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 $\geq$15 letters from week 54 to week 102; losing $<$15 letters (responders) from baseline to week 102; gaining $\geq$0, $\geq$1, $\geq$2, and $\geq$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 $\geq$15 letters than those re-randomized to discontinue after 1 year ($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 $\geq$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 $VEGF_{165}$ 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

Originally received: November 10, 2005.
Accepted: February 14, 2006. Manuscript no. 2005-1091.

Study results presented in part at: Association for Research in Vision and Ophthalmology Annual Meeting, May 2005, Fort Lauderdale, Florida.

Study sponsored by Eyetech Pharmaceuticals, Inc., New York, New York, and Pfizer Inc., New York, New York.

Correspondence and reprint requests to Usha Chakravarthy, MD, Centre for Vision Sciences, The Queen's University of Belfast and The Royal Victoria Hospital, Belfast BT12 6BA, Northern Ireland, United Kingdom. E-mail: u.chakravarthy@qub.ac.uk.

*Members of the study group taking authorship responsibility for this article and who had complete access to the data needed for this report are listed in "Appendix I" along with their pertinent financial conflict-of-interest statements.

ISSN 0161-6420/06/$–see front matter
doi:10.1016/j.ophtha.2006.02.064

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, $VEGF_{165}$ 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 intravitreous administration of pegaptanib sodium (a 28-ribonucleotide aptamer and a selective inhibitor of $VEGF_{165}$) 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.

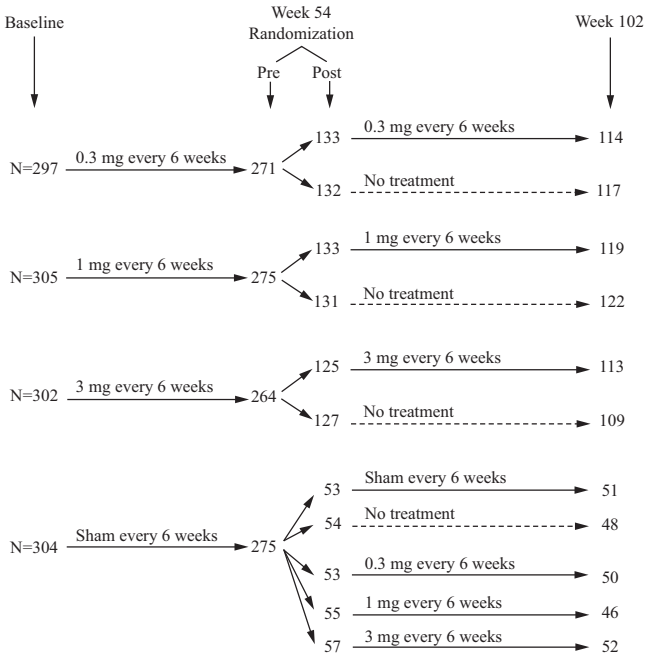


Figure 1. Number of patients randomized and assessed. Post = after; pre = before.

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 intravitreous 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) 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 (1:1:1:1:1) 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 reinstituted.

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 1:1:1:1:1 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 prespecified 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

	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*	
Treatment Group		*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*

	In Year 1		In Year 2	
Treatment Group	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

	Study 1003				Study 1004			
	0.3-mg Pegaptanib (N = 133)		Sham (N = 138)		0.3-mg Pegaptanib (N = 132)		Sham (N = 134)	
Angiographic Parameter	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.

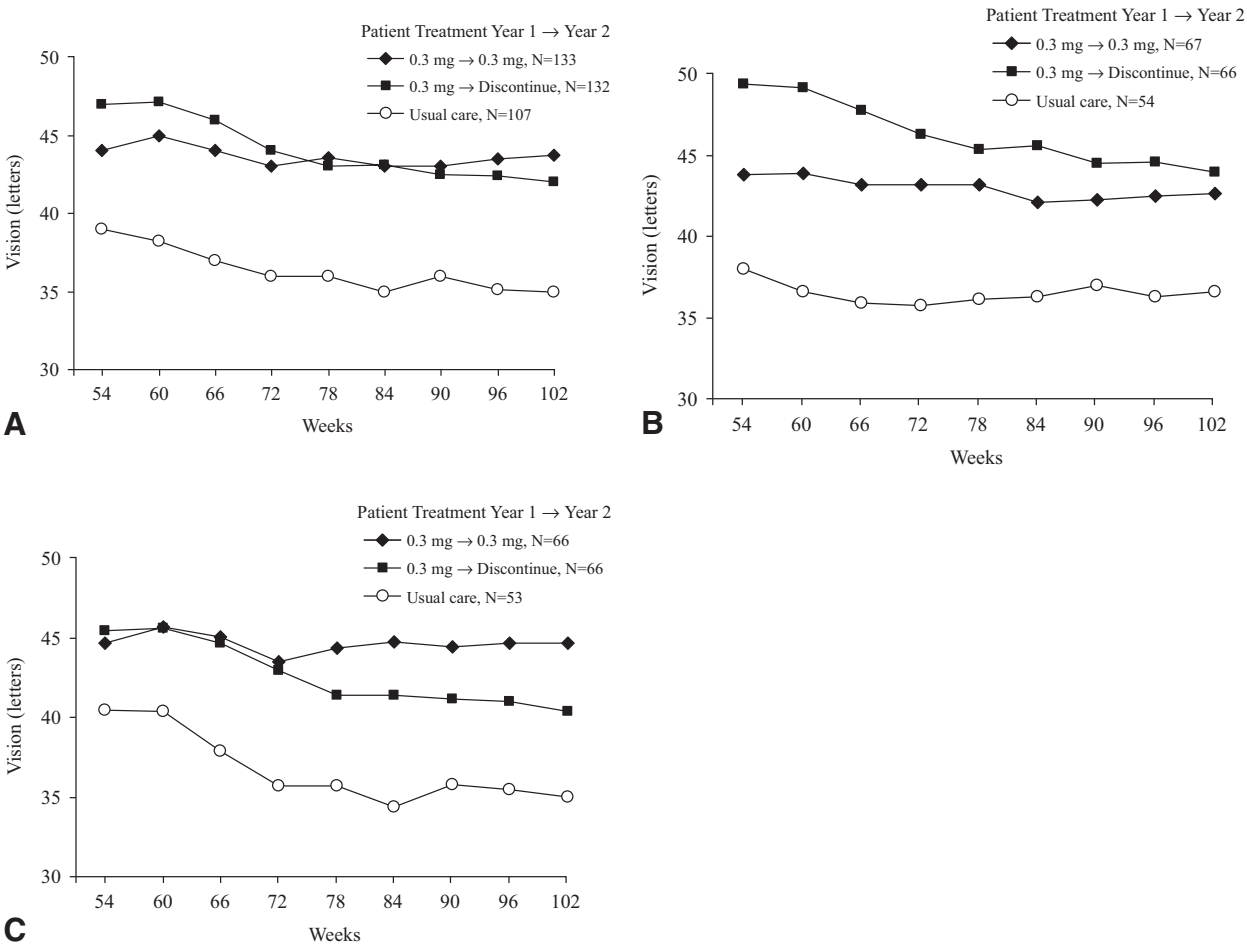


Figure 2. Mean visual acuity from week 54 to week 102. **A**, Studies 1003 and 1004 combined. **B**, Study 1003. **C**, Study 1004.

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

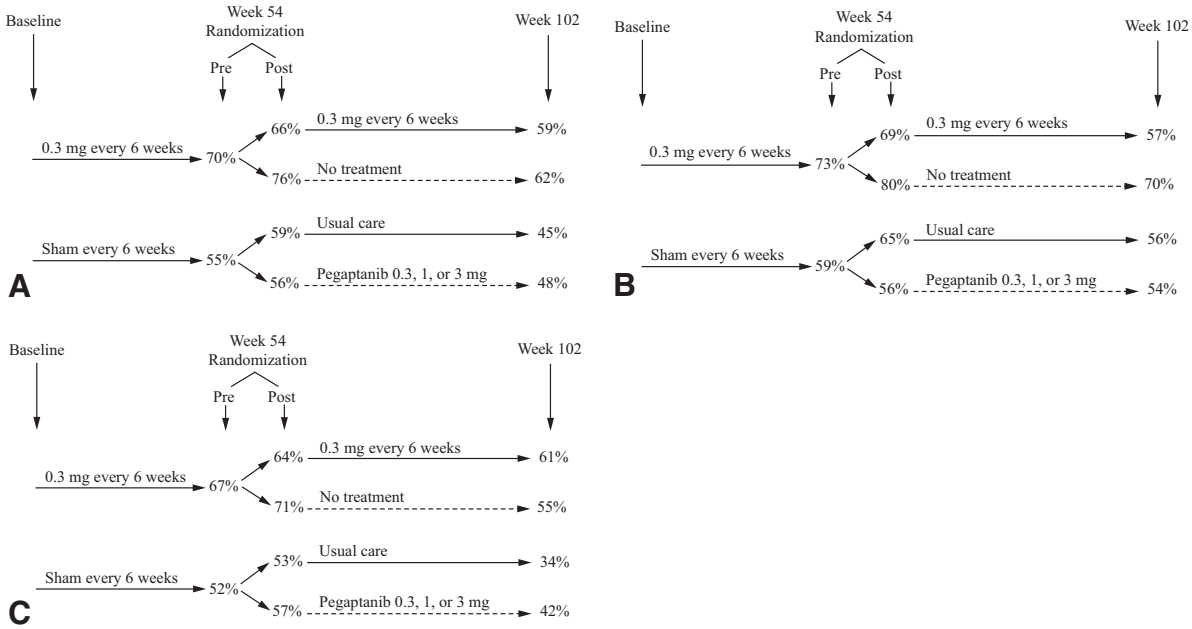


Figure 3. Responder rates. **A**, Studies 1003 and 1004 combined. **B**, Study 1003. **C**, Study 1004. Post = after; pre = before.

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.

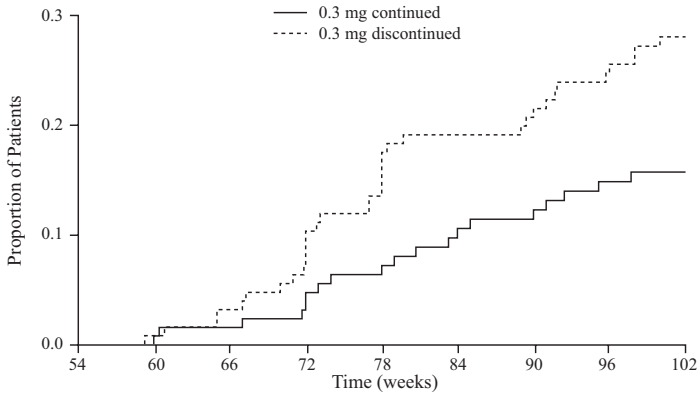
Discussion

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 $VEGF_{165}$ 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 intravitreous 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 $VEGF_{165}$ 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.

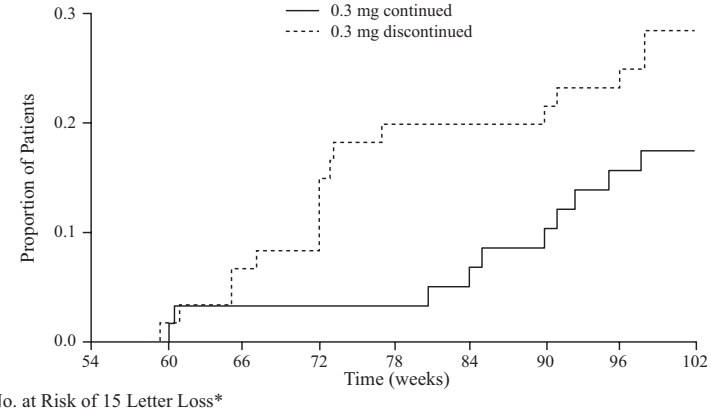
It is possible that the outcomes at week 102 for patients discontinuing therapy at year 1 might have been inflated by random imbalances at the week 54 re-randomization and by rescue treatments, thereby underestimating the importance of continued treatment for 2 years. There is also a likelihood that 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



No. at Risk of 15 Letter Loss*

0.3 mg continued	129	124	119	111	105	102	98	53
0.3 mg discontinued	126	122	112	103	101	98	91	34

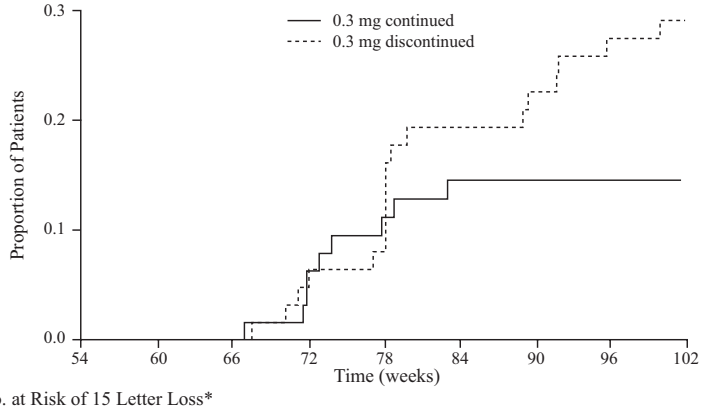
A



No. at Risk of 15 Letter Loss*

0.3 mg continued	64	60	59	57	55	53	49	29
0.3 mg discontinued	62	59	54	51	51	50	46	18

B



No. at Risk of 15 Letter Loss*

0.3 mg continued	65	64	60	54	50	49	49	24
0.3 mg discontinued	64	63	58	52	50	48	45	16

C

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.

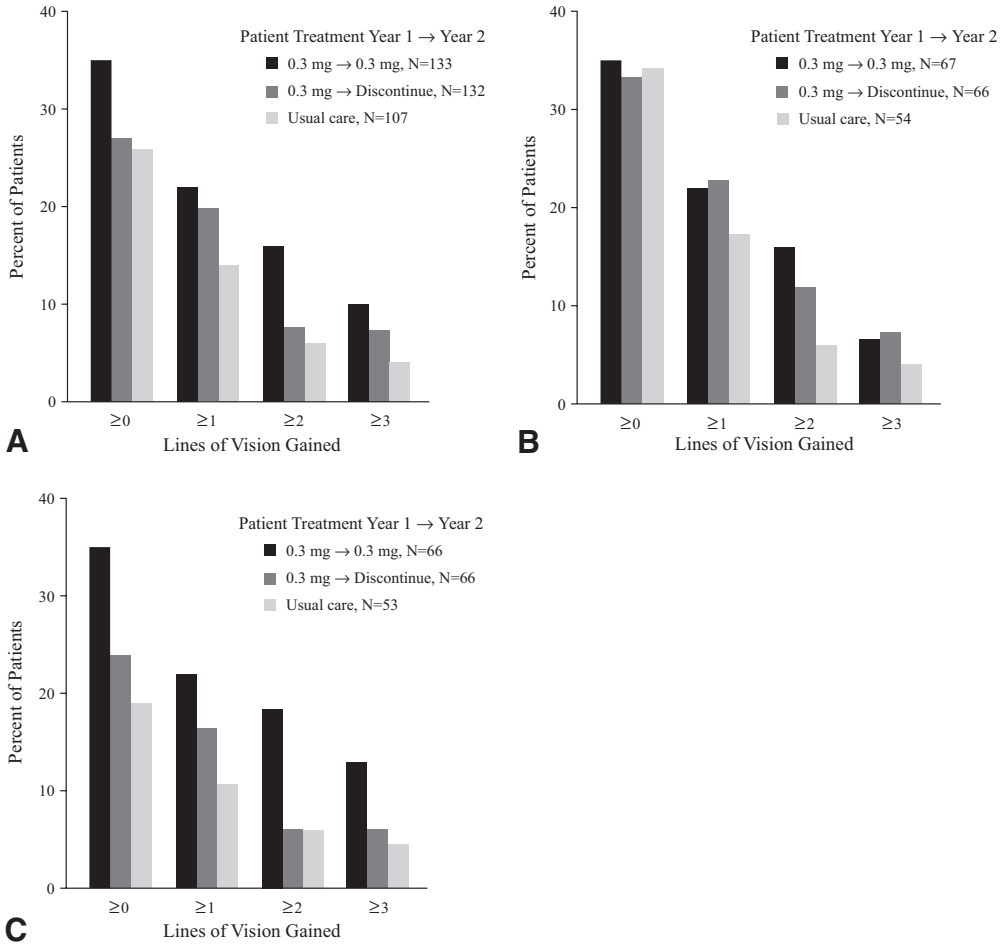


Figure 5. Vision gain. **A**, Studies 1003 and 1004 combined. **B**, Study 1003. **C**, Study 1004.

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 blindness all show that patients assigned to continued $VEGF_{165}$ 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 factor[37] 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 $VEGF_{165}$ 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 $VEGF_{165}$ inhibition with pegaptanib. Indeed, the baseline patient features that might predict response to a $VEGF_{165}$ 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

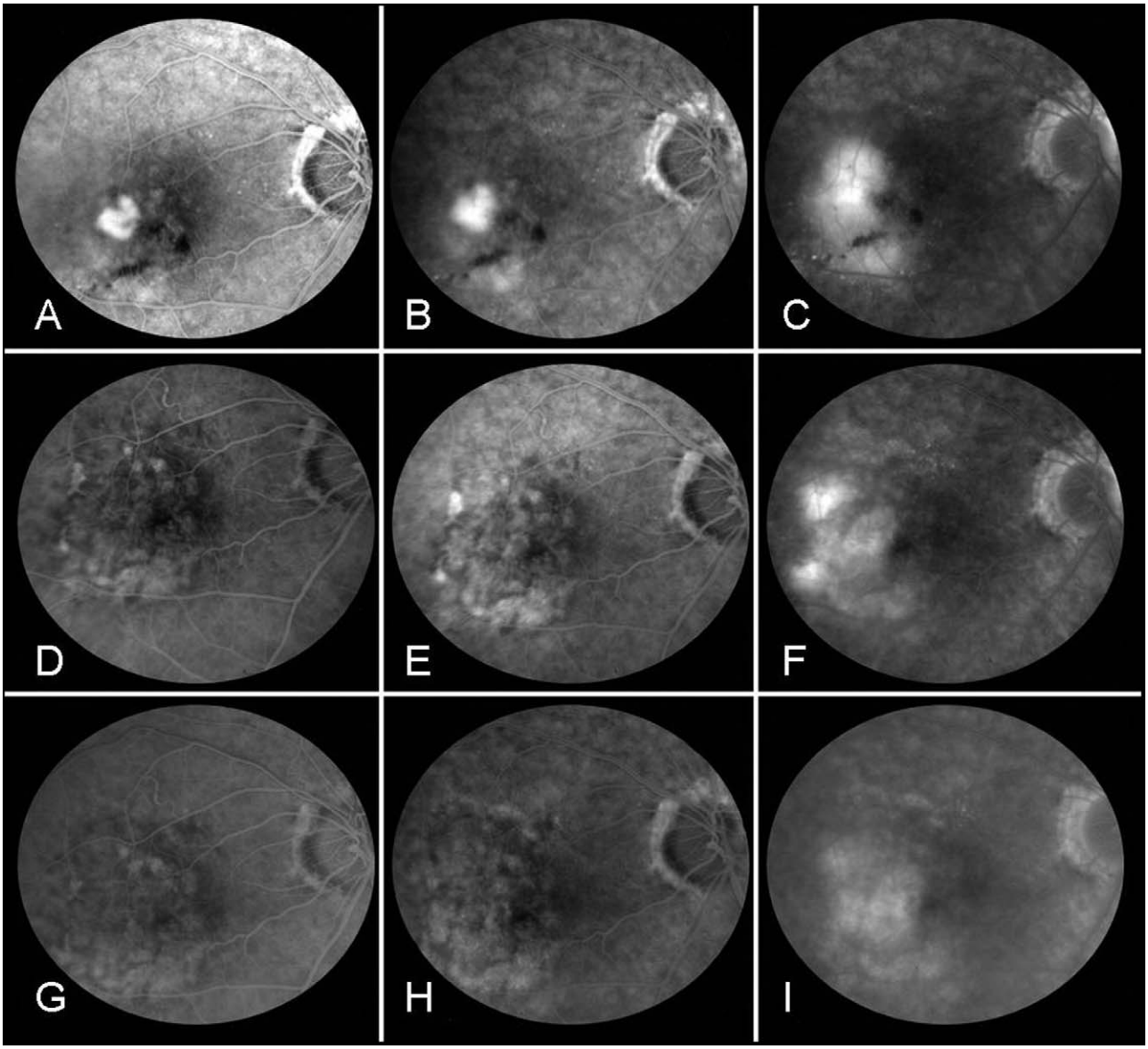


Figure 6. Representative case from the Vascular Endothelial Growth Factor Inhibition Study in Ocular Neovascularization. At baseline, the subject presented with a visual acuity (VA) of ~20/63 (Snellen equivalent) with exudative maculopathy. Early-phase (**A**), midphase (**B**), and late-phase (**C**) fluorescein angiograms showed a minimally classic subfoveal lesion. At week 54, VA improved to ~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 ~20/20.

influenced outcomes,[39] there is no readily apparent biologically plausible reason for such features to influence anti-$VEGF_{165}$ 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 ≥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 $VEGF_{165}$ 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

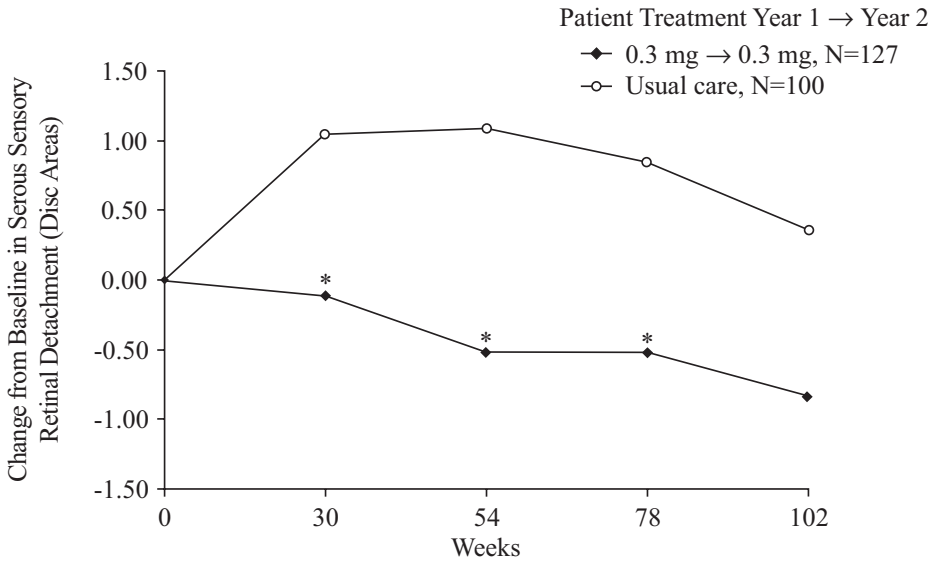


Figure 7. Change from baseline in serous sensory retinal detachment area. Least squares mean in disc areas adjusted for prior photodynamic therapy, lesion subtype, and study. For missing data, the last observation was carried forward. Missing covariate data for 6 patients in the 0.3 mg–0.3 mg group and 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 $VEGF_{165}$ 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 $VEGF_{165}$ 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 $VEGF_{165}$ is important throughout the evolution of active neovascular AMD.

References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844–51.
2. Owen CG, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? Br J Ophthalmol 2003; 87:312–7.
3. Macula Vision Research Foundation. Macular degeneration 101. You should know. Macular degeneration as a public health issue. Available at: http://www.mvrf.org/md101/youshouldknow.html#id3129390198. Accessed January 15, 2006.
4. Prevent Blindness America. Vision problems in the U.S. Prevalence of adult vision impairment and age-related eye disease in America. Section 3. 2002:22-5. Available at: http://www.preventblindness.org/vpus/amd.pdf. Accessed January 15, 2006.
5. Hart PM, Chakravarthy U, Mackenzie G, et al. Visual outcomes in the subfoveal radiotherapy study: a randomized controlled trial of teletherapy for age-related macular degeneration. Arch Ophthalmol 2002;120:1029–38.
6. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a random-

ized clinical trial including lesions with occult with no classic choroidal neovascularization—Verteporfin in Photodynamic Therapy report 2. Am J Ophthalmol 2001;131:541–60.
7. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials—TAP report 2. Arch Ophthalmol 2001;119:198–207.
8. Leung DW, Cachianes G, Kuang WJ, et al. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 1989;246:1306–9.
9. Alon T, Hemo I, Itin A, et al. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. Nat Med 1995;1:1024–8.
10. Asahara T, Takahashi T, Masuda H, et al. VEGF contributes to postnatal neovascularization by mobilizing bone marrow-derived endothelial progenitor cells. EMBO J 1999;18:3964–72.
11. Csaky KG, Baffi JZ, Byrnes GA, et al. Recruitment of marrow-derived endothelial cells to experimental choroidal neovascularization by local expression of vascular endothelial growth factor. Exp Eye Res 2004;78:1107–16.
12. Lamoreaux WJ, Fitzgerald ME, Reiner A, et al. Vascular endothelial growth factor increases release of gelatinase A and decreases release of tissue inhibitor of metalloproteinases by microvascular endothelial cells in vitro. Microvasc Res 1998;55:29–42.
13. Hiratsuka S, Nakamura K, Iwai S, et al. MMP9 induction by vascular endothelial growth factor receptor-1 is involved in lung-specific metastasis. Cancer Cell 2002;2:289–300.
14. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480–7.
15. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. Am J Ophthalmol 1994;118:445–50.
16. Lopez PF, Sippy BD, Lambert HM, et al. Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. Invest Ophthalmol Vis Sci 1996;37:855–68.
17. Frank RN, Amin RH, Eliott D, et al. Basic fibroblast growth factor and vascular endothelial growth factor are present in epiretinal and choroidal neovascular membranes. Am J Ophthalmol 1996;122:393–403.
18. Grossniklaus HE, Ling JX, Wallace TM, et al. Macrophage and retinal pigment epithelium expression of angiogenic cytokines in choroidal neovascularization. Mol Vis 2002;8:119–26.
19. Tolentino MJ, Miller JW, Gragoudas ES, et al. Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. Arch Ophthalmol 1996;114:964–70.
20. Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreous injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. Ophthalmology 1996;103:1820–8.
21. Tolentino MJ, McLeod DS, Taomoto M, et al. Pathologic features of vascular endothelial growth factor-induced retinopathy in the nonhuman primate. Am J Ophthalmol 2002;133:373–85.
22. Baffi J, Byrnes G, Chan CC, Csaky KG. Choroidal neovascularization in the rat induced by adenovirus mediated expression of vascular endothelial growth factor. Invest Ophthalmol Vis Sci 2000;41:3582–9.
23. Spilsbury K, Garrett KL, Shen WY, et al. Overexpression of vascular endothelial growth factor (VEGF) in the retinal pigment epithelium leads to the development of choroidal neovascularization. Am J Pathol 2000;157:135–44.
24. Schwesinger C, Yee C, Rohan RM, et al. Intrachoroidal neovascularization in transgenic mice overexpressing vascular endothelial growth factor in the retinal pigment epithelium. Am J Pathol 2001;158:1161–72.
25. Ohno-Matsui K, Hirose A, Yamamoto S, et al. Inducible expression of vascular endothelial growth factor in adult mice causes severe proliferative retinopathy and retinal detachment. Am J Pathol 2002;160:711–9.
26. Aiello LP, Pierce EA, Foley ED, et al. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. Proc Natl Acad Sci U S A 1995;92:10457–61.
27. Adamis AP, Shima DT, Tolentino MJ, et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. Arch Ophthalmol 1996;114:66–71.
28. Amano S, Rohan R, Kuroki M, et al. Requirement for vascular endothelial growth factor in wound- and inflammation-related corneal neovascularization. Invest Ophthalmol Vis Sci 1998;39:18–22.
29. Honda M, Sakamoto T, Ishibashi T, et al. Experimental subretinal neovascularization is inhibited by adenovirus-mediated soluble VEGF/flt-1 receptor gene transfection: a role of VEGF and possible treatment for SRN in age-related macular degeneration. Gene Ther 2000;7:978–85.
30. Krzystolik MG, Afshari MA, Adamis AP, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol 2002;120:338–46.
31. Ishida S, Usui T, Yamashiro K, et al. $VEGF_{164}$-mediated inflammation is required for pathological, but not physiological, ischemia-induced retinal neovascularization. J Exp Med 2003;198:483–9.
32. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351:2805–16.
33. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline. Choice of control group and related issues in clinical trials: E10. 2000:16-8. Available at: http://www.ich.org/LOB/media/MEDIA486.pdf. Accessed October 10, 2005.
34. VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration. Two-year safety results of the two prospective, multicenter, controlled clinical trials. Ophthalmology 2006;113:992–1001.
35. Frison L, Pocock SJ. Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design. Stat Med 1992;11:1685–704.
36. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report I. Arch Ophthalmol 1999;117:1329–45.
37. Senger DR, Connolly DT, Van de Water L, et al. Purification and NH2-terminal amino acid sequence of guinea pig tumor-secreted vascular permeability factor. Cancer Res 1990;50:1774–8.
38. Matsuoka M, Ogata N, Otsuji T, et al. Expression of pigment epithelium derived factor and vascular endothelial growth factor in choroidal neovascular membranes and polypoidal choroidal vasculopathy. Br J Ophthalmol 2004;88:809–15.
39. Treatment of Age-Related Macular Degeneration with Photo-

dynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in patients with age-related macular degeneration: additional information regarding baseline lesion composition's impact on vision outcomes—TAP report no. 3. Arch Ophthalmol 2002;120:1443–54.

Appendix I

The Writing Committee was convened by U. Chakravarthy, Centre for Vision Sciences, The Queen's University of Belfast and The Royal Victoria Hospital, Belfast, United Kingdom.

Writing Committee

U. Chakravarthy, Centre for Vision Sciences, The Queen's University of Belfast and The Royal Victoria Hospital, Belfast, United Kingdom (corresponding author); A. P. Adamis, E. T. Cunningham, Jr, M. Goldbaum, D. R. Guyer, B. Katz, Eyetech Pharmaceuticals, Inc., New York, New York; Manju Patel, Pfizer Inc., New York, New York. Dr Chakravarthy has been a member of advisory boards to Pfizer Inc.

Independent Data Monitoring Committee

A. Bird, Moorfields Eye Hospital, London, United Kingdom (chair); D. D'Amico, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts (chair emeritus); J. Herson, Johns Hopkins University, Baltimore, Maryland; R. Klein, University of Wisconsin, Madison, Wisconsin; H. Lincoff, New York–Presbyterian Weill Cornell Center, New York, New York; A. Patz, Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore, Maryland.

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

Steering Committee

M. Blumenkranz, Stanford University, Stanford, California; M. Buyse, International Drug Development Institute, Brussels, Belgium; M. Goldberg, Johns Hopkins University, Baltimore, Maryland; E. S. Gragoudas, J. Miller, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts; S. D. Schwartz, University of California at Los Angeles, Los Angeles, California; L. Singerman, Retina Associates of Cleveland, Cleveland, Ohio; L. Yannuzzi, Columbia University, New York, New York; A. P. Adamis, D. R. Guyer, D. O'Shaughnessy, Eyetech Pharmaceuticals, Inc., New York, New York.

Data Management and Statistics Group

M. Buyse, S. de Gronckel, G. Fesneau, E. Quinaux, D. Tremolet, K. Wang, International Drug Development Institute, Brussels, Belgium; A. Brailey, J. Finman, N. Ting, Pfizer Inc., Groton, Connecticut.

Eligibility and Classification Quality Assurance Team

N. M. Bressler, S. B. Bressler, R. Denblow, D. Philips, A. P. Schachat, O. D. Schein, S. Seabrook, S. Solomon, Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore, Maryland.

Independent Fundus Photograph and Angiogram Reading Center

M. Altaweel, B. A. Blodi, R. P. Danis, M. D. Davis, M. S. Ip, C. Hiner, J. Elledge, M. Webster, C. Hannan, J. Ficken, S. Alexander, M. Neider, H. Wabers, P. Vargo, E. Lambert, L. Kastorff, A. Carr, A. Shkiele, J. Baliker, University of Wisconsin, Madison, Wisconsin.

V.I.S.I.O.N. Clinical Trial Group

R. Guymer, Centre for Eye Research Australia, University of Melbourne, Melbourne, Australia; I. Constable, Lions Eye Institute, Nedlands, Australia; J. Arnold, S. Sarks, Marsden Eye Specialists, Parramatta, Australia; A. Chang, Eye and Vision Research Institute, Sydney, Australia; M. Gillies, Save Sight Institute, Sydney, Australia; P. Mitchell, Westmead Hospital, Westmead, Australia; A. Haas, Universitäts Augenklinik, Graz, Austria; M. Stur, Universitäts-Augenklinik, Vienna, Austria; A. Leys, UZ St. Rafaël, Leuven, Belgium; C. Moreira, E. Portella, Hospital de Olhos do Paraná, Curitiba, Brazil; M. de Avila, A. C. Taleb, Universidade Federal de Goiás, Goiânia, Brazil; J. Lavinsky, D. Lavinsky, Hospital das Clínical de Porto Alegre, Porto Alegre, Brazil; M. E. Farah, Universidade Federal de São Paulo, São Paulo, Brazil; G. Williams, Calgary Retina Consultants, Calgary, Canada; B. Leonard, University of Ottawa Eye Institute, Ottawa, Canada; R. Garcia, Eye Centre Pasqua Hospital, Regina, Canada; D. Maberley, Vancouver Hospital and Health Sciences Center, University of British Columbia Eye Care Center, Vancouver, Canada; J. M. Lopez, Pontificia Universidad Católica de Chile, Santiago, Chile; F. J. Rodriguez, Fundación Oftalmológica Nacional, Bogotá, Colombia; I. Fiser, Vinohrady Teaching Hospital, Prague, Czech Republic; M. Larsen, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; J.-F. Korobelnik, Groupe Hospitalier Pellegrin, Bordeaux, France; G. Soubrane, Centre Hospitalier Universitaire de Créteil-Paris XII, Créteil, France; F. Koenig, Centre de Recherche en Ophtalmologie, Lyon, France; A. Gaudric, Hopital Lariboisiere, Paris, France; A. Joussen, B. Kirchhof, University of Cologne, Cologne, Germany; S. Dithmar, F. G. Holz, University of Heidelberg, Heidelberg, Germany; P. Wiedemann, Universitätsklinikum Leipzig Klinik und Poliklinik, Leipzig, Germany; D. Pauleikhoff, St. Franziskus Hospital, Muenster, Germany; U. Schneider, University Eye Clinic Tübingen, Tübingen, Germany; I. Suveges, Semmelweis University, Budapest, Hungary; J. Gyory, Csolnoky Ferenc County Hospital, Kórház, Hungary; I. Rosenblatt, Rabin Medical Center, Petach-Tikva, Israel; A. Pollack, Kaplan Medical Center, Rehovot, Israel; A. Loewenstein, Ichilov Medical Center, Tel Aviv, Israel; A. Giovannini, Istituto di Scienze Oftalmologiche, Ancona, Italy; U. Menchini, II Clinica Oculistica Universitá degli Studi di Firenze, Florence, Italy; R. Brancato, Università Ospedale San Raffaele, Milan, Italy; F. Cardillo Piccolino, F. M. Grignolo, Università di Torino, Turin, Italy; F. Bandello, Policlinico Universitario, Udine, Italy; R. O. Schlingemann, Academic Medical Center, University of Amsterdam, The Netherlands; C. B. Hoyng, UMC St. Radboud, Institute of Ophthalmology, Nijmegen, The Netherlands; J. Kaluzny, Akademia Medyczna ul M. Sklodowskiej-Curie, Bydgoszcz, Poland; K. Pecold, Akademia Medyczna ul. Dluga, Pozna'n, Poland; J. Cunha-Vaz, R. da Silva, Associacão Para Investigacão Biomedica e Inovacão Em Luz e Imagem, Universidada de Coimbra, Coimbra, Portugal; J. M. Ruiz Moreno, VISSUM–Instituto Oftalmologico de Alicante, Alicante, Spain; J. Mones, Instituto de Microcirugia Ocular, Barcelona, Spain; M. Figueroa, Hospital Oftalmologico Internacional, Madrid, Spain; C. Pournaras, Hopital Cantonal de Geneva, Geneva, Switzerland; L. Zografos, Hopital Opthalmique Jules Gonin, Lausanne, Switzerland; N. Lois, Aberdeen Royal Infirmary, Aberdeen, United Kingdom; U. Chakravarthy, Queen's University Belfast Royal Victoria Hospital, Belfast, United Kingdom; P. Hykin, Moorfields Eye Hospital, London, United Kingdom; I. Chisholm, Southampton General Hospital, Southampton, United Kingdom; M. W. Johnson, W. K. Kellogg Eye Center, Ann Arbor, Michigan; D. M. Marcus, Medical College of Georgia, Augusta, Georgia; N. Mandava, University of Colorado Rocky Mountain Lions Eye Institute, Aurora, Colorado; J. A. Haller, Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore, Maryland; F. Cangemi, Vitreo-retinal Associates of New Jersey, Belleville, New Jersey; D. Boyer, Retina Vitreous Associates, Beverly Hills, California; I. Kim, J. Loewenstein, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts; J. Heier, Ophthalmic Consultants of Boston, Boston, Massachusetts; E. Reichel, New England Eye Center, Boston, Massachusetts; P. M. Falcone, Connecticut Retina Consultants, Bridgeport, Connecticut; D. J. Weissgold, University of Vermont College of Medicine, Burlington, Vermont; B. P. Conway, University of Virginia, Charlottesville, Virginia; R. Garfinkel, Retina Group of Washington, Chevy Chase, Maryland; B. Glaser, Glaser Murphy Retina Treatment Centers, Chevy Chase, Maryland; A. T. Lyon, Northwestern University Sorrel Rosin Eye Center, Chicago, Illinois; H. Lewis, Cleveland Clinic Cole Eye Institute, Cleveland, Ohio; J. A. Wells, Palmetto Retina Center, Columbia, South Carolina; L. Wilcox, Eye Center of Concord, Concord, New Hampshire; G. Fish, Texas Retina Associates, Dallas, Texas; D. Eliott, Kresge Eye Institute, Detroit, Michigan; S. Fekrat, Duke University Eye Center, Durham, North Carolina; B. Taney, Retina Vitreous Consultants, Fort Lauderdale, Florida; A. M. Eaton, Retina Health Center, Fort Myers, Florida; V. Deramo, L. I. Vitreo-retinal Consultants, Great Neck, New York; J. Wroblewski, Cumberland Valley Retina Center, Hagerstown, Maryland; D. Tom, New England Retina Associates, Hamden, Connecticut; D. R. Chow, D. H. Orth, K. H. Packo, Illinois Retina Associates, Harvey, Illinois; E. Holz, W. Mieler, Baylor College of Medicine, Houston, Texas; B. Kuppermann, University of California, Irvine, California; N. Sabates, Eye Foundation of Kansas

City, Kansas City, Missouri; H. Cummings, Southeastern Retina Associates, Knoxville, Tennessee; S. D. Pendergast, Retina Associates of Cleveland, Lakewood, Ohio; C. Gonzales, Jules Stein Eye Institute, Los Angeles, California; J. I. Lim, Doheny Eye Institute, University of Southern California, Keck School of Medicine, Los Angeles, California; S. Charles, Charles Retina Institute, Memphis, Tennessee; S. Sanislo, Stanford University School of Medicine, Menlo Park, California; P. Rosenfeld, Bascom Palmer Eye Institute, Miami, Florida; T. Connor, Eye Institute, Milwaukee, Wisconsin; H. Cantrill, VitreoRetinal Surgery, Minneapolis, Minnesota; R. Willson, Foundation for Retinal Research, New Orleans, Louisiana; K. Bailey-Freund, Manhattan Eye, Ear & Throat Retinal Research Office, New York, New York; R. Rosen, New York Eye and Ear Infirmary, New York, New York; R. Leonard, Dean A. McGee Eye Institute, Oklahoma City, Oklahoma; A. Brucker, Scheie Eye Institute, Philadelphia, Pennsylvania; A. Ho, Wills Eye Hospital Retina Research, Philadelphia, Pennsylvania; S. Sneed, Retinal Consultants of Arizona, Phoenix, Arizona; T. Friberg, UPMC Eye Center, Pittsburgh, Pennsylvania; M. Klein, Casey Eye Institute, Portland, Oregon; P. Tornambe, Retina Consultants, San Diego, Poway, California; G. Stoller, Ophthalmic Consultants of Long Island, Rockville Centre, New York; A. Capone, Jr, Associated Retinal Consultants, Royal Oak, Michigan; P. S. Bernstein, John Moran Eye Center, University of Utah, Salt Lake City, Utah; H. R. McDonald, H. Schatz, R. N. Johnson, West Coast Retina Medical Group, San Francisco, California; M. Nanda, Orange County Retina, Santa Ana, California; R. Avery, California Retina Consultants, Santa Barbara, California; K. Wong, Sarasota Retina Institute, Sarasota, Florida; W. S. Grizzard, Retina Associates of Florida, Tampa, Florida; P. Higgins, Retina Associates of New Jersey, Teaneck, New Jersey; H. Hudson, Retina Centers PC, Tucson, Arizona; L. Joffe, Retina Associates SW PC, Tucson, Arizona; M. Varenhorst, Vitreo-retinal Consultants and Surgeons, Wichita, Kansas; M. M. Slusher, Wake Forest University Eye Center, Winston-Salem, North Carolina.

Eyetech and Pfizer Staff

A. P. Adamis, F. Betts, E. T. Cunningham, Jr, K. Curtiss, M. Goldbaum, D. R. Guyer, E. Harrison, P. Healey, B. Katz, H. N. Masonson, D. O'Shaughnessy, Eyetech Pharmaceuticals, Inc., New York, New York; C. Beals, D. Eveleth, M. Patel, C. Starita, Pfizer Inc., New York, New York.

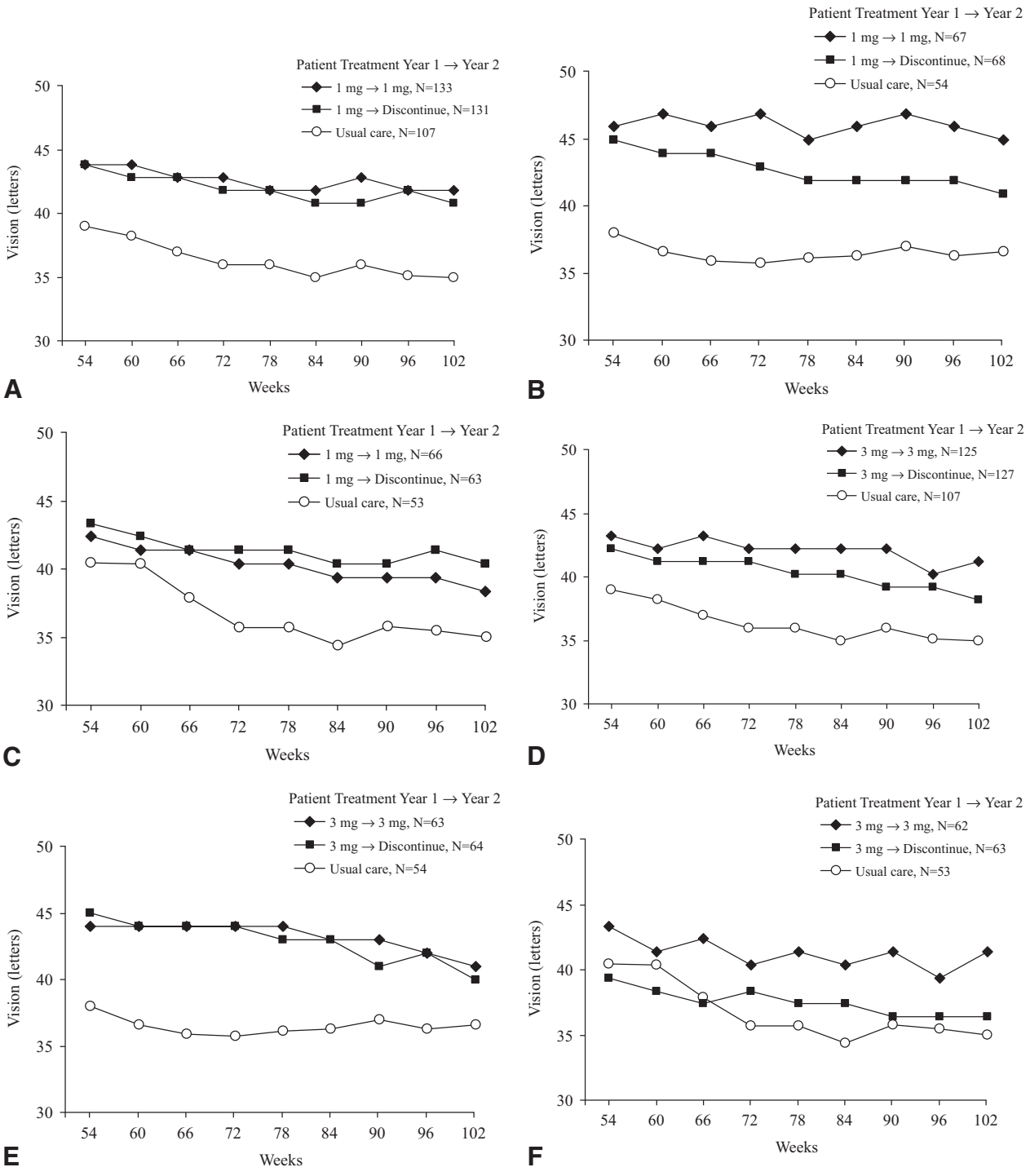


Figure 8. Mean visual acuity from week 54 to week 102. **A**, Studies 1003 and 1004 combined, 1-mg pegaptanib. **B**, Study 1003, 1-mg pegaptanib. **C**, Study 1004, 1-mg pegaptanib. **D**, Studies 1003 and 1004 combined, 3-mg pegaptanib. **E**, Study 1003, 3-mg pegaptanib. **F**, Study 1004, 3-mg pegaptanib.

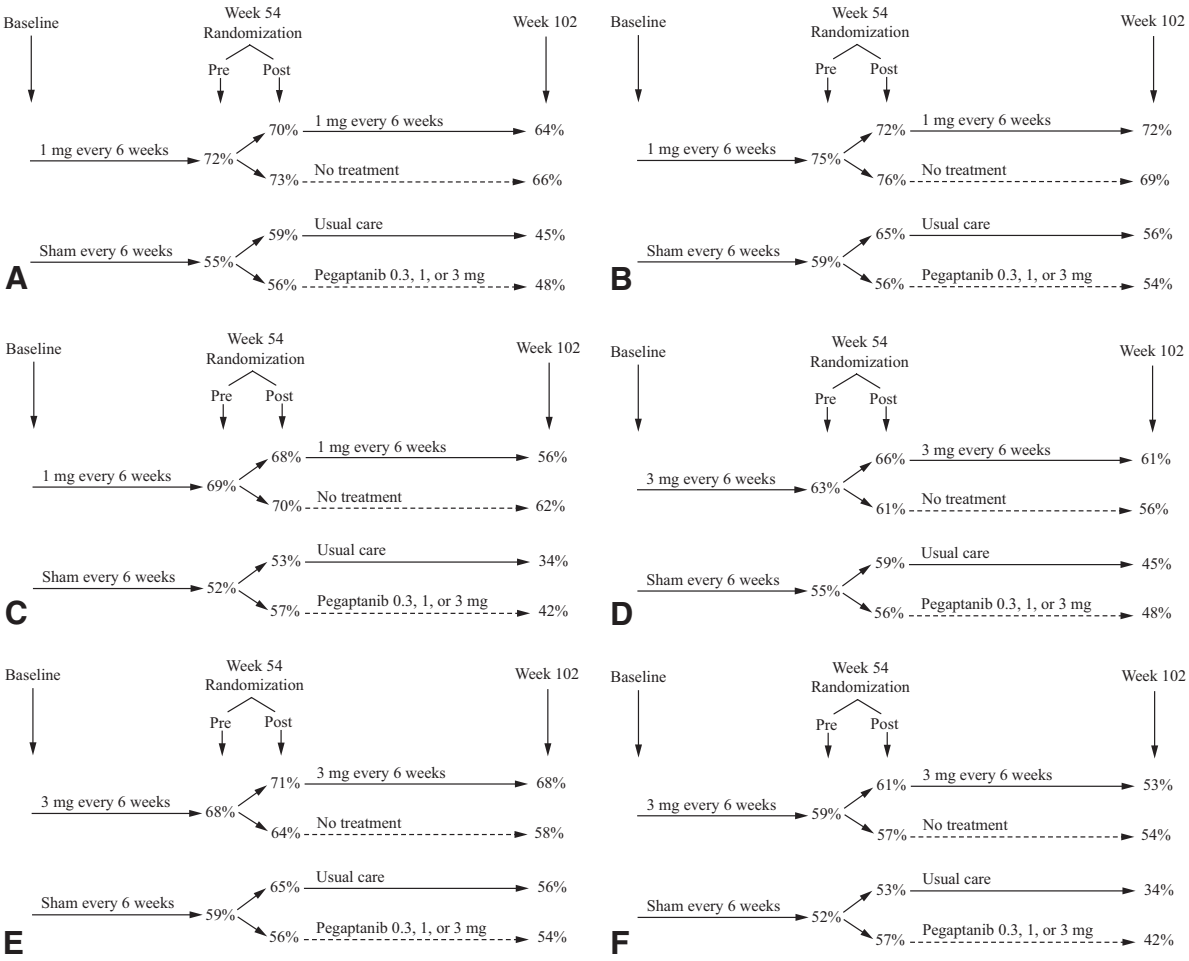
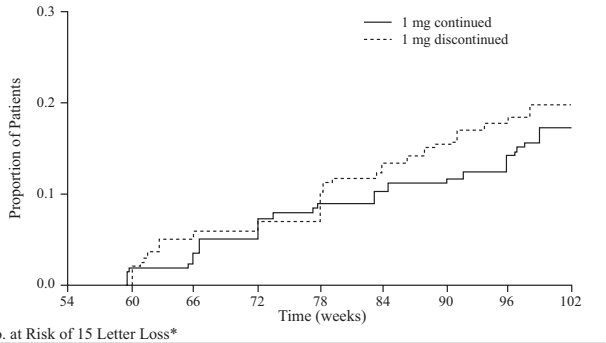


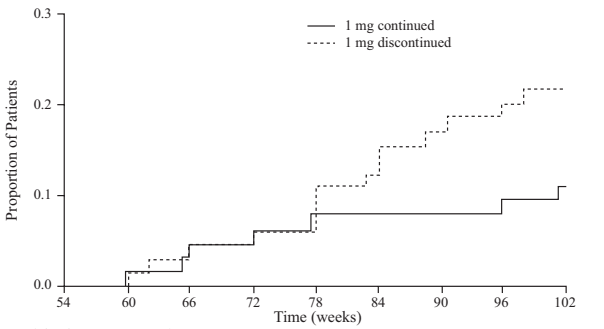
Figure 9. Responder rates. **A**, Studies 1003 and 1004 combined, 1-mg pegaptanib. **B**, Study 1003, 1-mg pegaptanib. **C**, Study 1004, 1-mg pegaptanib. **D**, Studies 1003 and 1004 combined, 3-mg pegaptanib. **E**, Study 1003, 3-mg pegaptanib. **F**, Study 1004, 3-mg pegaptanib. Post = after; pre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



No. at Risk of 15 Letter Loss*

1 mg continued	128	124	117	112	111	108	103	62
1 mg discontinued	127	121	118	111	107	103	99	63

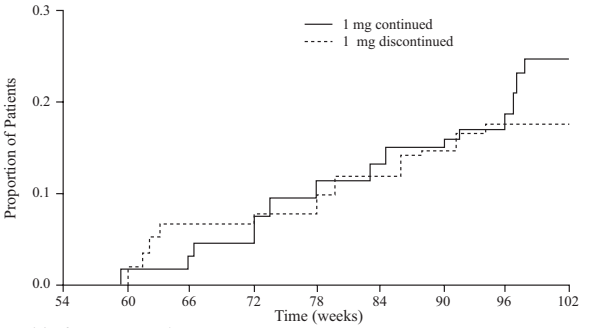
A



No. at Risk of 15 Letter Loss*

1 mg continued	64	61	59	57	57	57	55	19
1 mg discontinued	66	63	61	57	54	52	50	23

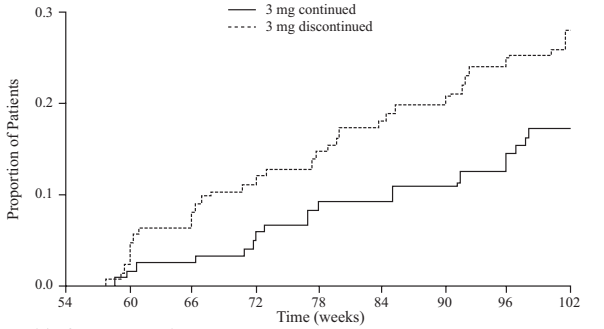
B



No. at Risk of 15 Letter Loss*

1 mg continued	64	63	58	55	54	51	48	29
1 mg discontinued	61	58	57	54	53	51	49	29

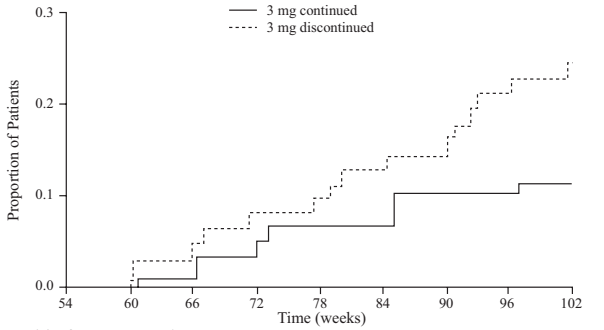
C



No. at Risk of 15 Letter Loss*

3 mg continued	119	118	112	107	105	103	97	69
3 mg discontinued	118	113	107	101	95	92	82	58

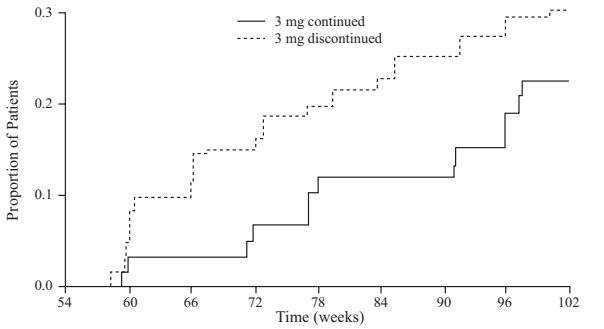
D



No. at Risk of 15 Letter Loss*

3 mg continued	60	59	57	55	55	53	51	38
3 mg discontinued	62	59	57	55	53	51	47	35

E



No. at Risk of 15 Letter Loss*

3 mg continued	59	59	55	51	50	50	45	22
3 mg discontinued	56	54	50	46	42	40	35	17

F

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.

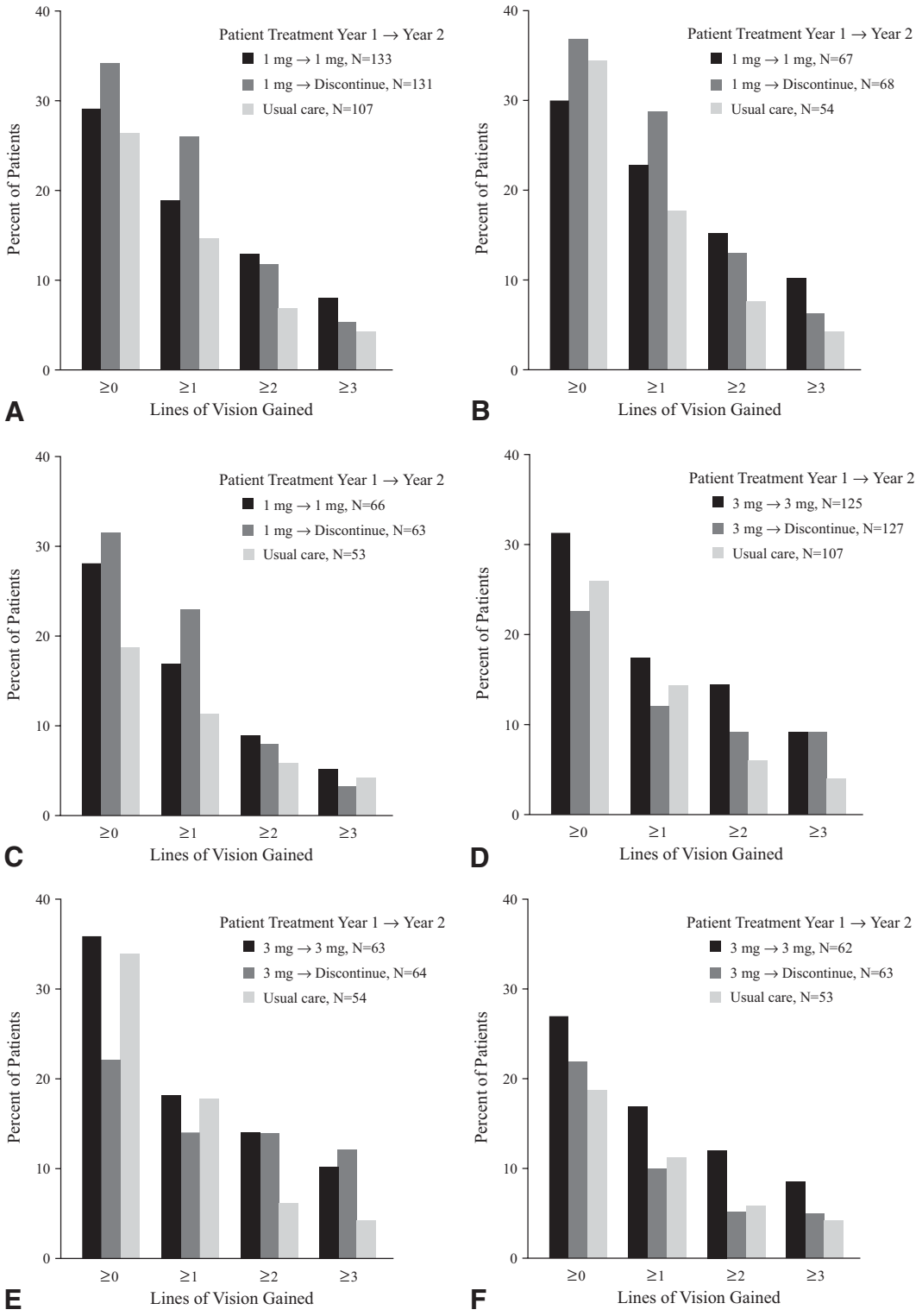


Figure 11. Vision gain. **A**, Studies 1003 and 1004 combined, 1-mg pegaptanib. **B**, Study 1003, 1-mg pegaptanib. **C**, Study 1004, 1-mg pegaptanib. **D**, Studies 1003 and 1004 combined, 3-mg pegaptanib. **E**, Study 1003, 3-mg pegaptanib. **F**, Study 1004, 3-mg pegaptanib.

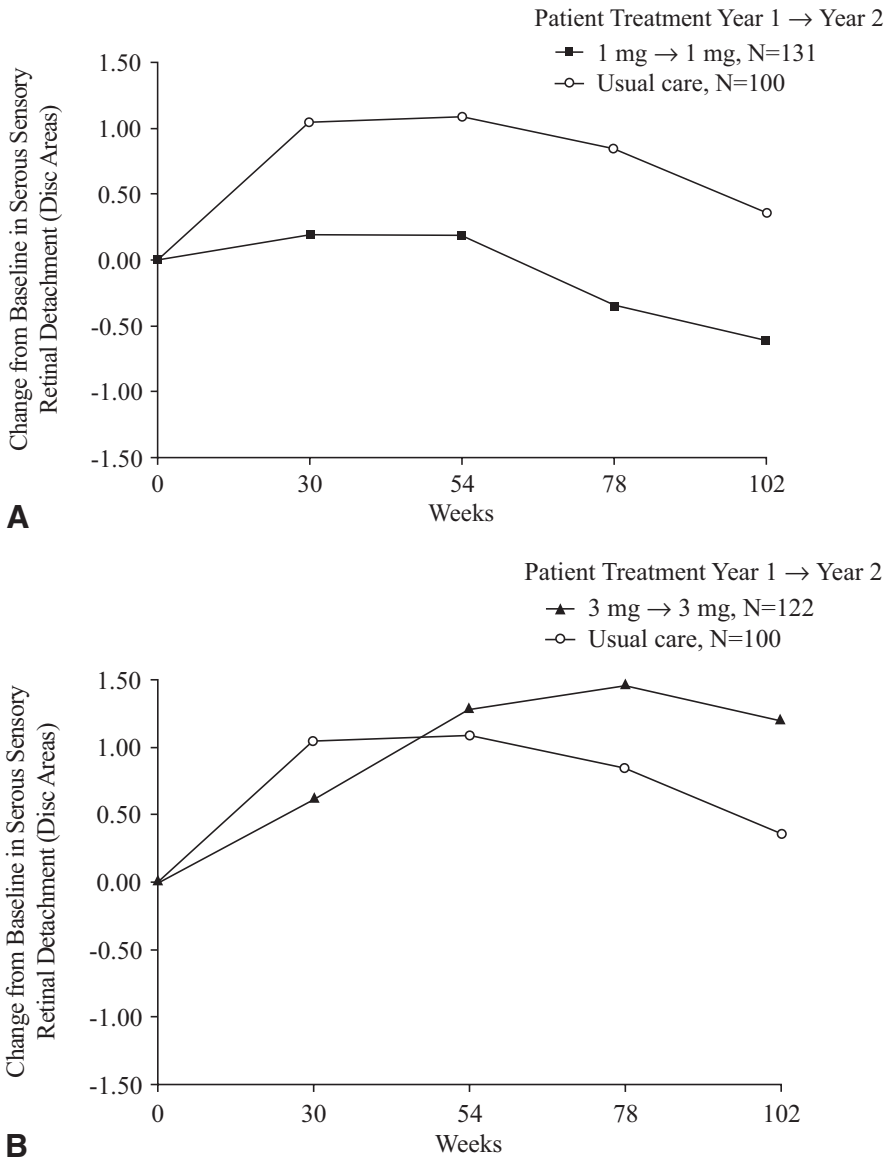


Figure 12. Change from baseline in serous sensory retinal detachment area. Least squares mean in disc areas adjusted for prior photodynamic therapy, lesion subtype, and study. For missing data the last observation was carried forward (LOCF). **A**, One-milligram pegaptanib. Missing covariate data for 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

	Study 1003					Study 1004				
Variables	*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

	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*	
Treatment Group		*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

	Study 1003					
	1-mg Pegaptanib (N = 135)		*3-mg Pegaptanib (N = 127)*		*Sham (N = 138)*	
Angiographic Parameter	*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*

	In Year 1		In Year 2	
Treatment Group	*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.