

Year 2 Efficacy Results of 2 Randomized Controlled Clinical Trials of Pegaptanib for Neovascular Age-Related Macular Degeneration

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

Objective: To evaluate the efficacy of a second year of pegaptanib sodium therapy in patients with neovascular age-related macular degeneration (AMD).

Design: Two concurrent, multicenter, randomized, double-masked, sham-controlled studies (V.I.S.I.O.N. [Vascular Endothelial Growth Factor Inhibition Study in Ocular Neovascularization] trials).

Participants: Patients with all angiographic neovascular lesion compositions of AMD were enrolled. In combined analyses, 88% (1053/1190) were re-randomized at week 54, and 89% (941/1053) were assessed at week 102.

Interventions: At week 54, those initially assigned to pegaptanib were re-randomized (1:1) to continue or discontinue therapy for 48 more weeks (8 injections). Those initially assigned to sham were re-randomized to continue sham, discontinue sham, or receive 1 of 3 pegaptanib doses.

Main Outcome Measures: Mean change in visual acuity (VA) over time and mean change in the standardized area under the curve of VA and proportions of patients experiencing a loss of ≥ 15 letters from week 54 to week 102; losing < 15 letters (responders) from baseline to week 102; gaining ≥ 0 , ≥ 1 , ≥ 2 , and ≥ 3 lines of VA; and progressing to legal blindness (20/200 or worse).

Results: In combined analysis, mean VA was maintained in patients continuing with 0.3-mg pegaptanib compared with those discontinuing therapy or receiving usual care. In patients who continued pegaptanib, the proportion who lost > 15 letters from baseline in the period from week 54 to week 102 was half (7%) that of patients who discontinued pegaptanib or remained on usual care (14% for each). Kaplan–Meier analysis showed that patients continuing 0.3-mg pegaptanib for a second year were less likely to lose ≥ 15 letters than those re-randomized to discontinue after 1 year ($P < 0.05$). The proportion of patients gaining vision was higher for those assigned to 2 years of 0.3-mg pegaptanib than receiving usual care. Progression to legal blindness was reduced for patients continuing 0.3-mg pegaptanib for 2 years.

Conclusions: Continuing visual benefit was observed in patients who were randomized to receive therapy with pegaptanib in year 2 of the V.I.S.I.O.N. trials when compared with 2 years' usual care or cessation of therapy at year 1. *Ophthalmology* 2006;113:1508–1521 © 2006 by the American Academy of Ophthalmology.



From a worldwide perspective, age-related macular degeneration (AMD) has been estimated to cause 8.7% of total blindness.¹ In the United Kingdom, 3.5% of individuals ≥ 75 years of age were visually impaired due to AMD.² It has been estimated that in the United States as many as 15 million people suffer from some form of AMD,³ with more than 1.6 million experiencing the active blood vessel growth and leakage associated with neovascular AMD.⁴ Many studies have shown that two thirds of eyes with this disorder have experienced moderate or severe vision loss within 2 years of inception.^{5–7}

The presence of vascular endothelial growth factor (VEGF), particularly the VEGF₁₆₅ isoform, has been implicated as a key mediator in the pathogenesis of blood vessel growth and leakage, both hallmarks of neovascular AMD. A pluripotent growth factor, VEGF stimulates blood vessel growth by promoting endothelial cell proliferation and survival,^{8,9} mobilizing bone marrow–derived endothelial cell precursors,^{10,11} upregulating the synthesis of enzymes that degrade the extracellular matrix, and facilitating blood vessel extravasation.^{12,13} Vascular endothelial growth factor

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has been demonstrated in the ocular fluid of patients suffering from a variety of ocular neovascularizing syndromes,^{14,15} where it is spatially and temporally associated with the abnormally proliferating vessels.^{16–18} Preclinical studies have demonstrated that VEGF is both sufficient^{19–25} and necessary^{26–30} for ocular neovascularization. Of the various VEGF isoforms, VEGF₁₆₅ is notable as a proinflammatory cytokine, stimulating both pathologic neovascularization and vascular permeability in the eye while not being required for physiologic vascularization.³¹

The V.I.S.I.O.N. (VEGF Inhibition Study in Ocular Neovascularization) trials were the first large-scale, multicenter, randomized controlled replicate trials to demonstrate that intravitreal administration of pegaptanib sodium (a 28-ribonucleotide aptamer and a selective inhibitor of VEGF₁₆₅) every 6 weeks was efficacious in reducing vision loss for a broad spectrum of patients with neovascular AMD at 1 year with a favorable safety profile.³² Pegaptanib sodium has received regulatory approval and is currently in clinical use around the world for neovascular AMD irrespective of lesion size or angiographic composition. As the V.I.S.I.O.N. trials were designed to continue for a minimum of 102 weeks to assess prospectively safety and efficacy, this report is a summary of the findings at the end of year 2.

Materials and Methods

Study Design

Two concurrent, randomized, double-masked, sham-controlled dose-ranging studies (studies 1003 and 1004) enrolled patients at sites in the U.S., Canada, Europe, Israel, Australia, and South America. Institutional review board/ethics committee approval was obtained at each participating center. Eligibility criteria ensured the inclusion of patients with a broad range of visual acuity (VA) and neovascular AMD characteristics.³² In brief, ≥50-year-old patients with subfoveal choroidal neovascularization with any type of angiographic lesion composition due to AMD and a best-corrected VA (BCVA) in the study eye of 20/40 to 20/320 were eligible. As this was the first study involving intravitreal administration of a biological agent, patients with VA worse than 20/800 in the fellow eye were excluded. Other exclusion criteria were a lesion size exceeding 12 disc areas, <50% of the lesion having active choroidal neovascularization, and hemorrhage accounting for >50% of the lesion. Lesions could comprise up to 25% scars or atrophy but could not contain any subfoveal scars or atrophy. Patients with <50% classic lesion composition were required to have either subretinal hemorrhage (comprising up to 50% of the lesion) and/or documented evidence of ≥3 lines' vision loss in the 12 weeks before baseline and/or lipid. Patients with a history of up to 1 previous administration of photodynamic therapy with verteporfin were eligible provided administration was within 8 to 13 weeks before enrollment.

At baseline (week 0 in year 1), patients in each study were randomized to 1 of 4 treatment groups (0.3-mg, 1-mg, or 3-mg pegaptanib sodium or sham) receiving intravitreal or sham injections every 6 weeks, up to a total of 9 in the first year. The study was powered to test the primary efficacy end point, the proportion of patients losing <15 letters of VA at week 54, at the 0.05 significance level.³² In the second year, study objectives were to (1) describe the safety experience of patients treated with pegaptanib sodium injection for 2 years, (2) assess the relative benefit of 2 years' active treatment versus 2 years' usual care, and (3)

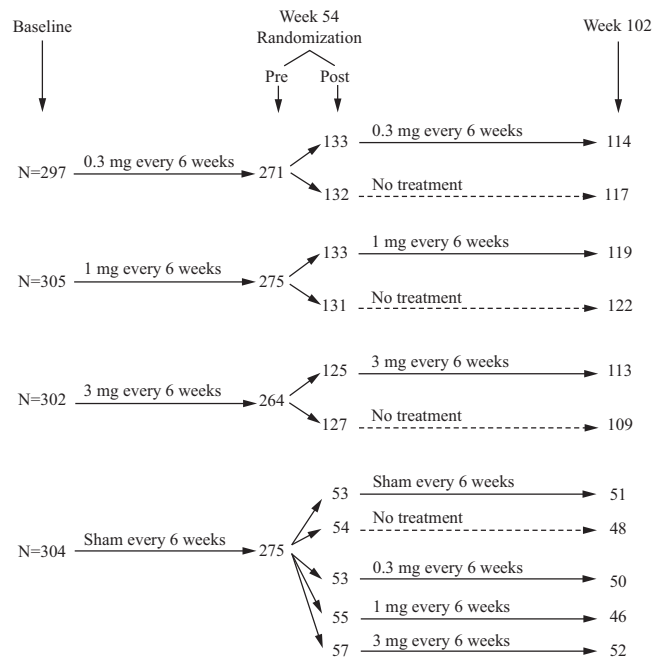


Figure 1. Number of patients randomized and assessed. Post = after; pre = before.

identify whether a second year of treatment provided an additional benefit beyond the first year. To achieve these multiple objectives, the prespecified study design included a randomized withdrawal of a proportion of patients from treatment at the end of year 1 (i.e., at week 54). Such designs have been described and are recommended by the International Conference on Harmonisation guidelines.³³

Patients were stratified during re-randomization at week 54 by study center and by week 54 VA in the study eye (>20/100 vs. ≤20/100). For ethical reasons, re-randomization was designed to (1) minimize the number of study patients who would be subjected to a sham procedure for 2 years, (2) minimize the number of study patients who would be without any active therapy for 2 years, and (3) allow treatment to be reinitiated (rescue therapy) during the second year in those re-randomized to stop treatment at week 54.

Thus, patients assigned to the sham group at week 0 were re-randomized (1:1:1:1) at week 54 to continue sham treatments, discontinue sham treatments, or be assigned to 1 of the 3 pegaptanib doses every 6 weeks. Patients assigned to pegaptanib at week 0 were re-randomized at week 54 on a 1:1 basis either to continue treatment every 6 weeks through week 102 (8 additional injections) or to stop treatment at week 54 (Fig 1). Patients who were re-randomized to stop treatment at week 54 were permitted to resume their year 1 treatment (sham or 1 of the 3 pegaptanib doses) if they had benefited from treatment in the first year (defined as the loss of ≤0 letters from baseline to week 54) and had lost ≥10 letters of VA after discontinuing pegaptanib or sham. Thus, for instance, if a patient randomized to sham during year 1 and re-randomized to discontinue at week 54 was found to have lost ≥10 letters at any post-re-randomization visit, the patient would be eligible to have sham treatments reinstated.

Patients who were re-randomized to stop treatment at week 54 were aware they were no longer receiving treatment. Patients continuing treatment into year 2 remained masked to their treatment assignment, as did the masked study investigators.

During the entire 102 weeks, masked investigators were permitted to administer photodynamic therapy with verteporfin at their discretion according to Food and Drug Administration–

Table 1. Study Flowchart—Assessments and Timing

	Study Week									
	54	60	66	72	78	84	90	96	102	EW
Treatment no.	1	2	3	4	5	6	7	8		
Re-randomization	X									
Pegaptanib sodium or sham injection	X*	X*	X*	X*	X*	X*	X*	X*		
Efficacy										
Refraction and VA (ETDRS)	B	S	S	S	B	S	S	S	B	B
Color fundus photographs [†]	B				B				B	B
Fluorescein angiogram [‡]	B				B				B	B
Indocyanine green angiograms/OCT [§]	B								B	B
Safety										
Physical examination [§]										
Adverse events/serious adverse events	X	X	X	X	X	X	X	X	X	X
IOP	B [¶]	S [¶]	S [¶]	S [¶]	B [¶]	S [¶]	S [¶]	S [¶]	B	B
Ophthalmic examination	B [¶]	S [¶]	S [¶]	S [¶]	B [¶]	S [¶]	S [¶]	S [¶]	B	B
Vital signs	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X*	X*	X*	X*	X*	X*	X*	X*	X*	X
Electrocardiogram									X	X
Telephone safety check [#]	X*	X*	X*	X*	X*	X*	X*	X*		

B = assessment of both eyes; ETDRS = Early Treatment Diabetic Retinopathy Study; EW = early withdrawal (before week 102); IOP = intraocular pressure; OCT = optical coherence tomography; S = assessment of study eye only; VA = visual acuity; X = assessment.

*Treated (pegaptanib or sham) patients only.

[†]Sent to independent reading center for efficacy and safety assessments.

[‡]Some selected sites performed optional indocyanine green angiograms or OCT, but no analyses of data were performed.

[§]Performed postbaseline only if indicated.

^{||}Applanation tonometry at baseline and for confirmation of IOP > 30 mmHg.

[¶]Before treatment, at least 30 min after treatment, and 1 wk after treatment.

[#]Telephone safety check carried out 3 days after treatment.

approved use (i.e., for predominantly classic lesions only) to patients regardless of study treatment assignment.

Year 2 Patient Assessments

Patient assessments in the second year were similar to those in the first year and are summarized in Table 1. Before study treatment at each 6-week visit, certified masked examiners measured BCVA using the Early Treatment Diabetic Retinopathy Study chart. Routine biochemical and hematological analyses were conducted, and vital signs were recorded at each visit before treatment. An ophthalmologic examination and intraocular pressure measurements were performed at each visit just before administration of the study drug and at 30 minutes and 1 week after treatment. Color fundus photography and fluorescein angiography were performed at baseline and at weeks 30, 54, 78, and 102. Fluorescein angiographic measurements of total lesion size, choroidal neovascularization size, and leakage size and color fundus photograph measurements of serous sensory retinal detachment (RD) areas were performed in a masked fashion according to a standardized protocol at the University of Wisconsin reading center. All fluorescein angiograms and color fundus photographs were graded systematically for evaluation of disease progression and changes in retinal anatomy unexpected in the natural course of the disease. Exit assessments were conducted on all patients who withdrew from the study. Those who withdrew due to an adverse event were kept under review until the event resolved or until an adequate explanation was obtained for the event. Safety findings are reported in a separate article.³⁴

Efficacy End Points

End points in year 2 were chosen to accommodate the study design and take into account discontinuation during the trial. Year 2

efficacy end points included the mean change in VA over time from week 54 to week 102 and Kaplan–Meier proportions of the loss of an additional 15 letters of vision from week 54 to week 102 (comparing patients who continued with active therapy with those who discontinued). For completeness, calculations of the proportion of patients losing <15 letters of VA from baseline to week 102 and of the proportion of patients who progressed to legal blindness in the study eye also were performed. We also report the proportion of patients gaining ≥ 0 , ≥ 1 , ≥ 2 , and ≥ 3 lines of VA; VA changes for patients who resumed their year 1 therapy after the loss of ≥ 10 letters of VA after discontinuation at week 54 (rescued patients); and fluorescein angiographic changes over time for reading center estimates of lesion size, total choroidal neovascularization (classic plus occult), leak area, and change in area of serous sensory RD.

Statistical Analyses

The 2 V.I.S.I.O.N. trials (studies 1003 and 1004) are presented individually and as a combined analysis. The combined analysis provides a more accurate point estimate of the data. These analyses are based on intent to treat and include all patients who were re-randomized at week 54. For visits where an efficacy assessment was missing, the last observation was carried forward except where noted. Analyses were performed for patients based on the treatment group to which they were assigned at re-randomization (i.e., at the beginning of year 2).

The mean change in VA from week 54 was determined for each treatment visit as a summary measure of treatment trends. These results were confirmed further using a standardized area under the curve (AUC) of VA in which the observed VA for each patient at each time point was used to calculate the AUC using the trapezoidal rule. After the AUC was calculated, it was divided by time from baseline (in weeks) to the last available VA to give the

Table 2. Patient Dropouts and Mean Number of Treatments during Year 2 in the Re-randomized Population—Studies 1003 and 1004 Combined

Reason for Dropout	0.3 mg–0.3 mg (N = 133)	0.3 mg–Discontinue (N = 132)	1 mg–1 mg (N = 133)	1 mg–Discontinue (N = 131)	3 mg–3 mg (N = 125)	3 mg–Discontinue (N = 127)	Sham–Pegaptanib* (N = 165)	Usual Care† (N = 107)
Patient request‡	13	6	16	9	12	6	13	6
Death	1	1	1	1	0	5	2	1
Adverse event	5	3	2	1	4	0	5	2
Investigator/sponsor decision	2	1	1	0	5	1	1	1
Protocol violation	0	0	0	0	0	0	4	1
Lost to follow-up	1	0	1	1	0	1	0	0
Other	5	2	2	1	1	2	5	1
Mean (SD) no. of treatments§	6.9 (2.2)	0.9 (1.9)	6.8 (2.4)	0.7 (1.7)	6.8 (2.2)	0.8 (1.9)	6.8 (2.4)	3.9 (3.8)

SD = standard deviation.

*Patients originally assigned to sham and re-randomized to any of the 3 pegaptanib doses are presented collectively.

†Usual care includes all sham patients who were re-randomized either to continue sham or to discontinue sham at week 54.

‡Included withdrawal of consent, patients no longer wished to participate, change in family or home circumstances, withdrawal of consent after adverse events, and general poor health reasons.

§From a maximum of 8 injections for patients assigned to continue treatment. Some discontinued patients restarted treatment in the second year, explaining the presence of treatments in the discontinued patient cohorts.

standardized result in letters. The benefits of the AUC method are that all observed VA data are included and there is no arbitrary imputation such as last observation carried forward for any unobserved data; the standardized AUC generally has less patient-to-patient variability and leads to a smaller variance per treatment group.³⁵ The change from baseline in standardized AUC was analyzed in an analysis of covariance model with baseline lesion angiographic subtype, prior use of photodynamic therapy, and baseline VA as covariates.

Kaplan–Meier estimates of proportions with loss of ≥15 letters after week 54 (regardless of the change in VA from baseline to week 54) were calculated for patients continuing with pegaptanib therapy versus those discontinuing at week 54. This analysis allowed the proportion of events of ≥15-letter loss to be captured at the time when it occurred, unlike a straightforward analysis of the proportions of patients who have lost <15 letters at a specified time (responder rate), which can underestimate treatment effects, particularly if rescue treatments prevented further vision loss. An important distinction between the Kaplan–Meier and responder rate analyses that were performed is that the former represents a 15-letter loss using week 54 as baseline, whereas the latter represents a 15-letter loss using week 0 as baseline. A disadvantage of using Kaplan–Meier analysis to describe vision-related outcomes

is that once a 15-letter loss has developed these data are censored, and even if the patient recovers vision, the outcome for that patient is failure. This can lead to underestimation of effect when the outcome is a recoverable event unlike death.

The proportions of patients losing <15 letters’ vision from baseline in the different treatment groups were compared using the Cochran–Mantel–Haenszel test adjusted for study, prior photodynamic therapy, and baseline lesion angiographic subtype. Treatment groups also were compared descriptively with regard to gain of vision, VA changes in rescued patients, fundus photographic and angiographic changes over time, and photodynamic therapy use.

The randomized withdrawal design allowed all 3 research objectives to be addressed. However, the 1:1:1:1 re-randomization applied to the first-year sham group resulted in a considerable reduction in the number of patients re-randomized to receive sham for 2 years. To address this problem, the year 2 control group (usual care) included all sham patients who were re-randomized either to continue sham or to discontinue sham at week 54. Support for pooling these patient groups came from similar VA results in each.

As stated previously, the primary efficacy end point was pre-specified at week 54. Therefore, definitive statistical conclusions

Table 4. Vision Characteristics at Weeks 0 and 54 in the Re-randomized Population

Variables	Study 1003			Study 1004		
	0.3–0.3 mg (N = 67)	0.3 mg–Discontinue (N = 66)	Usual Care (N = 54)	0.3 mg–0.3 mg (N = 66)	0.3 mg–Discontinue (N = 66)	Usual Care (N = 53)
Mean VA (letters)						
Week 0	53.6	53.8	49.8	52.3	52.7	55.7
Week 54	44.0	49.5	38.1	44.3	45.1	40.1
Responder rate [n (%)]						
Week 54	46 (69)	53 (80)	35 (65)	42 (64)	47 (71)	28 (53)
Legal blindness [n (%)]						
Week 0	7 (10)	7 (11)	9 (17)	15 (23)	9 (14)	5 (9)
Week 54	26 (38)	15 (23)	29 (54)	30 (45)	24 (36)	27 (51)

VA = visual acuity.

Table 5. Change in Standardized Area under the Curve of Visual Acuity in the Re-randomized Population

	Changes from Week 0 to Weeks 6, 54, and 102 in Patients Continuing Therapy vs. Usual Care		Changes from Week 54 to Week 102 in Patients Continuing vs. Discontinuing Therapy	
	0.3 mg–0.3 mg (N = 133)	Usual Care (N = 107)	0.3 mg–0.3 mg (N = 133)	0.3 mg–Discontinue (N = 132)
Week 6				
LS mean (SE)	–0.56 (0.49)	–1.45 (0.55)		
P value	0.1402			
Week 54				
LS mean (SE)	–4.54 (1.18)	–8.16 (1.32)		
P value	0.0129			
Week 102				
LS mean (SE)	–5.88 (1.33)	–11.24 (1.49)	–0.60 (0.61)	–3.04 (0.60)
P value	0.0012		0.0041	

LS = least squares; SE = standard error.

based on the week 102 data are limited, and P values, where reported, are nominal.

Results

Patient Disposition

Figure 1 illustrates randomization and re-randomization at baseline and week 54 and patient flow. Eighty-eight percent (1053/1190) of patients who received at least 1 treatment were re-randomized at week 54; 89% (941/1053) of patients re-randomized at week 54 were assessed at week 102, and percentages were similar across study arms. The primary reason for patient withdrawal before re-randomization was patient request; less frequent reasons included protocol deviation and loss to follow-up. Note that some patients were re-randomized but never received treatment; the main reason for these discontinuations also was patient request. Fewer dropouts occurred in the patient groups not receiving treatment (Table 2). During the second year, the mean number of treatments for all patients re-randomized to continue therapy was approximately 7 of a possible 8 treatments.

Patient groups were similar with regard to demographic characteristics at re-randomization (Table 3 [available at <http://aaojournal.org>]). The preponderance of patients were white, a slight majority were female, and mean ages ranged from 75 to 77 years, a profile similar to those reported in earlier trials of neovascular AMD.^{6,36}

Re-randomization produced VA imbalances between treatment groups, within and between studies, at both week 0 and week 54

(Table 4). These imbalances occurred purely by chance. Differences were evident in mean VA, responder rates, and percentages of patients who were legally blind in the study eye (Table 4).

Efficacy

For simplicity and clinical applicability, efficacy results are described only for the Food and Drug Administration–approved dose of 0.3-mg pegaptanib (Tables 5–9, Figs 2–7, discussed below). Data for the other treatment arms are available at <http://aaojournal.org> (Tables 10–15, Figs 8–12). We present the results first for the combined data and next separately by study (1003 and 1004).

Mean Visual Acuity. In the combined analysis, the mean VA of patients continuing with 0.3-mg pegaptanib remained stable during the second year of therapy (Fig 2A). Mean VA decreased in patients re-randomized to stop pegaptanib after 1 year of therapy, and VA also decreased in those who received usual care continuously from baseline. This last group had the poorest visual outcome. When analyzed separately, similar findings were noted in both trials (Fig 2B, C). In study 1003, the mean VA of patients continuing 0.3-mg pegaptanib remained stable during the second year, whereas the mean VA of patients stopping therapy at the end of the first year decreased from week 54 to week 102. Patients receiving usual care remained stable, with relatively poor vision, during the second year. Re-randomization produced imbalanced groups, as measured by the mean VA at week 54 of patients continuing versus patients discontinuing 0.3-mg pegaptanib (approximately 44-letter mean VA [approximately 20/125 Snellen equivalent] vs. 50-letter mean VA [approximately 20/100 Snellen equivalent] at the start of the second year, respectively; Fig 2B).

Table 6. Progression to Legal Blindness at Weeks 54 and 102 in the Re-randomized Population

Treatment Group	Studies 1003 and 1004 Combined			Study 1003			Study 1004		
	Baseline VA Better than 20/200 (N)	VA 20/200 or Worse		Baseline VA Better than 20/200 (N)	VA 20/200 or Worse		Baseline VA Better than 20/200 (N)	VA 20/200 or Worse	
		Week 54 [n (%)]	Week 102 [n (%)]		Week 54 [n (%)]	Week 102 [n (%)]		Week 54 [n (%)]	Week 102 [n (%)]
0.3 mg–0.3 mg	111	38 (34)	39 (35)	60	20 (33)	21 (35)	51	18 (35)	18 (35)
0.3 mg–discontinue	116	28 (24)	44 (38)	59	11 (19)	19 (32)	57	17 (30)	25 (44)
Usual care	93	44 (47)	51 (55)	45	21 (47)	22 (49)	48	23 (48)	29 (60)

VA = visual acuity.

Table 7. Discontinued Patients Who Resumed Therapy in the Re-randomized Population

	0.3 mg–Discontinue	Sham–Discontinue
Resuming therapy [n/N (%)]	28/132 (21)	8/54 (15)
Week at which rescue initiated [mean (SD)]	73.7 (12.4)	72.8 (10.8)
VA change from week 54 to rescue [mean letters (SD)]	–12.6 (10.6)	–13.4 (5.6)
VA change from rescue to week 102 [mean letters (SD)]	–1.8 (12.5)	–4.8 (15.3)

SD = standard deviation; VA = visual acuity.

Table 9. Photodynamic Therapy with Verteporfin Use in the Re-randomized Population*

Treatment Group	In Year 1		In Year 2	
	n/N	%	n/N	%
0.3 mg–0.3 mg	21/133	16	9/133	7
0.3 mg–discontinue	34/132	26	13/132	10
Sham–pegaptanib†	44/165	27	10/165	6
Usual care	25/107	23	14/107	13

*Includes baseline and postbaseline photodynamic therapy, regardless of photodynamic therapy before study enrollment.
†Patients originally assigned to sham and re-randomized to any of the 3 pegaptanib doses are presented collectively.

In study 1004, the mean VA of patients continuing 0.3-mg pegaptanib remained stable during the second year, whereas the mean VA of patients stopping therapy at the end of the first year decreased from week 54 to week 102. Visual acuity in the usual care group continued to fall during the second year. Unlike study 1003, re-randomization in study 1004 produced balanced groups at week 54, as measured by the mean VA of patients continuing and patients discontinuing 0.3-mg pegaptanib (approximately 45-letter mean VA [approximately 20/125 Snellen equivalent] at the start of the second year for both; Fig 2C).

Patients continuing pegaptanib lost less VA from baseline to weeks 6, 54, and 102, as measured by the standardized AUC, compared with usual care controls and compared with patients randomized to stop treatment at week 54 ($P < 0.05$ for comparisons at weeks 54 and 102, $P > 0.05$ for comparison at week 6; Table 5).

Responder Rates. In the combined analysis, the responder rate for patients continuing pegaptanib decreased by 7% from week 54 to week 102, which compared favorably with the 14% decrease in those assigned to 2 years' usual care and the 14% decrease in those re-randomized to stop pegaptanib after 1 year (Fig 3A).

Findings in the individual studies were comparable to those of the combined analysis in that responder rates for the group that received 2 years' 0.3-mg pegaptanib exceeded that of the group that received usual care from baseline through 102 weeks (Fig 3B, C).

In study 1003 (Fig 3B), patients continuing to receive 0.3-mg pegaptanib, patients receiving usual care, and those randomized to discontinue experienced similar reductions in responder rate from week 54 to week 102. Eighteen of the 66 discontinued patients were rescued during the second year, and of these, 10 avoided a 15-letter loss at the week 102 assessment. In study 1004 (Fig 3C), the responder rate for patients continuing to receive 0.3-mg pegaptanib decreased by 3%, compared with a decrease of 16% for patients assigned to discontinue. Ten of the 66 discontinued patients were rescued during the second year, and of these, 5 avoided a 15-letter loss at the week 102 assessment. Imbalances between groups due to re-randomization were less pronounced than in study 1003 (Fig 3B, C).

Responder rates for the usual care groups differed by 22 per-

Table 8. Angiographic Changes over Time in the Re-randomized Population

Angiographic Parameter	Study 1003				Study 1004			
	0.3-mg Pegaptanib (N = 133)		Sham (N = 138)		0.3-mg Pegaptanib (N = 132)		Sham (N = 134)	
	0.3 mg–0.3 mg (N = 67)	0.3 mg–Discontinue (N = 66)	Sham–Pegaptanib* (N = 84)	Usual Care (N = 54)	0.3 mg–0.3 mg (N = 66)	0.3 mg–Discontinue (N = 66)	Sham–Pegaptanib* (N = 81)	Usual Care (N = 53)
Total lesion size†								
Baseline		3.8		3.9		3.6		4.3
Week 54	5.6	5.6	6.2	6.5	5.2	5.9	7.1	6.9
Week 78	5.9	6.1	6.4	6.9	5.4‡	6.5	7.4	7.5
Week 102	6.1	6.3	6.5	7.1	5.6‡	6.8	7.7	8.1
Total choroidal neovascularization size†								
Baseline		3.1		3.4		3.1		3.8
Week 54	4.8	4.8	5.5	5.9	4.6	4.8	5.8	5.7
Week 78	4.8	5.0	5.7	5.9	4.8	5.4	5.8	6.0
Week 102	4.9	4.9	5.6	5.7	4.9	5.5	6.0	6.3
Total leak size†								
Baseline		3.3		3.4		3.2		3.6
Week 54	4.2	4.8	4.8	5.2	4.0	4.4	5.4	4.9
Week 78	3.8	4.3	4.3	5.0	4.2	4.9	5.3	4.7
Week 102	3.6	3.5	3.4	4.3	3.7	4.5	4.5	4.3

*Patients originally assigned to sham and re-randomized to any of the 3 pegaptanib doses are presented collectively.

†Mean, in disc areas. In addition to choroidal neovascularization, lesion size could include subretinal hemorrhage, scar, and/or atrophy as described in the entry criteria.

‡ $P < 0.05$; pegaptanib treatment vs. sham at each time point.

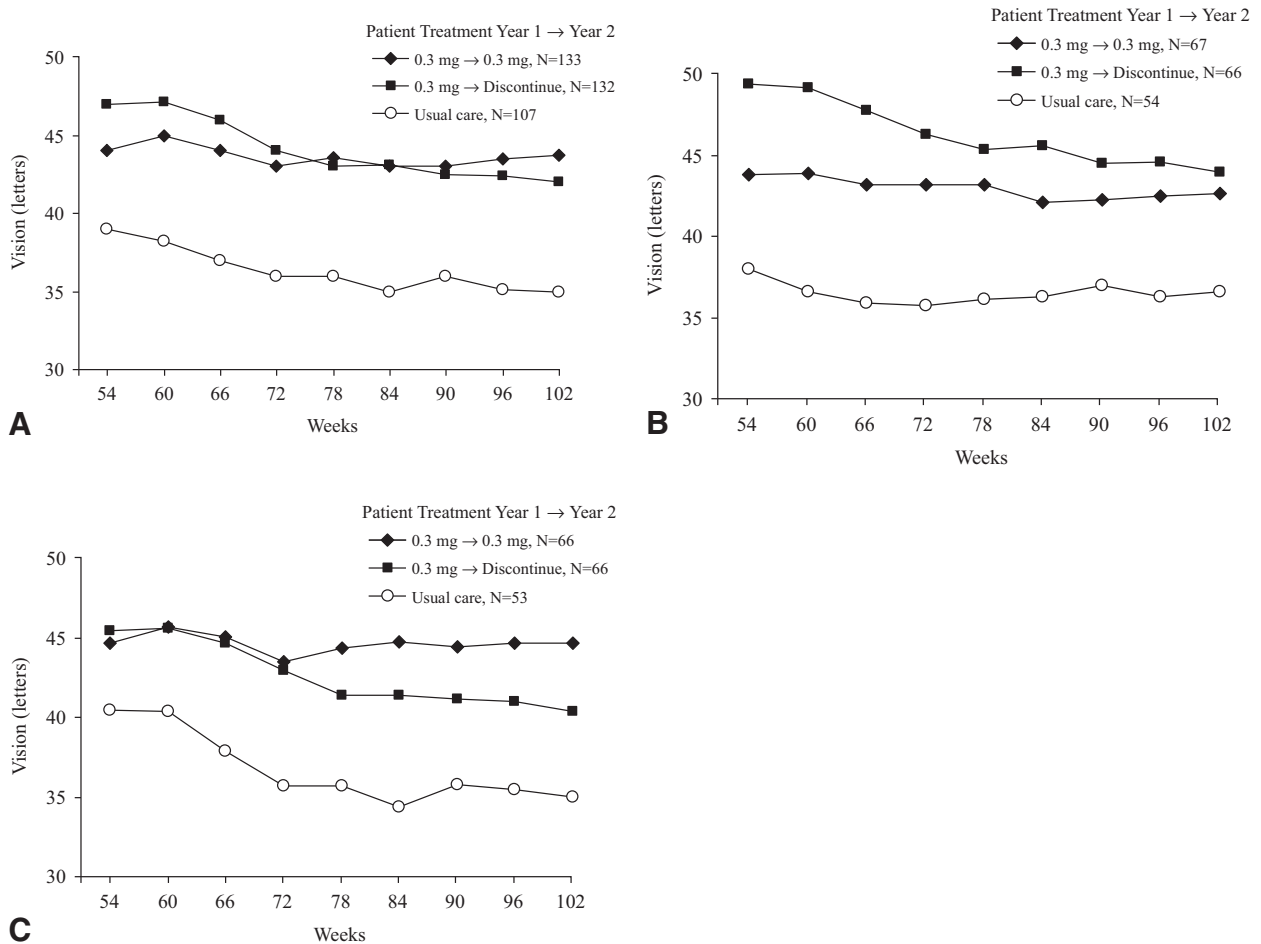


Figure 2. Mean visual acuity from week 54 to week 102. A, Studies 1003 and 1004 combined. B, Study 1003. C, Study 1004.

centage points between the 2 trials at week 102 (56% [30/54] vs. 34% [18/53], respectively), consistent with the chance imbalance in the starting responder rates at the week 54 re-randomization (65% [35/54] vs. 53% [28/53], respectively).

Proportion with a 15-Letter Loss. The proportion of patients who experienced a loss of ≥ 15 letters was lower for those who received 2 years' therapy with 0.3-mg pegaptanib than for those who were randomized to discontinue treatment at the end of year 1. These visual events were more frequent in patients randomized to discontinue after 1 year of pegaptanib therapy than in those who received 2 years' treatment (35 events vs. 21 events; $P < 0.05$). The time-to-event analysis showed that the event-free interval was longer for patients treated with 0.3-mg pegaptanib than for those discontinuing treatment. These results were consistent between studies (Fig 4).

Progression to Legal Blindness. Among patients with VA better than 20/200 at baseline, patients treated with continuous 0.3-mg pegaptanib were protected from progression to legal blindness in the study eye at year 2 (34% [38/111] at week 54 and 35% [39/111] at week 102 were 20/200 or worse in the study eye; Table 6). In contrast, the percentage progressing to legal blindness increased both for patients assigned to discontinue 0.3-mg pegaptanib and for patients treated with usual care (discontinued patients: 24% [28/116] at week 54 and 38% [44/116] at week 102; usual care: 47% [44/93] at week 54 and 55% [51/93] at week 102).

Gaining Vision. Ten percent of pegaptanib-treated patients gained ≥ 3 lines' vision after 2 years. In both trials, the percentage

of patients gaining vision was higher for the patients assigned to 2 years' 0.3-mg pegaptanib than for patients receiving usual care (Fig 5).

Rescue Treatment. Patients discontinued from pegaptanib were more likely to resume therapy than patients discontinued from sham (Table 7). As indicated by the standard deviation around the means, there was a broad spectrum of (1) time points at which rescue was initiated, (2) loss in VA from week 54 to the time of rescue, and (3) change in VA from rescue to week 102. Results were similar across treatment groups. Fifteen of the 28 pegaptanib-rescued patients avoided a 15-letter loss from baseline to week 102, compared with 2 of the 8 sham-rescued patients. Table 7 also shows that patients rescued with pegaptanib had a better mean letter score than patients resuming sham from rescue to week 102 (-1.8 letters vs. -4.8 letters).

Fundus Imaging. Results of the analysis of fluorescein angiographic outcomes are summarized in Table 8. Early-, mid-, and late-phase stereoscopic angiographic frames from a patient randomized to 2 years' 0.3-mg pegaptanib are shown in Figure 6. For all groups, expansion of lesion and choroidal neovascularization area was more rapid during year 1 than during year 2. Eyes that received pegaptanib treatment exhibited lesions that were smaller than those of patients receiving usual care.

The mean increase in lesion area was greater in patients assigned to discontinue pegaptanib than in those continuing treatment during the second year. The mean area of serous sensory RD decreased at every measured time point from baseline through 2

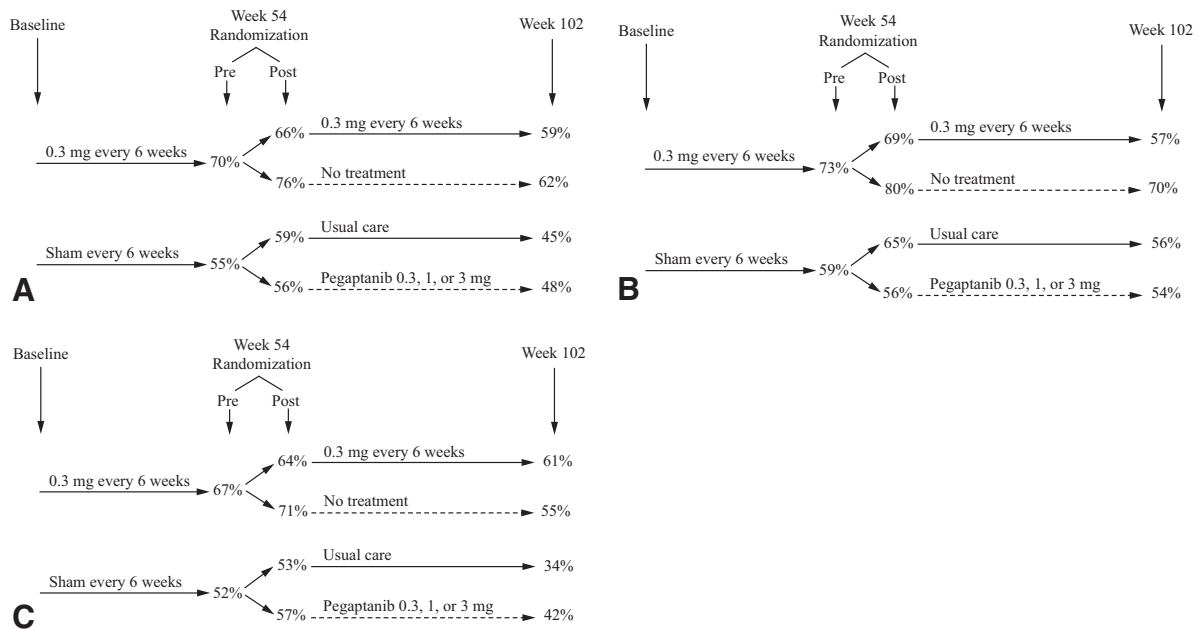


Figure 3. Responder rates. A, Studies 1003 and 1004 combined. B, Study 1003. C, Study 1004. Post = after; pre = before.

years in patients treated with pegaptanib. In contrast, in patients receiving usual care an increase in the area of serous sensory detachment was evident, peaking at year 1. Although this reduced over year 2, it never reached the baseline (Fig 7).

Photodynamic Therapy Use. A minority of patients ever received photodynamic therapy (Table 9), and a smaller percentage of patients received photodynamic therapy in year 2 than in year 1. The percentage of patients receiving photodynamic therapy was higher in the usual care group than in any other group during the second year.

Discussion

The wide eligibility criteria in the V.I.S.I.O.N. trials permitted enrollment of a diverse mix of neovascular AMD presentations. Specifically, occult-only or any combination of occult and classic angiographic lesion compositions was eligible. Furthermore, highly aggressive lesions with up to 6 disc areas of hemorrhage as well as more chronic lesions with up to 25% scarring and fibrosis were eligible. To avoid enrollment of totally quiescent or involuted occult lesions, documented evidence of a 15-letter loss in the 12 weeks before enrollment was one of the criteria. The V.I.S.I.O.N. trials demonstrated not only that pegaptanib reduced the risk of vision loss regardless of lesion composition or size at the primary time point, 1 year, but also that this benefit was maintained during year 2. Over the 2 years, patients randomized to continuous inhibition of VEGF₁₆₅ with 0.3-mg pegaptanib were more likely to experience a visual benefit—including VA gain and protection from legal blindness—than patients assigned to either 2 years’ usual care or discontinuation of therapy after 1 year’s treatment. There was no evidence that concomitant treatment with photodynamic therapy, which was allowed at the investigators’ discretion, confounded the results.

The design of the second year of the study differed from the traditional parallel group structure to achieve the multiple prespecified objectives. Given the intravitreal route of administration and the 6-week dosing interval, it was important to assess whether superior outcomes for pegaptanib compared with usual care persisted during the second year and also to establish whether 1 year of VEGF₁₆₅ inhibition would suffice. The International Conference on Harmonisation–recommended randomized withdrawal study design therefore was implemented to help answer these additional questions.

End points in the second year of the trials were chosen to accommodate the unique design. Thus, for instance, the time-to-event Kaplan–Meier analysis was selected and showed that the proportion of patients protected from a 15-letter loss in the second year was significantly higher with continuing pegaptanib therapy and superior to discontinuation at the end of year 1. It is notable that although patients randomized to discontinue pegaptanib were at a greater risk of vision loss than those continuing with therapy, the results demonstrated that vision loss after discontinuation did not exceed the rate expected by natural history—that is, no rebound effect due to discontinuation was observed.

It is possible that the outcomes at week 102 for patients discontinuing therapy at year 1 might have been inflated by random imbalances at the week 54 re-randomization and by rescue treatments, thereby underestimating the importance of continued treatment for 2 years. There is also a likelihood that rescue therapy given to a sizeable proportion of patients during year 2 and the subsequent protection through the potential avoidance of a 3-line loss from baseline to week 102 contributed to a further underestimation of the value of treatment. Thus, for example, if all 15 patients rescued during year 2 had lost ≥ 3 lines, the responder rate would have been lowered by an additional 11 percentage points in those randomized to discontinue therapy (from 62% to

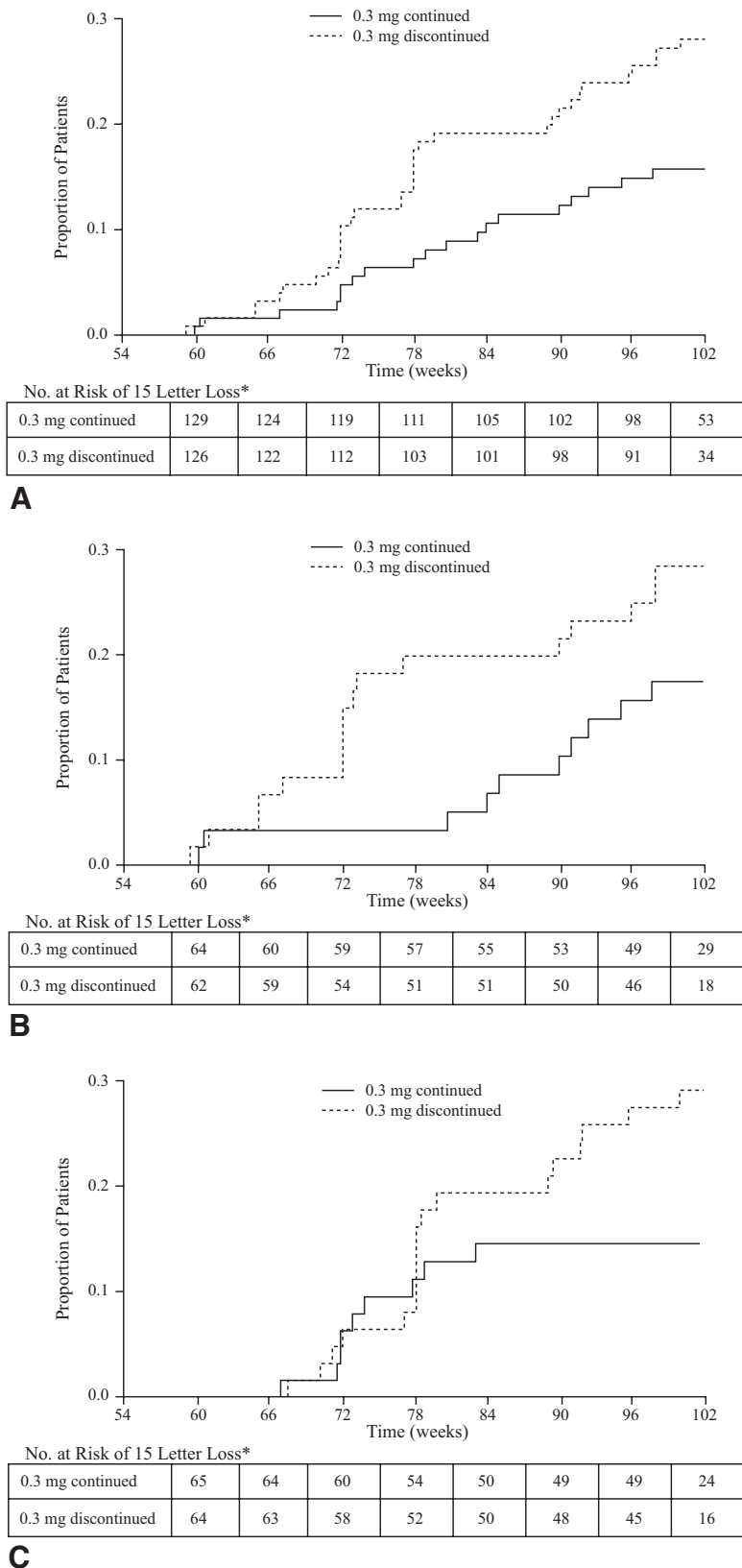


Figure 4. First observed loss of 15 letters of vision. **A**, Studies 1003 and 1004 combined. **B**, Study 1003. **C**, Study 1004. *Patients who were censored are not included in the table.

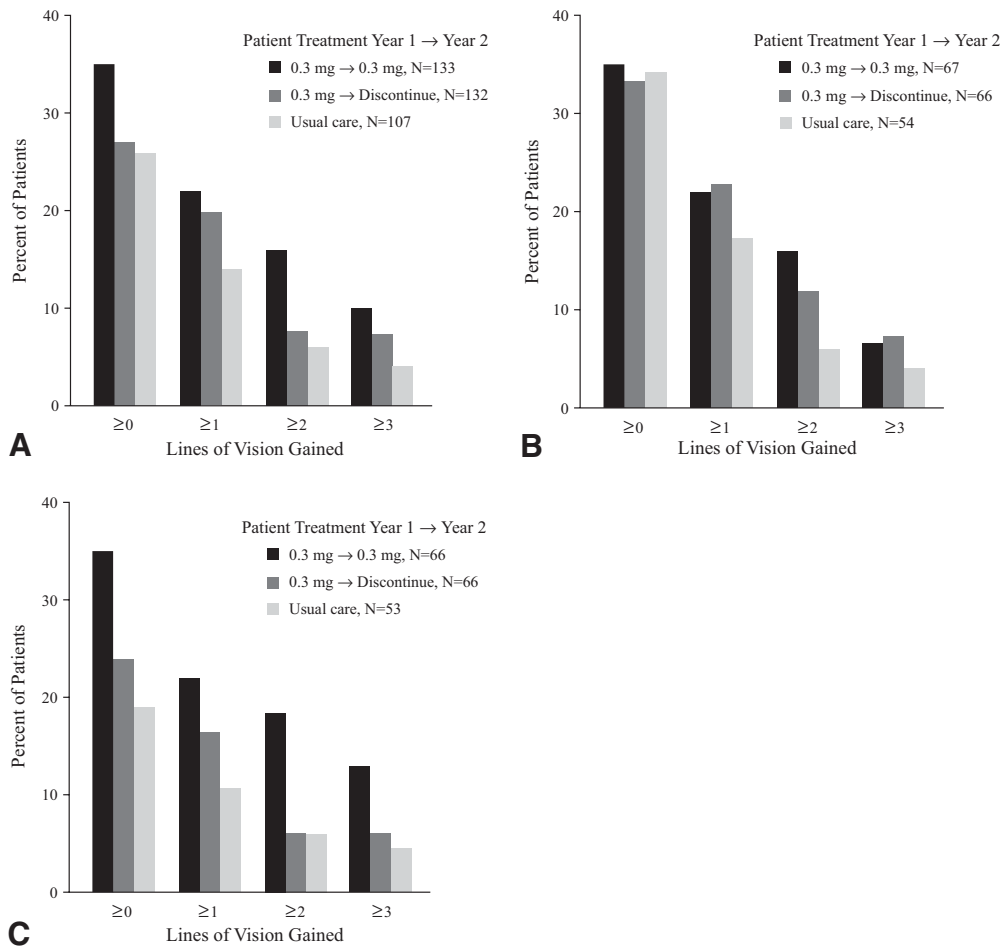


Figure 5. Vision gain. A, Studies 1003 and 1004 combined. B, Study 1003. C, Study 1004.

51%) and by 4 percentage points in those discontinuing with sham (from 43% to 39%). This is the reason that Kaplan–Meier was selected as an alternative analysis.

There were no differences in responder rates for the 0.3-mg pegaptanib dose in the 2 studies at week 102 (57% in study 1003 and 61% in study 1004). However, the responder rate for patients assigned to usual care differed considerably between the 2 studies due to an unusually better outcome in this group in study 1003 at week 102 (56% in study 1003 and 34% in study 1004). Natural history data show that 30% to 40% of neovascular AMD patients lose <15 letters after 2 years,^{5–7} indicating that the poor outcome (34% responder rate) seen in study 1004 is typical, whereas that of study 1003 is very likely an aberration. Although any of the confounding features previously mentioned could account for this aberration, there is no evidence that it could be attributed to the effect of concomitant photodynamic therapy, as a lower percentage of patients received this therapy in study 1003 when compared with study 1004.

As no singular end point or analysis at week 102 completely avoided bias, it is instructive to assess the totality of the data for internal consistency. Mean change in VA over time, Kaplan–Meier analyses, responder rates, and proportions of patients gaining VA or progressing to legal blind-

ness all show that patients assigned to continued VEGF₁₆₅ inhibition with 0.3-mg pegaptanib for 2 years were more likely to benefit than those assigned either to usual care for 2 years or to stop treatment after 1 year. These data are consistent with a continuing action of VEGF throughout the period of active lesion evolution, as would be anticipated from its importance in promoting choroidal neovascularization^{22–24,29,30} and from its unique role as an extremely potent vascular permeability factor³⁷ in mediating the leakage that is one of the hallmarks of exudative AMD. This continuing action also is reflected in the presence of VEGF staining in lesions containing choroidal neovascularization, whereas it is absent in lesions containing only scar tissue and atrophy.³⁸ Although pegaptanib data beyond 2 years are not yet available, this suggests that VEGF₁₆₅ inhibition may not be useful in end-stage inactive lesions.

The trials were not designed to identify whether patients with particular baseline characteristics might experience enhanced or diminished benefit from 2 years' continuous VEGF₁₆₅ inhibition with pegaptanib. Indeed, the baseline patient features that might predict response to a VEGF₁₆₅ inhibitor are not known definitively. Unlike photodynamic therapy, where meta-analyses of the verteporfin trials suggested that baseline VA and/or lesion type/size may have

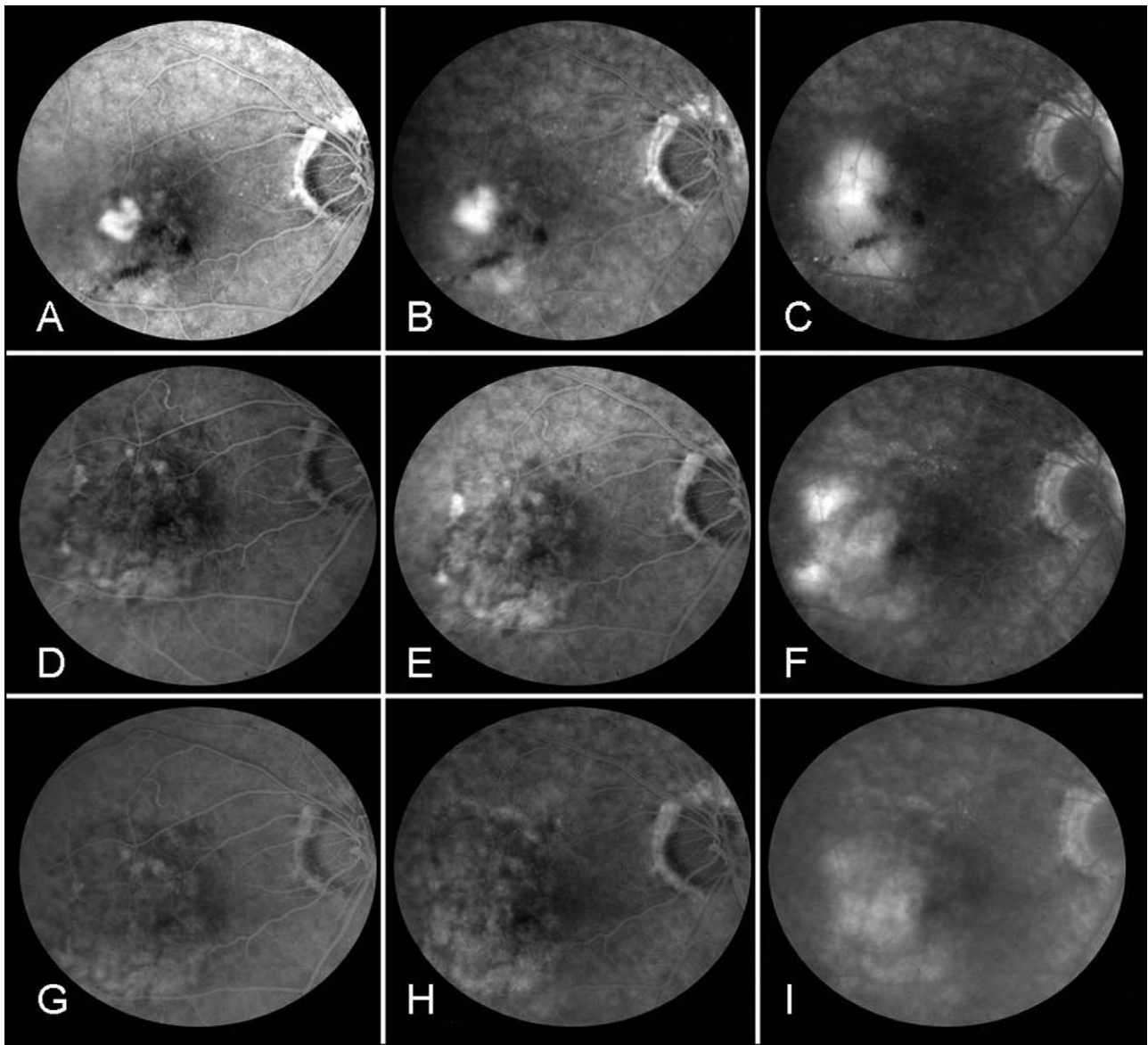


Figure 6. Representative case from the Vascular Endothelial Growth Factor Inhibition Study in Ocular Neovascularization. At baseline, the subject presented with a visual acuity (VA) of $\sim 20/63$ (Snellen equivalent) with exudative maculopathy. Early-phase (A), midphase (B), and late-phase (C) fluorescein angiograms showed a minimally classic subfoveal lesion. At week 54, VA improved to $\sim 20/40$, and despite the total lesion enlargement, there was decreasing leakage, with less presence of the classic component (D–F). At week 102, the macula was flatter, with persistency of occult choroidal neovascularization but no classic component (G–I). Final VA was $\sim 20/20$.

influenced outcomes,³⁹ there is no readily apparent biologically plausible reason for such features to influence anti-VEGF₁₆₅ activity. In fact, exploratory statistical analyses through year 1 uncovered no evidence that pegaptanib efficacy was affected by baseline lesion size, angiographic subtype, VA, or demographics.³² Such exploratory subgroup analyses were not appropriate during the second year because the already small subgroups were further decreased by $\geq 50\%$ after the week 54 re-randomization. Nonetheless, trials may be warranted to attempt to identify whether other patient characteristics (e.g., early lesions, retinal angiomatous proliferation, retinal pigmented epithelium status) may influence outcomes of therapy with anti-VEGF agents.

The reduction in serous RDs and the lower rate of lesion expansion in pegaptanib-treated eyes constitute evidence of VEGF₁₆₅ inhibition and explain the therapeutic benefit observed in the V.I.S.I.O.N. trials. Although these data are helpful in understanding the pathophysiology of choroidal neovascularization in treated eyes, current methods of grading fluorescein angiograms are limited in their ability to characterize parametrically the activity of neovascular lesions. Notably, assessment of neovascular lesions with angiography may vary from physician to physician and even between independent reading centers. Traditional fluorescein angiography parameters are assessed based on measurements made on single frames of the angiogram (area of lesion, choroidal

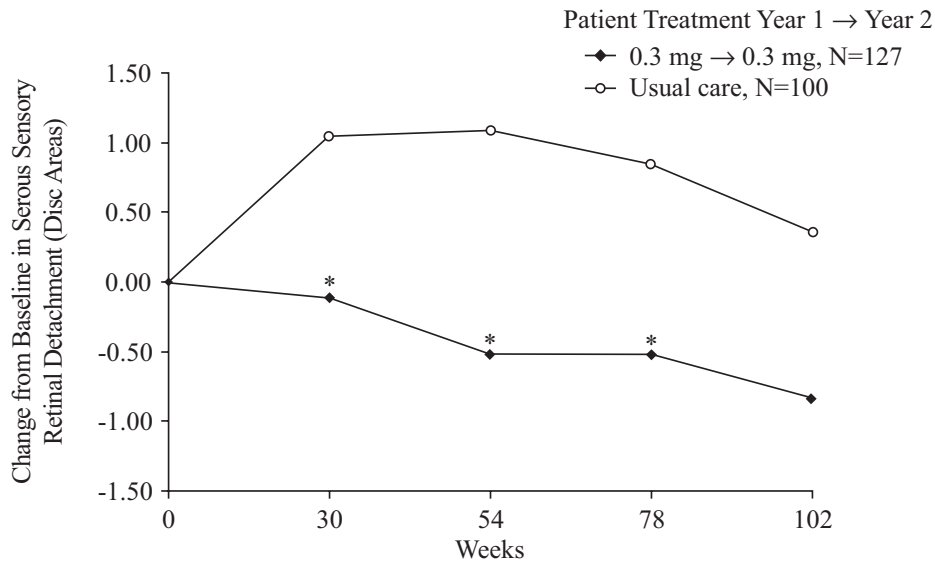


Figure 7. Change from baseline in serous sensory retinal detachment area. Least squares mean in disc areas adjusted for prior photodynamic therapy, lesion subtype, and study. For missing data, the last observation was carried forward. Missing covariate data for 6 patients in the 0.3 mg–0.3 mg group and 7 patients in the usual care group. * $P < 0.05$ compared to usual care.

neovascularization, or leak), are 2-dimensional measures of a 3-dimensional complex, and ignore spatial and temporal features of the pathology. Although simple area measurements are valuable for planning laser photocoagulation or photodynamic therapy, no validated methods exist that assess disease activity at the foveal center and/or assess the anatomical and functional integrity of the neurosensory retina and its retinal pigmented epithelium. If such parameters that assess retinal and retinal pigment epithelial health were available, they may correlate better with the effects of pharmacological therapies such as pegaptanib that are designed to preserve foveal anatomy and function.

The V.I.S.I.O.N. trials showed that 2 years' continued VEGF₁₆₅ inhibition with pegaptanib provided patients with the best chance of preserving vision—evidence based on data from 2 prospective, randomized, double-masked, controlled trials of >1200 patients and, therefore, reliable in describing the patient population studied. However, clinical trials cannot possibly answer all outstanding questions relevant to patient management for a given intervention. Although evidence-based clinical decisions are less subject to the biases associated with anecdotal experience, some clinicians will be tempted to determine treatment response using personal algorithms. To date, there is no definitive evidence that using VA loss alone to determine when to stop or resume VEGF₁₆₅ inhibition (rescue) will permit consistent VA recovery. Further, there is no objective evidence that anatomical changes as seen on any one imaging modality, such as optical coherence tomography or fluorescein angiography, consistently correlate with or predict pegaptanib treatment response. To that end, a controlled prospective trial with optical coherence tomography is ongoing. Thus, until reliable data are available, it seems prudent for clinicians to weigh strongly the trial results within the context of the role of VEGF in the pathophysiology of the disease

together with a myriad of other patient-specific characteristics in creating a composite risk/benefit assessment.

The totality of the data, including mean change in VA over time, Kaplan–Meier analysis of proportions with a 15-letter loss of VA, responder analysis, and proportion of patients progressing to legal blindness in the study eye, indicates that 2 years' 0.3-mg pegaptanib dosed every 6 weeks provided patients with superior visual outcomes compared with 2 years' usual care or discontinuing pegaptanib after 1 year. These data suggest that VEGF₁₆₅ is important throughout the evolution of active neovascular AMD.

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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. trial.

Appendix II

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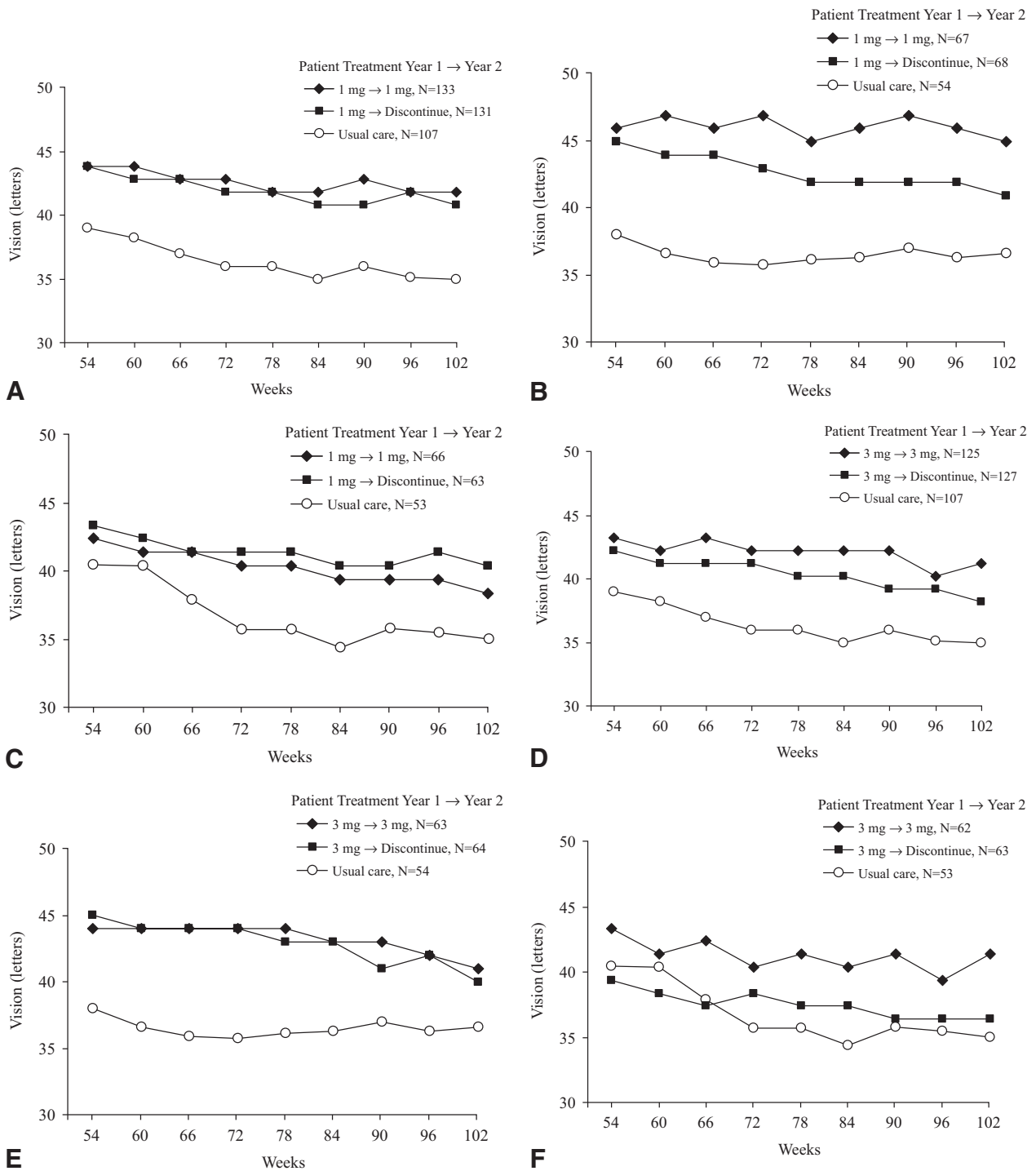


Figure 8. Mean visual acuity from week 54 to week 102. A, Studies 1003 and 1004 combined, 1-mg pegaptanib. B, Study 1003, 1-mg pegaptanib. C, Study 1004, 1-mg pegaptanib. D, Studies 1003 and 1004 combined, 3-mg pegaptanib. E, Study 1003, 3-mg pegaptanib. F, Study 1004, 3-mg pegaptanib.

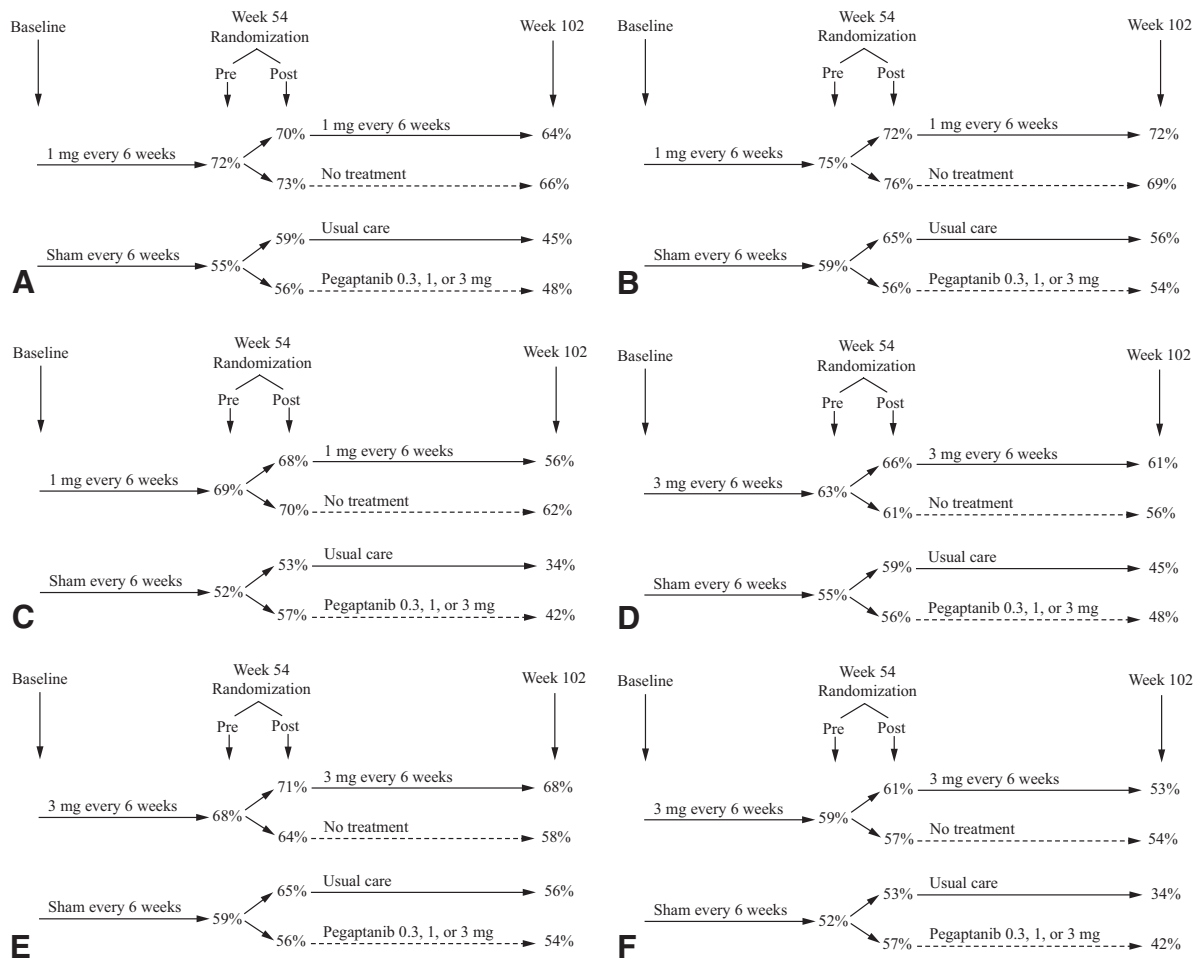


Figure 9. Responder rates. A, Studies 1003 and 1004 combined, 1-mg pegaptanib. B, Study 1003, 1-mg pegaptanib. C, Study 1004, 1-mg pegaptanib. D, Studies 1003 and 1004 combined, 3-mg pegaptanib. E, Study 1003, 3-mg pegaptanib. F, Study 1004, 3-mg pegaptanib. Post = after; pre = before.

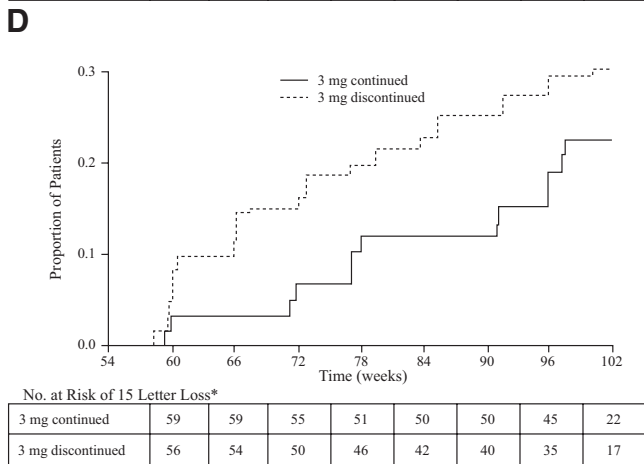
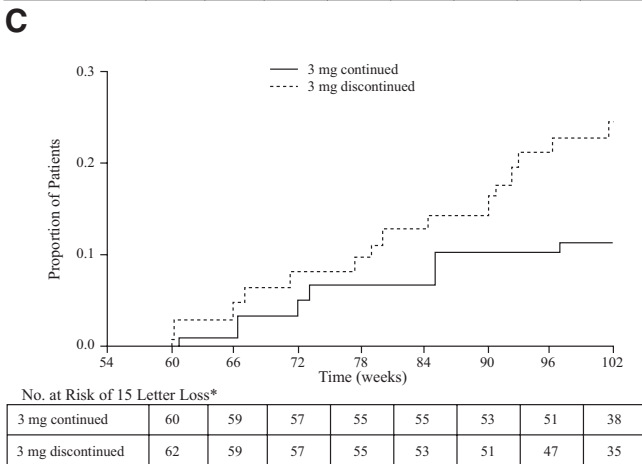
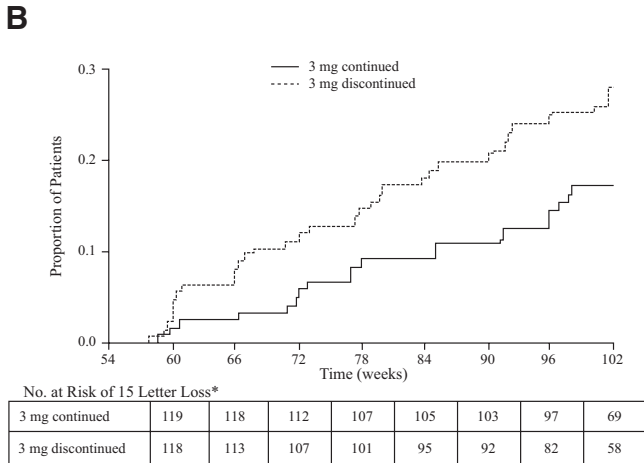
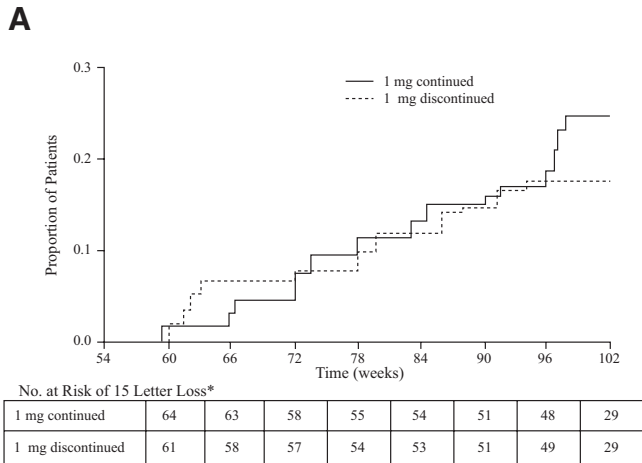
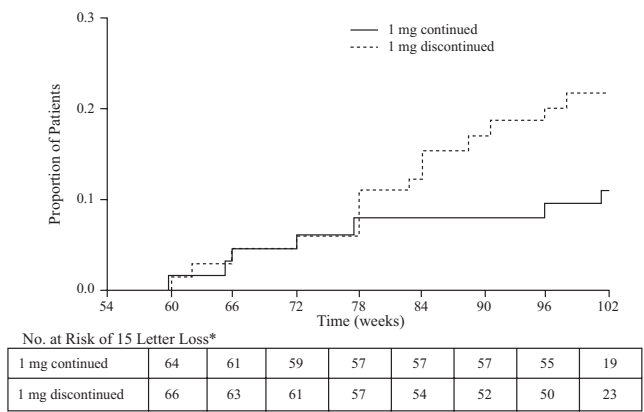
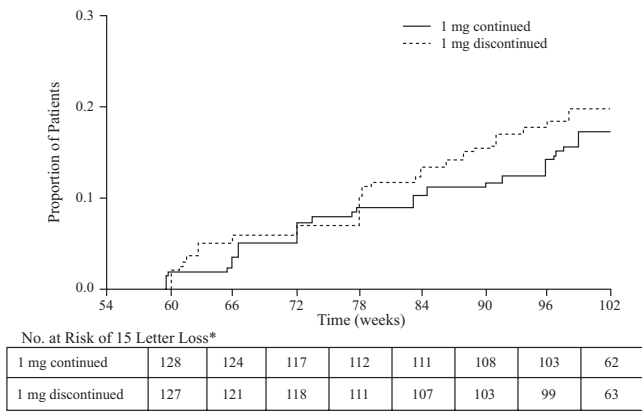


Figure 10. First observed loss of 15 letters of vision. **A**, Studies 1003 and 1004 combined, 1-mg pegaptanib. **B**, Study 1003, 1-mg pegaptanib. **C**, Study 1004, 1-mg pegaptanib. **D**, Studies 1003 and 1004 combined, 3-mg pegaptanib. **E**, Study 1003, 3-mg pegaptanib. **F**, Study 1004, 3-mg pegaptanib. *Patients who were censored are not included in the table.

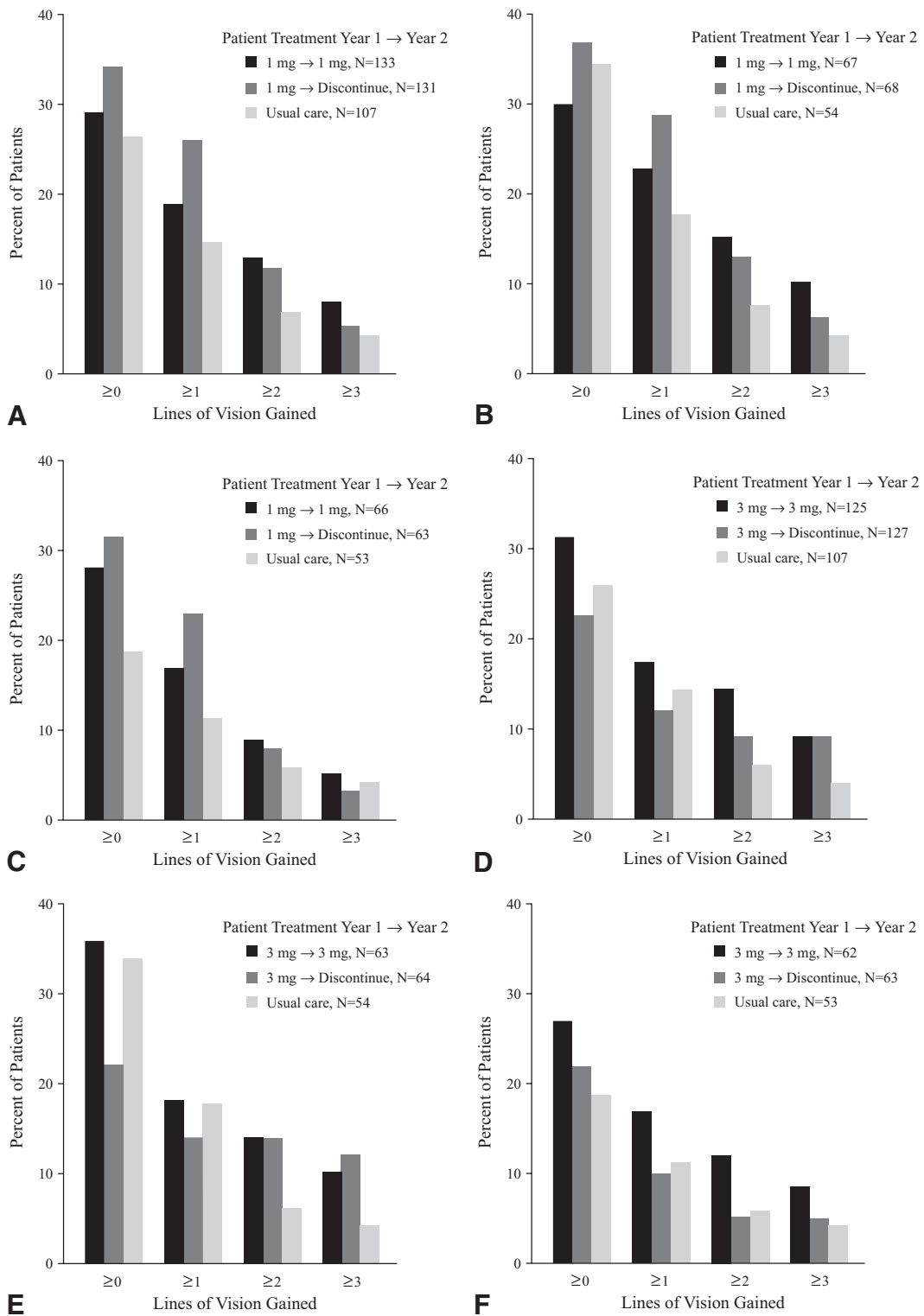


Figure 11. Vision gain. **A**, Studies 1003 and 1004 combined, 1-mg pegaptanib. **B**, Study 1003, 1-mg pegaptanib. **C**, Study 1004, 1-mg pegaptanib. **D**, Studies 1003 and 1004 combined, 3-mg pegaptanib. **E**, Study 1003, 3-mg pegaptanib. **F**, Study 1004, 3-mg pegaptanib.

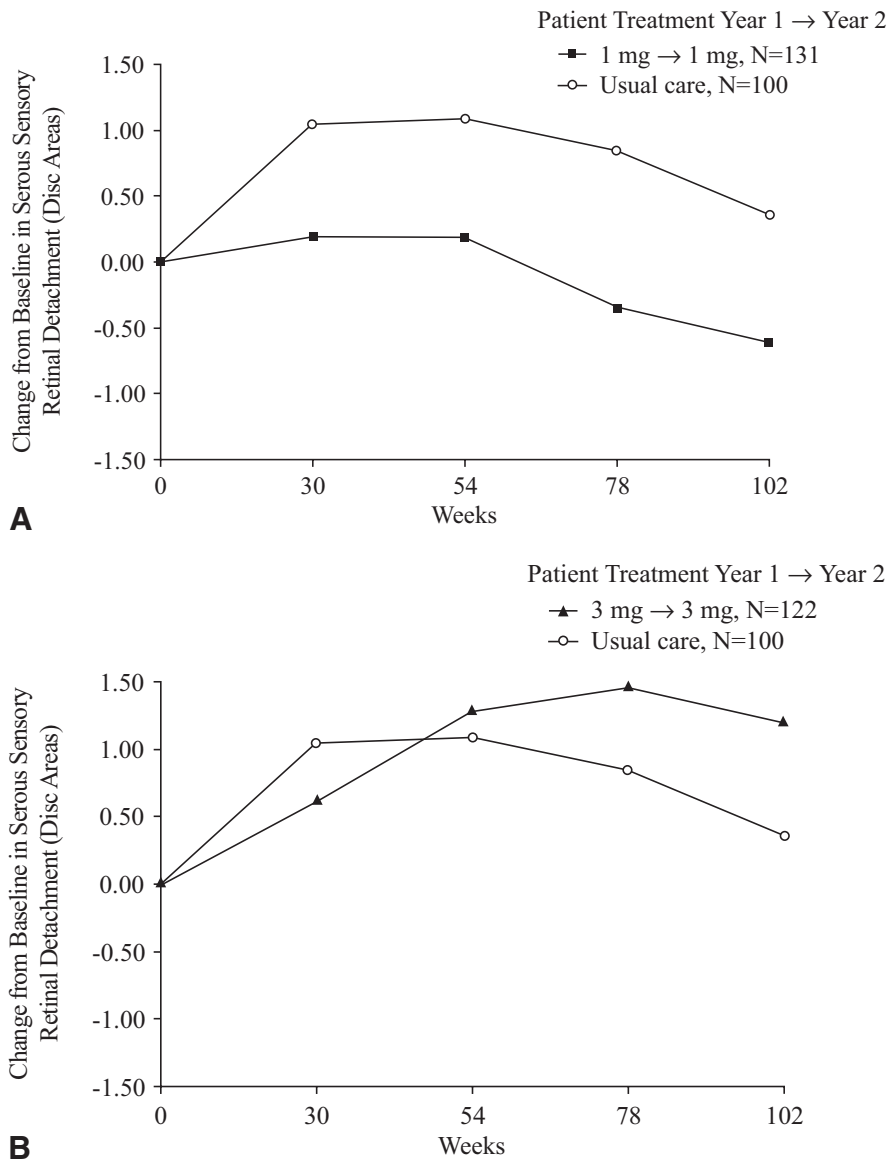


Figure 12. Change from baseline in serous sensory retinal detachment area. Least squares mean in disc areas adjusted for prior photodynamic therapy, lesion subtype, and study. For missing data the last observation was carried forward (LOCF). **A**, One-milligram pegaptanib. Missing covariate data for 2 patients in the 1 mg–1 mg group and 7 patients in the usual care group. **B**, Three-milligram pegaptanib. Missing covariate data for 3 patients in the 3 mg–3 mg group and 7 patients in the usual care group.

Table 3. Demographic Characteristics at Re-randomization at Week 54—Studies 1003 and 1004 Combined

Variables	0.3 mg–0.3 mg (N = 133)	0.3 mg–Discontinue (N = 132)	1 mg–1 mg (N = 133)	1 mg–Discontinue (N = 131)	3 mg–3 mg (N = 125)	3 mg–Discontinue (N = 127)	Sham–Pegaptanib* (N = 165)	Usual Care (N = 107)
Female/male (%)	55/45	54/46	51/49	59/41	70/30	59/41	59/41	63/37
Age (yrs) [mean (SD)]	77.0 (6.3)	75.6 (8.2)	75.6 (7.2)	74.7 (7.1)	75.6 (7.0)	76.0 (7.7)	75.4 (7.2)	76.2 (7.4)
Range	57–90	53–88	53–92	52–90	57–91	53–91	54–90	52–89
Race (%)								
White	97	95	96	98	94	99	95	96
Hispanic	2	4	2	2	5	1	4	2
Asian	0	2	0	1	1	0	1	0
Black	0	0	1	0	0	0	0	1
Other	1	0	1	0	0	0	1	1

SD = standard deviation.

*Patients originally assigned to sham and re-randomized to any of the 3 pegaptanib doses are presented collectively.

Table 10. Vision Characteristics at Weeks 0 and 54 in the Re-randomized Population

Variables	Study 1003					Study 1004				
	1 mg–1 mg (N = 67)	1 mg–Discontinue (N = 68)	3 mg–3 mg (N = 63)	3 mg–Discontinue (N = 64)	Usual Care (N = 54)	1 mg–1 mg (N = 66)	1 mg–Discontinue (N = 63)	3 mg–3 mg (N = 62)	3 mg–Discontinue (N = 63)	Usual Care (N = 53)
Mean VA (letters)										
Week 0	53.4	48.9	50.1	52.6	49.8	50.8	50.1	55.0	51.7	55.7
Week 54	46.4	45.0	43.6	44.5	38.1	42.0	43.2	42.6	39.3	40.1
Responder rate [n (%)]										
Week 54	48 (72)	52 (76)	45 (71)	41 (64)	35 (65)	45 (68)	44 (70)	38 (61)	36 (57)	28 (53)
Legal blindness [n (%)]										
Week 0	12 (18)	15 (22)	14 (22)	10 (15)	9 (17)	13 (20)	15 (24)	6 (10)	12 (19)	5 (9)
Week 54	26 (39)	27 (40)	25 (40)	21 (33)	29 (54)	29 (44)	29 (46)	24 (39)	34 (54)	27 (51)

VA = visual acuity.

Table 11. Change in Standardized Area under the Curve of Visual Acuity in the Re-randomized Population

	Changes from Week 0 to Weeks 6, 54, and 102 in Patients Continuing Therapy versus Usual Care			Changes from Week 54 to Week 102 in Patients Continuing versus Discontinuing Therapy			
	1 mg–1 mg (N = 133)	3 mg–3 mg (N = 125)	Usual Care (N = 107)	1 mg–1 mg (N = 133)	1 mg–Discontinue (N = 131)	3 mg–3 mg (N = 125)	3 mg–Discontinue (N = 127)
Week 6							
LS mean (SE)	–0.04 (0.49)	–0.66 (0.49)	–1.45 (0.55)				
P value	0.0195	0.1966					
Week 54							
LS mean (SE)	–3.82 (1.19)	–5.30 (1.18)	–8.16 (1.32)				
P value	0.0029	0.0530					
Week 102							
LS mean (SE)	–5.76 (1.34)	–7.21 (1.33)	–11.24 (1.49)	–1.82 (0.66)	–2.67 (0.65)	–1.26 (0.79)	–2.25 (0.81)
P value	0.0009	0.0159		0.3517		0.3632	

LS = least squares; SE = standard error.

Table 12. Progression to Legal Blindness at Weeks 54 and 102 in the Re-randomized Population

Treatment Group	Studies 1003 and 1004 Combined			Study 1003			Study 1004		
	Baseline VA Better than 20/200 (N)	VA 20/200 or Worse		Baseline VA Better than 20/200 (N)	VA 20/200 or Worse		Baseline VA Better than 20/200 (N)	VA 20/200 or Worse	
		Week 54 [n (%)]	Week 102 [n (%)]		Week 54 [n (%)]	Week 102 [n (%)]		Week 54 [n (%)]	Week 102 [n (%)]
1 mg–1 mg	108	35 (32)	38 (35)	55	15 (27)	12 (22)	53	20 (38)	26 (49)
1 mg–discontinue	101	31 (31)	34 (34)	53	16 (30)	19 (36)	48	15 (31)	15 (31)
3 mg–3 mg	105	37 (35)	51 (49)	49	16 (33)	23 (47)	56	21 (38)	28 (50)
3 mg–discontinue	105	40 (38)	55 (52)	54	15 (28)	28 (52)	51	25 (49)	27 (53)
Usual care	93	44 (47)	51 (55)	45	21 (47)	22 (49)	48	23 (48)	29 (60)

VA = visual acuity.

Table 13. Discontinued Patients Who Resumed Therapy in the Re-randomized Population

	1 mg–Discontinue	3 mg–Discontinue	Sham–Discontinue
Resuming therapy [n/N (%)]	21/131 (16)	23/127 (19)	8/54 (15)
Week at which rescue initiated [mean (SD)]	72.9 (10.3)	74.6 (12.0)	72.8 (10.8)
VA change from week 54 to rescue [mean letters (SD)]	–10.1 (7.3)	–10.4 (8.9)	–13.4 (5.6)
VA change from rescue to week 102 [mean letters (SD)]	3.2 (11.6)	3.8 (9.9)	–4.8 (15.3)

SD = standard deviation; VA = visual acuity.

Table 14. Angiographic Changes over Time

Angiographic Parameter	Study 1003					
	1-mg Pegaptanib (N = 135)		3-mg Pegaptanib (N = 127)		Sham (N = 138)	
	1 mg-1 mg (N = 67)	1 mg-Discontinue (N = 68)	3 mg-3 mg (N = 63)	3 mg-Discontinue (N = 64)	Sham-Pegaptanib* (N = 84)	Usual Care (N = 54)
Total lesion size [†]						
Baseline		3.8		3.8		3.9
Week 54	5.4	6.1	6.0	6.4	6.2	6.5
Week 78	5.8	6.8	6.3	6.4	6.4	6.9
Week 102	5.9	6.8	6.3	6.6	6.5	7.1
Total choroidal neovascularization size [†]						
Baseline		3.3		3.2		3.4
Week 54	4.5 [‡]	4.9	5.1	5.3	5.5	5.9
Week 78	4.8	5.4	5.6	5.2	5.7	5.9
Week 102	5.0	5.4	5.6	5.5	5.6	5.7
Total leak size [†]						
Baseline		3.4		3.2		3.4
Week 54	3.8	4.0	4.0	4.8	4.8	5.2
Week 78	3.9	4.4	4.0	4.6	4.3	5.0
Week 102	3.5	3.9	3.5	4.6	3.4	4.3

*Patients originally assigned to sham and re-randomized to any of the 3 pegaptanib doses are presented collectively.

[†]Mean, in disc areas. In addition to choroidal neovascularization, lesion size could include subretinal hemorrhage, scar, and/or atrophy as described in the

[‡] $P < 0.05$; pegaptanib treatment vs. sham at each time point.

in the Re-randomized Population

Study 1004					
1-mg Pegaptanib (N = 129)		3-mg Pegaptanib (N = 125)		Sham (N = 134)	
1 mg-1 mg (N = 66)	1 mg-Discontinue (N = 63)	3 mg-3 mg (N = 62)	3 mg-Discontinue (N = 63)	Sham-Pegaptanib* (N = 81)	Usual Care (N = 53)
	4.4		3.7		4.3
5.7 [‡]	6.4	6.1	6.6	7.1	6.9
5.7 [‡]	7.0	6.6	6.8	7.4	7.5
6.1 [‡]	7.3	7.2	6.7	7.7	8.1
	3.8		3.3		3.8
4.9 [‡]	5.1	4.8	5.3	5.8	5.7
4.8 [‡]	5.8	5.3	5.1	5.8	6.0
5.0 [‡]	5.7	5.4	5.2	6.0	6.3
	3.6		3.4		3.6
4.4	3.7	4.8	4.9	5.4	4.9
4.2	4.3	5.0	4.2	5.3	4.7
4.1	3.8	4.3	4.2	4.5	4.3

entry criteria.

Table 15. Photodynamic Therapy with Verteporfin Use in the Re-randomized Population*

Treatment Group	In Year 1		In Year 2	
	n/N	%	n/N	%
1 mg-1 mg	35/133	26	13/133	10
1 mg-discontinue	17/131	13	13/131	10
3 mg-3 mg	25/125	20	8/125	6
3 mg-discontinue	31/127	24	15/127	12
Sham-pegaptanib [†]	44/165	27	10/165	6
Usual care	25/107	23	14/107	13

*Includes baseline and postbaseline photodynamic therapy, regardless of photodynamic therapy before study enrollment.

[†]Patients originally assigned to sham and re-randomized to any of the 3 pegaptanib doses are presented collectively.