treatment period. Open = open-label.

group. Most ocular adverse events were attributed by the investigator to the injection procedure, with few events being attributed to the study drug. As expected, the incidence of ocular adverse events in the fellow eye was much lower than that in the study eye (35% vs. 94%, respectively; Table 3).

Fluorescein angiography review by the independent reading center revealed no retinal vascular or choroidal abnormalities in the study eye that were not expected in the natural progression of neovascular AMD. There were no notable delays in arteriovenous transit time, abnormalities in choroidal perfusion, or arteriolar occlusions.

Intraocular Pressure Assessments

There was no evidence of a persistent increase in IOP associated with up to 60 weeks of treatment with pegaptanib sodium. Mean IOP at 30 minutes after injection was 3 to 8 mmHg higher than mean preinjection IOP, with the largest increases seen in the 3-mg randomized group. The mean IOP returned to preinjection levels in all treatment groups by the next IOP measurement, 1 week after injection (Fig 5). Elevations in IOP to ≥ 35 mmHg (a monitoring threshold suggested by the Independent Data Monitoring Committee) at any time during the study occurred in 2 of 54 (4%) patients receiving 1-mg pegaptanib sodium in the randomized cohort, 12 of 56 (21%) patients receiving 3 mg in the randomized cohort, and 7 of 37 (19%) patients receiving 3 mg in the open-label cohort (Table 5), [available at <http://aaojournal.org>]. The percentage of patients experiencing such elevations did not increase with greater numbers of injections. Three patients receiving 3-mg pegaptanib sodium underwent a single postinjection paracentesis, for per injection frequencies of 0.2% (1/529) and 0.6% (2/361) in the randomized and open-label groups, respectively.

Discussion

Compliance was high with pegaptanib sodium intravitreal injections of 1 and 3 mg over a 1-year treatment period in this population of patients with AMD. Overall, the total number of injections administered was 1407, and the mean number of injections received was 9.6 of a possible 10 treatments, indicating high compliance throughout the 54 weeks of treatment.

No systemic safety concerns were observed, as most events other than eye disorders were infrequent and were of the type often seen in the elderly population. The ability to interpret and draw conclusions from our findings, however, is limited by the lack of a control group for comparison, the very small numbers of patients to evaluate safety, and the relatively short time, as compared with the pivotal efficacy and safety trials. Evaluation of BP and urine protein, both of which are known to be affected by systemic VEGF inhibition,^{27,28} suggested no evidence of a pegaptanib treatment effect on these parameters. No safety concerns with respect to laboratory tests, vital signs, or ECG recordings were observed. The frequency of patients with abnormal albumin-to-creatinine ratios throughout the study was likely the result of multiple measurements (47 up to week 60) of a parameter that is highly variable and commonly abnormal in this patient population, many of whom have concurrent illnesses of hypertension and diabetes.

There was no evidence of serum antipegaptanib IgG and IgM antibodies throughout the first year of treatment. These findings should be interpreted with caution due to

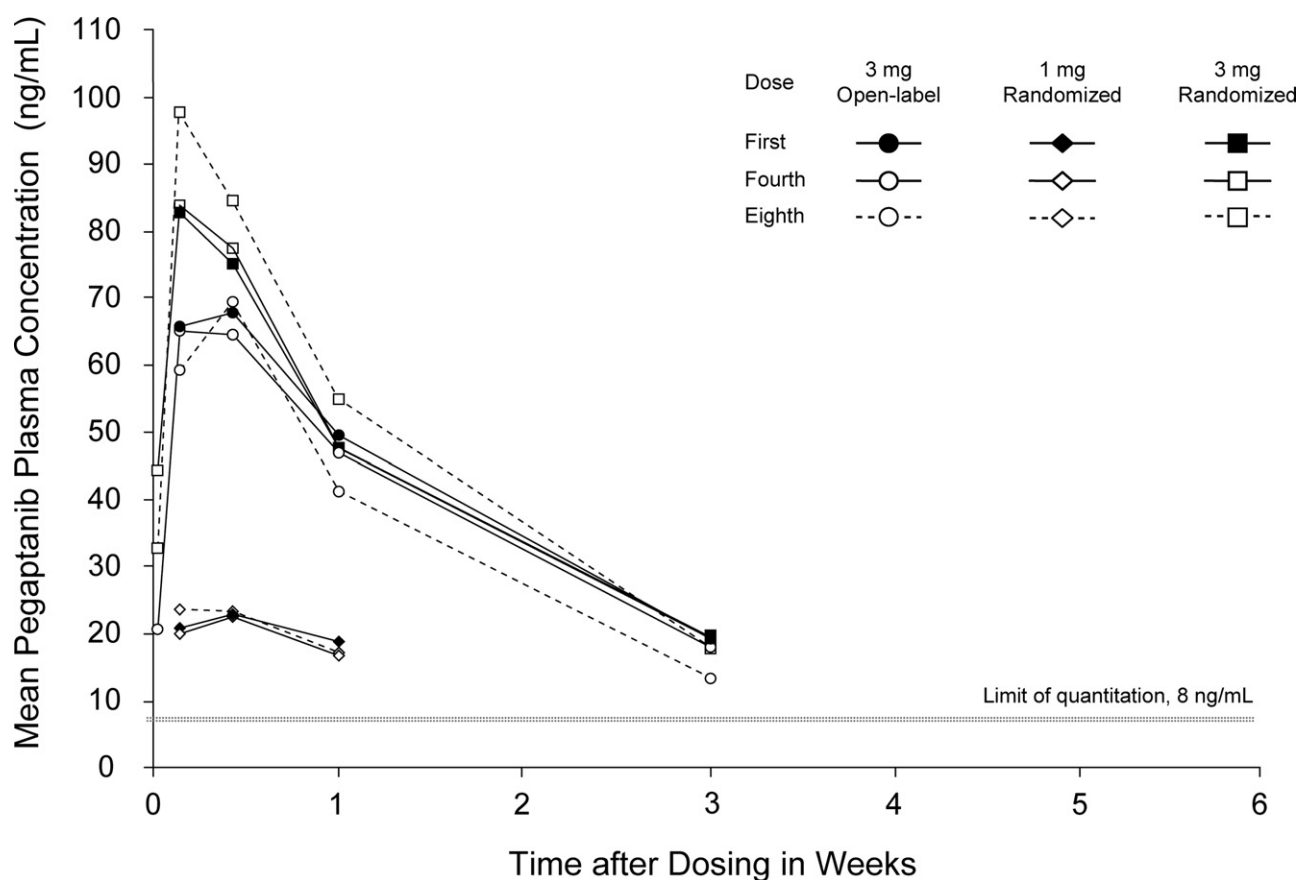


Figure 4. Mean pegaptanib plasma concentration–time profiles after the first, fourth, and eighth doses.

the lack of a positive control serum with which to validate the assay. The inability to generate a control serum is consistent with the hypothesis that pegaptanib is poorly immunogenic. Furthermore, the similar pegaptanib plasma concentration–time profiles observed after the first, fourth, and eighth injections provide indirect evidence that a significant antibody response was not developed after repeated injections.

The approved dose based on data from the pivotal efficacy trials¹⁵ is 0.3 mg, 3- and 10-fold lower than the doses used in this study. Thus, systemic exposure achieved with the 0.3-mg study dose might be expected to be 3- and 10-fold lower than those reported here for the 1-mg and 3-mg intravitreal doses, respectively. Pegaptanib plasma concentrations measured after administration of the approved dose of 0.3 mg would be expected to be below the lower quantifiable assay limit (<8 ng/ml) in most patients throughout the 6-week dosing interval. Although pegaptanib levels are low, they are orders of magnitude greater than normal circulating VEGF levels in adult humans (100 pg/ml).²⁹ Even though levels are potentially significant, pegaptanib would not be expected to saturate all systemic VEGFs because it most preferentially binds VEGF₁₆₅. As the pegaptanib plasma concentration–time profiles were similar for the first, fourth, and eighth doses, pegaptanib does not accumulate in the plasma when multiple intravitreal doses are administered every 6 weeks.

Although elevated VEGF levels are present during angiogenesis in the embryo and during disease in the adult, continuous basal levels of VEGF are required for endothelial cells to survive prolonged periods and function properly.³⁰ Because VEGF is a potent vasodilator and may play a role in maintaining adequate blood flow to organs,^{31,32} elevated BP may be a consequence of reduced circulating VEGF levels.³⁰ In addition to the impact on vasoactivity, renal glomerular capillary function is under the strict gene–dose-dependent control of VEGF.³³ If renal VEGF falls below a critical level, glomerular endothelial cells swell, capillary loops collapse, and proteinuria develops.³⁰ Indeed, Lutun and Carmeliet³⁰ have proposed that renal parameters and BP be used as surrogate markers of systemic VEGF inhibition.

In clinical practice, hypertension, often associated with proteinuria, has been observed after administration of systemic anti-VEGF therapies. Published reports indicate that the hypertension related to systemic anti-VEGF therapy persists throughout therapy^{28,34} and is manageable with antihypertensive agents.³⁴ In the pivotal phase III studies of intravitreally administered ranibizumab, however, the rates of hypertension and proteinuria were well balanced when compared with the control group.^{35,36} Similarly, there was no evidence of an association between pegaptanib treatment and hypertension or proteinuria in this study. The lack of evidence of systemic VEGF inhibition, as assessed

Table 3. Summary of Adverse Events up to Week 60 [n (%)]

Patients with	Open-Label Cohort (3 mg)* (N = 37)	Randomized Cohort			All Patients (N = 147)
		1 mg (N = 54)	3 mg (N = 56)	All Randomized (N = 110)	
At least 1 adverse event	37 (100)	54 (100)	54 (96)	108 (98)	145 (99)
At least 1 ocular adverse event†	35 (95)	52 (96)	52 (93)	104 (95)	139 (95)
Study eye	35 (95)	52 (96)	51 (91)	103 (94)	138 (94)
Fellow eye	11 (30)	23 (43)	18 (32)	41 (37)	52 (35)
At least 1 serious adverse event‡	8 (22)	9 (17)	11 (20)	20 (18)	28 (19)
Cardiac disorders	2 (5)	5 (9)	2 (4)	7 (6)	9 (6)
Gastrointestinal disorders	2 (5)	0 (0)	2 (4)	2 (2)	4 (3)
Injury, poisoning, procedural complications	0 (0)	2 (4)	3 (5)	5 (5)	5 (3)

*Due to a labeling error, 31 of the 37 patients received 0.3 mg instead of 3 mg on ≥ 1 occasions between weeks 24 and 48.

†None of the events in the fellow eye was considered by the investigator to be related to study treatment; approximately 84% of events in the study eye were attributed to injection procedure.

‡Medical Dictionary for Regulatory Activities terms for serious adverse event system organ classes with an incidence $\geq 5\%$.

by measurement of BP and urine protein, is a direct reflection of pegaptanib's pharmacokinetic and pharmacodynamic properties. Moreover, as the doses tested in this study were 3- to 10-fold higher than the recommended 0.3 mg per eye dose regimen, it is likely that an even greater safety margin is obtained in patients being treated for AMD.

Adverse events were mainly ocular in nature, related to the injection procedure, and generally mild or moderate in intensity. Although this study did not have a sham control group, the overall incidence of ocular events and types of events were similar to those reported in the pivotal efficacy and safety trials that provided the primary evidence supporting the safety of the approved 0.3-mg dose.^{15,23} Common ocular adverse events in the pivotal trials were ob-

served in a higher proportion of sham-treated eyes than in fellow eyes of patients receiving pegaptanib. It is likely that some events occurring in study eyes in the present trial were related to the preparation procedure rather than the intravitreal injection itself. Increases in IOP were manageable and transient in nature. There were no retinal vascular abnormalities in study eyes that were unexpected given the natural history of neovascular AMD. There were no cases of endophthalmitis, RD, or traumatic cataract in study eyes during the 1-year treatment period. The only study eye disorder considered serious (retinal hemorrhage) was considered by the investigator to be secondary to the natural progression of AMD and unrelated to pegaptanib treatment. The ability to draw conclusions from our findings is limited,

Table 4. Nonocular Adverse Events Reported by $\geq 10\%$ of Patients Treated with Pegaptanib Sodium up to Week 60 [n (%)]

All Causality Adverse Event Preferred Term*	Open-label Cohort (3 mg)† (N = 37)	Randomized Cohort			All Patients (N = 147)
		1 mg (N = 54)	3 mg (N = 56)	All Randomized (N = 110)	
Gastrointestinal disorders					
Diarrhea NOS	1 (3)	1 (2)	6 (11)	7 (6)	8 (5)
Infections and infestations					
Upper respiratory tract infection NOS	6 (16)	3 (6)	4 (7)	7 (6)	13 (9)
Urinary tract infection NOS	1 (3)	3 (6)	6 (11)	9 (8)	10 (7)
Musculoskeletal and connective tissue					
Arthralgia	4 (11)	1 (2)	4 (7)	5 (5)	9 (6)
Pain in limb	4 (11)	1 (2)	2 (4)	3 (3)	7 (5)
Psychiatric disorders					
Depression	4 (11)	2 (4)	2 (4)	4 (4)	8 (5)
Anxiety	4 (11)	2 (4)	1 (2)	3 (3)	7 (5)
Respiratory, thoracic, and mediastinal					
Nasopharyngitis	2 (5)	12 (22)	2 (4)	14 (13)	16 (11)
Bronchitis NOS	1 (3)	6 (11)	2 (4)	8 (7)	9 (6)
Vascular disorders					
Hypertension aggravated‡	4 (11)	7 (13)	5 (9)	12 (11)	16 (11)
Hypertension NOS	1 (3)	2 (4)	9 (16)	11 (10)	12 (8)

NOS = not otherwise specified.

*Medical Dictionary for Regulatory Activities.

†Due to a labeling error, 31 of the 37 patients received 0.3 mg instead of 3 mg on ≥ 1 occasions between weeks 24 and 48.

‡Hypertension was reported in 63% of patients at baseline; reports by the investigators of "increased hypertension" or "worsening of hypertension" were coded as "hypertension aggravated" per the Medical Dictionary for Regulatory Activities.

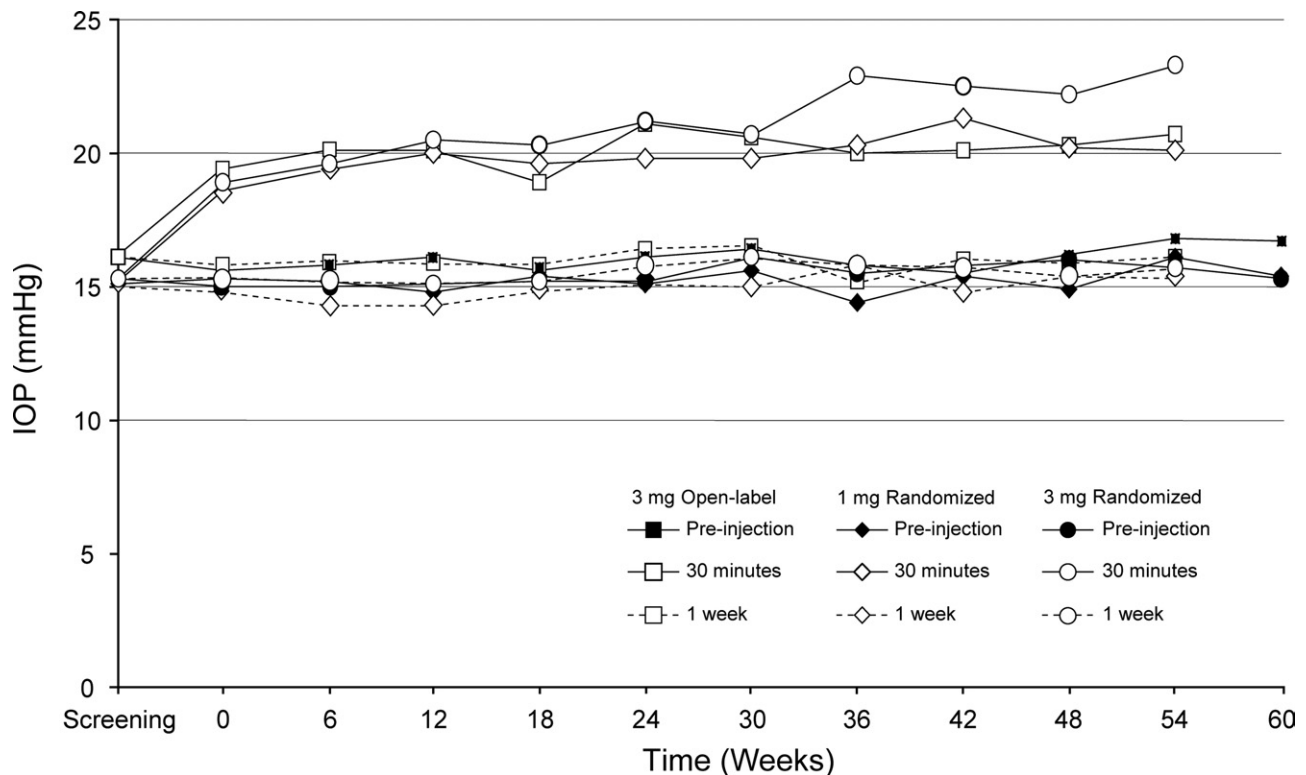


Figure 5. Mean preinjection, 30-minute, and 1-week postinjection intraocular pressure (IOP) values.

however, by the lack of a control group for comparison, very small numbers of patients to evaluate safety, and short time relative to the pivotal efficacy and safety trials.

In summary, no systemic safety concerns were observed with pegaptanib sodium injection at doses of 1 and 3 mg over a 1-year treatment period in patients with neovascular AMD. There also was no evidence of safety concerns with respect to laboratory results, ECGs, or vital signs. Adverse events were mainly ocular in nature and generally mild or moderate in intensity. Most such events were judged to be related to the injection procedure. Pegaptanib is a selective VEGF antagonist and showed a favorable safety profile.

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Appendix

The following investigators, data managers, and research coordinators participated in the study.

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Table 5. Summary of Patients Who Experienced Intraocular Pressure (IOP) ≥ 35 mmHg [n (%)]

Patients Who	Open-Label Cohort (3 mg)* (N = 37)	Randomized Cohort			All Patients (N = 147)
		1 mg (N = 54)	3 mg (N = 56)	All Randomized (N = 110)	
Experienced IOP ≥ 35 mmHg on ≥ 1 injection days	7 (19)	2 (4)	12 (21)	14 (13)	21 (14)
Had a paracentesis on ≥ 1 injection days	2 (5)	0 (0)	1 (2)	1 (1)	3 (2)

*Due to a labeling error, 31 of the 37 patients received 0.3 mg instead of 3 mg on ≥ 1 occasions between weeks 24 and 48.