Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1

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• PURPOSE: To evaluate the efficacy and safety of ranibizumab administered monthly for three months and then quarterly in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

• DESIGN: Phase IIIb, multicenter, randomized, double-masked, sham injection-controlled trial in patients with predominantly or minimally classic or occult with no classic CNV lesions.

• METHODS: Patients were randomized 1:1:1 to 0.3 mg ranibizumab (n = 60), 0.5 mg ranibizumab (n = 61), or sham (n = 63) treatment groups. The primary efficacy endpoint was mean change from baseline visual acuity (VA) at month 12.

• RESULTS: Mean changes from baseline VA at 12 months were −16.3, −1.6, and −0.2 letters for the sham, 0.3 mg, and 0.5 mg groups, respectively ($P \leq .0001$, each ranibizumab dose vs sham). Ranibizumab arrested CNV growth and reduced leakage from CNV. However, the treatment effect declined in the ranibizumab groups during quarterly dosing (e.g., at three months the mean changes from baseline VA had been gains of 2.9 and 4.3 letters for the 0.3 mg and 0.5 mg doses, respectively). Results of subgroups analyses of mean change from baseline VA at 12 months by baseline age, VA, and lesion characteristics were consistent with the overall results. Few serious ocular or nonocular adverse events occurred in any group.

• CONCLUSIONS: Ranibizumab administered monthly for three months and then quarterly provided significant VA benefit to patients with AMD-related subfoveal CNV and was well tolerated. The incidence of serious ocular or nonocular adverse events was low. (Am J Ophthalmol 2008;145:239–248. © 2008 by Elsevier Inc. All rights reserved.)

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Oct 5, 2007.

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RANIBIZUMAB (LUCENTIS; GENENTECH, INC, SOUTH San Francisco, California, USA) is an intravitreally administered recombinant, humanized, monoclonal antibody antigen-binding fragment (Fab) that neutralizes all known active forms of vascular endothelial growth factor-A (VEGF-A). It is the first treatment shown to not only prevent loss of visual acuity (VA) but also improve VA on average in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). In the two pivotal phase III trials—the MARINA Study in patients with minimally classic or occult with no classic CNV[1] and the ANCHOR Study in patients with predominantly classic CNV[2]—ranibizumab was injected monthly.

The phase IIIb PIER Study was designed to determine whether a less frequent ranibizumab dosing schedule (monthly for three months and then once every three months) would also prevent loss of VA in patients with AMD-related subfoveal CNV with or without a classic component, and to provide additional safety information. This alternative dosing regimen was selected for testing based on evidence from phase I and II studies indicating that the pharmacodynamic activity of ranibizumab (0.3 and 0.5 mg) administered intravitreally monthly for three doses may last 90 days.[3,4]

METHODS

PIER IS A TWO-YEAR, PHASE IIIB, MULTICENTER, RANDOMized, double-masked, sham injection–controlled study of the efficacy and safety of ranibizumab in patients with AMD-related subfoveal CNV, with or without classic CNV. After providing written informed consent, patients entered a screening period (≤28 days), with eligibility determined by the investigator. A central reading center (University of Wisconsin Fundus Photograph Reading Center, Madison, Wisconsin) later re-assessed the CNV types based on fluorescein angiograms, but this did not affect patients' eligibility. See Supplemental Table A (available at AJO.com) for full eligibility criteria.

Only patients ≥50 years old were eligible. One eye per subject (the "study eye") received study treatment. If both eyes were eligible, the one with better VA was selected

0002-9394/08/$34.00
doi:10.1016/j.ajo.2007.10.004
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unless, for medical reasons, the other was more appropriate. Key inclusion criteria for the study eye were primary or recurrent subfoveal CNV secondary to AMD, with the total CNV area (classic plus occult CNV) composing ≥50% of the total AMD lesion area; total AMD lesion size ≤12 disk areas (DA); and best-corrected VA of 20/40 to 20/320 (Snellen equivalent) measured per a standard testing protocol using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at a distance of 4 meters. Eyes with minimally classic or occult with no classic CNV were eligible only if they met any of three criteria for presumed disease progression: ≥10% increase in lesion size based on a fluorescein angiogram obtained ≤one month before day zero, inclusive, vs one obtained ≤six months before day zero, inclusive; or >one Snellen line (or equivalent) VA loss within the prior six months; or CNV-associated subretinal hemorrhage ≤one month before day zero. Eyes with predominantly (>50% of the lesion) classic CNV were not required to meet the criteria for presumed disease progression. Key exclusion criteria were any prior treatment with verteporfin photodynamic therapy (PDT), external-beam radiation therapy, transpupillary thermotherapy, or subfoveal laser photocoagulation (or juxtafoveal or extrafoveal laser photocoagulation ≤one month before day zero); permanent structural damage to the central fovea; or subretinal hemorrhage involving the fovea if ≥1 DA or ≥50% of the total lesion area. Patients were excluded if either eye had been treated in a prior antiangiogenic drug trial, or if the nonstudy eye received PDT ≤seven days before day zero.

Using a dynamic randomization algorithm, subjects were randomly assigned 1:1:1 to receive 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injections. Randomization was stratified by VA score at day zero (≤54 letters [approximately worse than 20/80] vs ≥55 letters [approximately 20/80 or better], CNV type (minimally classic vs occult with no classic vs predominantly classic CNV), and study center.

To achieve double-masking of treatment assignment, at least two investigators participated at each study site: an "injecting" ophthalmologist unmasked to treatment assignment (ranibizumab vs sham) but masked to ranibizumab dose, and a masked "evaluating" ophthalmologist for efficacy and safety assessments. All other study site personnel (other than those assisting with study treatment administration), central reading center personnel, and the subjects were masked to treatment assignment.

The ranibizumab groups received their assigned dose by intravitreal injection every month for three doses (day zero, months one and two), followed by doses every three months (months five, eight, 11, 14, 17, 20, and 23). Ranibizumab injection procedures have been described previously.[1,2] For the sham-injected control group, an empty syringe without a needle was used, with pressure applied to the anesthetized and antiseptically prepared eye at the site of a typical intravitreal injection. Pre- and postinjection procedures (described previously[1,2]) were identical for all groups.

The original study protocol specified that each treatment group would follow the same injection schedule. Thus, during the 24-month study, a total of 10 ranibizumab or sham injections were to be given, with six of the 10 during the first 12 months. After careful review of recent clinical data, including 12-month data from the two pivotal phase III studies,[1,2] the study protocol was amended on February 27, 2006 to allow control subjects who had completed the month-12 visit (the assessment timepoint for the primary efficacy analysis) to cross over to 0.5 mg ranibizumab for the remainder of the treatment period (subjects in the ranibizumab groups continued their originally assigned dose of 0.3 or 0.5 mg). On August 21, 2006, the protocol was again amended to increase assessments from quarterly to monthly after month 12, and to switch subjects randomized to the 0.3 mg dose to the 0.5 mg dose for the remainder of their study treatment. Also, because ranibizumab was by this time approved by the U.S. Food and Drug Administration (FDA), subjects were allowed to receive ranibizumab in the fellow eye as well as the study eye. No subjects were unmasked to their original treatment assignment as a result of these protocol amendments.

Assessments were performed at scheduled clinic visits. The first ranibizumab (0.3 or 0.5 mg) or sham treatment was administered on day zero. At subsequent injection visits, subjects underwent a preinjection safety evaluation. In addition to injection visits (day zero and months one, two, five, eight, 11, 14, 17, 20, and 23), clinic visits were scheduled at months three, 12, and 24. At each scheduled visit, subjects received a full ophthalmologic assessment, including VA testing using ETDRS charts at a test distance of 4 meters, slit-lamp biomicroscopy, fundoscopy, and intraocular pressure (IOP) measurement. Fundus photography and fluorescein angiography (FA) were done at day zero and months three, five, eight, 12, and 24. Optical coherence tomography (OCT) was done at selected study sites at day zero and months one, two, three, five, eight, 12, and 24. The primary efficacy endpoint was mean change from baseline to 12 months in VA score. The following key secondary VA endpoints were also assessed at 12 months: proportion of subjects losing ≤15 letters (≈3 lines) from baseline; proportion gaining ≥15 letters from baseline; proportion with a Snellen equivalent of 20/200 or worse (legal blindness = 20/200 or worse in both eyes); mean change from baseline in the near activities, distance activities, and vision-specific dependency NEI VFQ-25 subscales; and mean change from baseline in total area of CNV and total area of leakage from CNV (based on central reading center assessment). Prespecified exploratory endpoints included the proportion of subjects who had lost ≤30 letters (≈6 lines) from baseline VA at 12 months, the mean change from baseline at three months, and mean change from three months to 12 months.

Key safety assessments were the incidence and severity of ocular and nonocular adverse events, changes in vital

TABLE 1. Ranibizumab for Neovascular Age-Related Macular Degeneration: Subject Demographics and Baseline Study Eye Characteristics

Characteristic	Sham (n = 63)	Ranibizumab 0.3 mg (n = 60)	Ranibizumab 0.5 mg (n = 61)
Gender—no. (%)			
Male	20 (31.7)	26 (43.3)	28 (45.9)
Female	43 (68.3)	34 (56.7)	33 (54.1)
Race—no. (%)			
White	59 (93.7)	57 (95.0)	56 (91.8)
Other	4 (6.3)	3 (5.0)	5 (8.2)
Age—years			
Mean (SD)	77.8 (7.1)	78.7 (6.3)	78.8 (7.9)
Range	59–92	60–93	54–94
Age group—no. (%)			
50–64 years	4 (6.3)	1 (1.7)	4 (6.6)
65–74 years	12 (19.0)	12 (20.0)	12 (19.7)
75–84 years	36 (57.1)	37 (61.7)	31 (50.8)
≥85 years	11 (17.5)	10 (16.7)	14 (23.0)
Prior therapy for AMD—no. (%)			
Any	35 (55.6)	35 (58.3)	33 (54.1)
Laser photocoagulation	3 (4.8)	5 (8.3)	7 (11.5)
Medication*	1 (1.6)	1 (1.7)	3 (3.3)
Supplements	34 (54.0)	33 (55.0)	28 (45.9)
Years since first diagnosis of neovascular AMD†			
Mean (SD)	0.3 (0.5)	0.7 (1.6)	0.7 (1.2)
Range	0.0–3.0	0.0–9.1	0.0–5.0
Visual acuity (letters with approximate Snellen equivalent)‡			
Mean (SD)	55.1 (13.9)	55.8 (12.2)	53.7 (15.5)
≤54, 20/80—no. (%)	25 (39.7)	29 (48.3)	27 (44.3)
≥55, 20/80—no. (%)	38 (60.3)	31 (51.7)	34 (55.7)
Visual acuity (approximate Snellen equivalent)‡—no. (%)			
20/200 or worse	10 (15.9)	3 (5.0)	10 (16.4)
Better than 20/200 but worse than 20/40	42 (66.7)	49 (81.7)	36 (59.0)
20/40 or better	11 (17.5)	8 (13.3)	15 (24.6)
CNV lesion subtype—no. (%)			
Occult with no classic	20 (31.7)	29 (48.3)	30 (49.2)
Minimally classic	29 (46.0)	22 (36.7)	18 (29.5)
Predominantly classic	14 (22.2)	8 (13.3)	13 (21.3)
Cannot classify	0	1 (1.7)	0
Total area of lesion§			
Mean (SD) (DA)	4.24 (3.25)	4.38 (3.30)	4.01 (2.64)
Range (DA)	0.10–17.00	0.09–20.30	0.03–10.00
≤4 DA—no. (%)	33 (52.4)	32 (54.2)	31 (50.8)
>4 DA—no. (%)	30 (47.6)	27 (45.8)	30 (49.2)
Total area of CNV (DA)§			
Mean (SD)	3.56 (3.25)	3.80 (3.43)	3.29 (2.27)
Range	0.02–17.00	0.00–20.30	0.03–9.65
Leakage from CNV, plus RPE staining (DA)§			
Mean (SD)	4.25 (3.55)	4.49 (3.58)	3.99 (2.61)
Range	0.20–19.00	0.00–22.50	0.50–9.70

AMD = age-related macular degeneration; CNV = choroidal neovascularization; DA = disk areas; RPE = retinal pigment epithelium; SD = standard deviation.

*Triamcinolone acetonide in the sham and 0.3 mg ranibizumab groups; alteplase and a multiple vitamin / mineral formulation in the 0.5 mg ranibizumab group.

†For this parameter, the numbers of subjects are as follows: sham, n = 62; 0.3 mg ranibizumab, n = 59; 0.5 mg ranibizumab, n = 61.

‡Measured using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at a starting distance of 4 meters.

§For this parameter, the numbers of subjects are as follows: sham, n = 63; 0.3 mg ranibizumab, n = 59; 0.5 mg ranibizumab, n = 61.

signs, and the incidence of positive serum antibodies to ranibizumab. Slit-lamp examination and indirect ophthalmoscopy were performed before each study injection. Grading scales for flare/cells and vitreous hemorrhage density (see Supplemental Tables B1 to B3 for grading criteria) were used to grade intraocular inflammation or vitreous hemorrhage, assessed by slit-lamp examination. IOP was measured using applanation tonometry before and 60 ± 10 minutes after each study treatment.

Safety analyses, performed using descriptive statistics and including all treated subjects, were based on the treatment actually received. Efficacy analyses used the intent-to-treat approach and included all subjects as randomized. Missing values were imputed using the last-observation-carried-forward method. All pairwise comparisons between the ranibizumab groups and the sham group used a statistical model including only two treatment groups (active vs control) at a time. For the primary efficacy endpoint, a Hochberg-Bonferroni adjustment[5] was made for multiple treatment comparisons of each ranibizumab dose group with the sham group. For secondary efficacy endpoints, a Type I error management plan was used to adjust for multiplicity of treatment comparisons and secondary endpoints. Unless otherwise noted, efficacy analyses were stratified by CNV classification at baseline (minimally classic vs occult with no classic vs predominantly classic CNV), as determined by the central reading center, and by baseline VA (≤54 vs ≥55 letters). For binary endpoints, stratified Cochran χ^2 tests were used for between-groups comparisons of proportions of subjects meeting the endpoint. Analysis of variance or analysis of covariance models were used to analyze continuous endpoints.

The study sample size was based on the primary efficacy endpoint. Calculations were based on a 1:1:1 randomization ratio (0.3 mg vs 0.5 mg ranibizumab vs sham), the Student *t* test for comparing mean changes from baseline to 12 months in VA (for each ranibizumab group vs sham), and the Hochberg–Bonferroni multiple comparison procedure at an overall α level of .05. The power of the Hochberg–Bonferroni multiple comparison procedure was evaluated using Monte Carlo simulations. The target sample size of 180 subjects provided 90% power in the intent-to-treat analysis to detect a nine-letter difference between one or both ranibizumab dose groups and the sham group in mean change in VA at month 12, according to the Hochberg–Bonferroni criterion (assumptions based on results of the TAP[6] and VIP[7] trials and anticipated proportions of each CNV type).

Prior PDT in the study eye was an exclusion criterion, but subjects with predominantly classic CNV at study entry or whose CNV was confirmed by the central reading center to have converted during the study from minimally classic or occult with no classic to predominantly classic CNV could receive verteporfin PDT treatment in the study eye given according to the Visudyne prescribing information[8] (i.e., the physician should reevaluate the patient every three months and if CNV leakage is detected on FA, therapy should be repeated) and at the discretion of the investigator per standard of care. Treatment of minimally classic or occult with no classic CNV with PDT is not approved by the U.S. FDA, but was permitted in this study if the investigator deemed PDT to be indicated and the lesion met all of the following criteria: ≥ 20-letter loss from baseline VA recorded at all study visits over a three-month period that included at least two study visits, total CNV lesion area ≤4 DA, and active CNV as defined in the inclusion criteria (Supplemental Table A). Subjects receiving PDT in the study eye could continue study treatment, but PDT could not be given less than 28 days before or less than 21 days after a study injection. Also, PDT in the nonstudy eye could not be given less than five days before or less than 21 days after a study injection. No independent check was done to determine if investigators followed the instructions regarding PDT administration that were provided in the study protocol, nor was the clinical judgment of the investigator regarding suitability of the subject for PDT questioned or independently verified.

Treatment of either eye with other anti-VEGF drugs was prohibited. When pegaptanib sodium (Macugen) was approved by the U.S. FDA in January 2005, subjects were allowed to opt for treatment with this agent but were to be discontinued from their randomized study treatment and followed for the remainder of the study period.

RESULTS

BETWEEN SEPTEMBER 7, 2004 AND MARCH 16, 2005, 184 SUBjects were enrolled at 43 investigative sites in the U.S. and were randomly assigned to study treatment: 60 to 0.3 mg ranibizumab, 61 to 0.5 mg ranibizumab, and 63 to sham injection. Subject disposition is summarized in Supplemental Table C (available at AJO.com). Treatment compliance was good in the ranibizumab groups, with 85% or more of subjects receiving each scheduled injection. In the sham group, 27% of subjects permanently discontinued treatment before month 12, most often because the subject's condition mandated another therapeutic intervention. A month-12 VA score was obtained from 97% of each ranibizumab group and 86% of the sham group.

The treatment groups were well balanced overall for demographic and baseline ocular characteristics (Table 1). Each group was predominantly White and nearly two-thirds female, with a mean age of ≈78 years. The baseline mean VA score was 53 to 56 letters (approximate Snellen equivalent, 20/63 to 20/80) across groups. The first diagnosis of neovascular AMD was within the prior year in 87% of subjects. Overall, 80% of subjects had either occult with no classic or minimally classic CNV lesions, but occult with no classic CNV was more common in the ranibizumab groups than in the sham group (nearly half vs

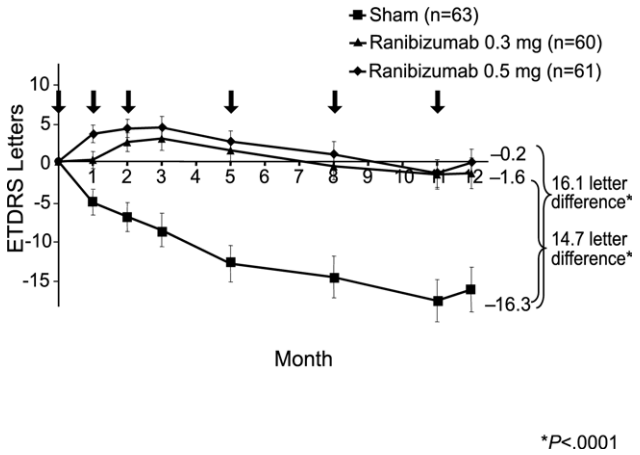

FIGURE 1. Ranibizumab for neovascular age-related macular degeneration (AMD). Mean change from baseline visual acuity, measured as letters read on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, at monthly intervals. At month 12, the 0.3 mg ranibizumab group and the 0.5 mg ranibizumab group differed from the sham group by 14.7 and 16.1 letters, respectively ($P < .0001$). The arrows indicate that ranibizumab or sham injections occurred at day zero, month one, month two, month five, month eight, and month 11.

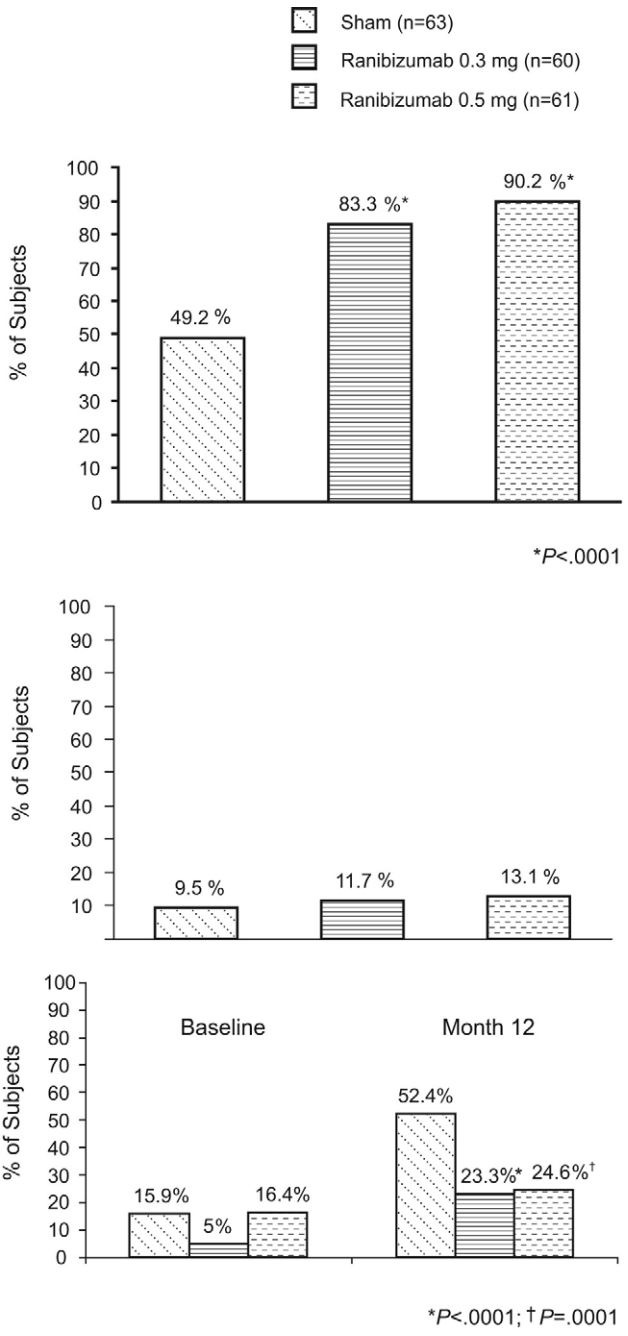

FIGURE 2. Ranibizumab for neovascular AMD. Percentages of the three treatment groups who (Top) at 12 months had lost fewer than 15 letters from baseline visual acuity score, (Middle) at 12 months had gained 15 or more letters from baseline visual acuity score, and (Bottom) had a Snellen equivalent visual acuity of 20/200 or worse at baseline (left) and at month 12 (right). P values are vs the sham treatment group.

less than one-third of study eye lesions, respectively). Nearly half of each group had lesion sizes ≥4 DA. The mean total areas of the AMD lesion, the CNV component, and leakage from CNV plus retinal pigment epithelium (RPE) staining were similar among the groups.

Of the 184 randomized subjects, 19 (10.3%) received one or more treatments with PDT in the study eye during the first treatment year: 17 subjects in the sham-injection group (27.0%), one subject in the 0.3 mg group (1.7%), and one subject in the 0.5 mg group (1.6%). Of the 14 subjects (22.2%) in the sham group who had predominantly classic CNV at study entry, four received at least one PDT treatment in the first year (total = five PDT administrations). None of the 21 subjects (17.4%) in the ranibizumab groups with predominantly classic CNV at study entry received PDT.

Figure 1 shows the mean change from baseline VA by study month for the first treatment year. At 12 months (primary endpoint), sham-treated subjects had lost a mean of 16.3 letters, whereas ranibizumab-treated subjects had lost a mean of 1.6 letters (0.3 mg dose; $P = .0001$ vs sham) or 0.2 letters (0.5 mg dose; $P < .0001$ vs sham). Thus, the difference from the sham group after one year of treatment was 14.7 letters in the 0.3 mg ranibizumab group and 16.1 letters in the 0.5 mg ranibizumab group. Moreover, each of the ranibizumab groups was statistically significantly different from the sham group at month one, following a single injection of ranibizumab ($P = .02$ for 0.3 mg dose, $P < .0001$ for 0.5 mg dose), and at each monthly assessment (all $P < .02$). After the initial three monthly doses, both ranibizumab groups showed a more than 10-letter benefit in mean VA compared with the sham group.

Results for key vision-related secondary endpoints at 12 months are summarized in Figure 2. Significantly greater proportions of the ranibizumab groups than the sham group

TABLE 2. Ranibizumab for Neovascular Age-Related Macular Degeneration: Mean Change from Baseline in the Total Area of Choroidal Neovascularization and the Total Area of Leakage from Choroidal Neovascularization at Month 12

Change from Baseline at Month 12	Sham Injection (n = 63)	Ranibizumab 0.3 mg (n = 59*)	Ranibizumab 0.5 mg (n = 61)
Change in total area of CNV (DA)			
Mean (SD)	2.08 (2.66)	0.18 (2.13)	0.43 (1.86)
95% CI for mean	(1.41 to 2.75)	(−0.37 to 0.74)	(−0.04 to 0.91)
P value (vs Sham)†		.0001	.0002
Change in total area of leakage from CNV + intense RPE staining (DA)			
Mean (SD)	1.40 (3.77)	−1.41 (2.69)	−1.29 (2.48)
95% CI for mean	(0.45 to 2.35)	(−2.12 to −0.71)	(−1.93 to −0.66)
P value (vs Sham)		<.0001	<.0001

CI = confidence interval; CNV = choroidal neovascularization; DA = disk areas; RPE = retinal pigment epithelium; SD = standard deviation.

Note: The last-observation-carried-forward method was used to impute missing data. Strata were defined using two factors: baseline CNV classification (minimally classic vs occult with no classic vs predominantly classic) and baseline visual acuity score (≤54 vs ≥55 letters).

*One subject randomized to the 0.3 mg ranibizumab group withdrew before receiving any study treatment.

†*P* values are based on pairwise analysis of covariance (ANCOVA) models adjusted for the two stratification factors and baseline value of the endpoint.

had lost fewer than 15 letters from baseline VA: 83.3% and 90.2% of the 0.3 mg and 0.5 mg groups, respectively, compared with 49.2% of the sham group ($P < .0001$ for each dose level vs sham). However, the three treatment groups did not differ significantly in the proportions gaining at least 15 letters: 9.5% in the sham group, 11.7% in the 0.3 mg ranibizumab group, and 13.1% in the 0.5 ranibizumab group. Significantly smaller proportions of the ranibizumab groups than the sham group had VA of 20/200 or worse Snellen equivalent at month 12: 23.3% and 24.6% of the 0.3 mg and 0.5 mg groups, respectively, compared with 52.4% of the sham group ($P = .0002$ and $P < .001$, respectively vs sham). However, the proportion with VA this poor at baseline was smaller in the 0.3 mg dose group (5%) than in the 0.5 mg ranibizumab group (16.4%) and sham group (16.4%), which may partially account for the smaller proportion in this dose group at month 12. There was no statistically significant difference between either ranibizumab dose group and the sham control for any of the three NEI VFQ-25 subscales that were prespecified as secondary endpoints. However, post hoc analysis indicated that significantly more subjects in the ranibizumab groups reported clinically meaningful (≥10-point increases) in the near activities subscale scores compared with sham (32% for 0.3 mg ranibizumab group, 31% for 0.5 mg ranibizumab group and 14% for sham group, $P < .05$ vs sham for both ranibizumab groups).

Prespecified subgroup analyses of the month 12 VA results were performed for several baseline characteristics: age (less than 75 and 75 or over), gender, and, for the study eye, VA score (≤54 letters vs ≥55 letters), total lesion size (≤4 vs >4), occult CNV present at baseline (yes vs no), and CNV angiographic type at baseline. In these subgroup analyses the treatment effect of ranibizumab at both doses

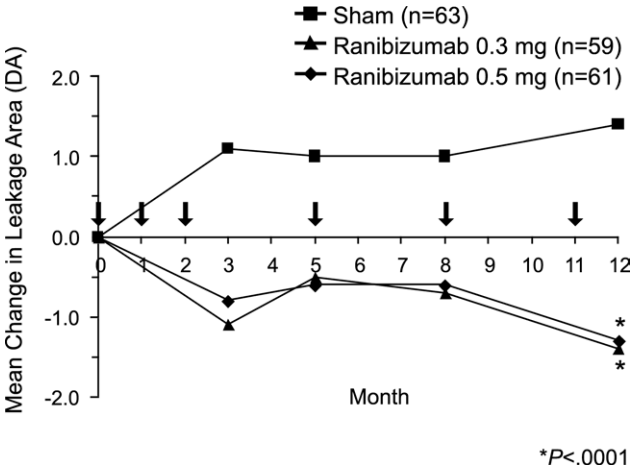

FIGURE 3. Ranibizumab for neovascular AMD. Mean change over time in the area of leakage from choroidal neovascularization (CNV) plus intense progressive retinal pigment epithelium staining. At month 12, each of the ranibizumab-treated groups showed significantly less leakage than the sham-treated group ($P < .0001$). The arrows indicate that ranibizumab or sham injections occurred at day zero, month one, month two, month five, month eight, and month 11.

compared with sham injection was consistent with the overall results. For the subgroups of age, gender, baseline VA greater than or equal to 55 letters, baseline lesion size less than or equal to 4 DA, occult CNV present at baseline, and occult with no classic CNV, both ranibizumab dose groups were significantly different from the sham injection group ($P < .05$). For the subgroups of occult CNV absent at baseline and predominantly classic CNV, the 0.3 mg dose group was significantly different from the sham injection group ($P < .05$). For the baseline

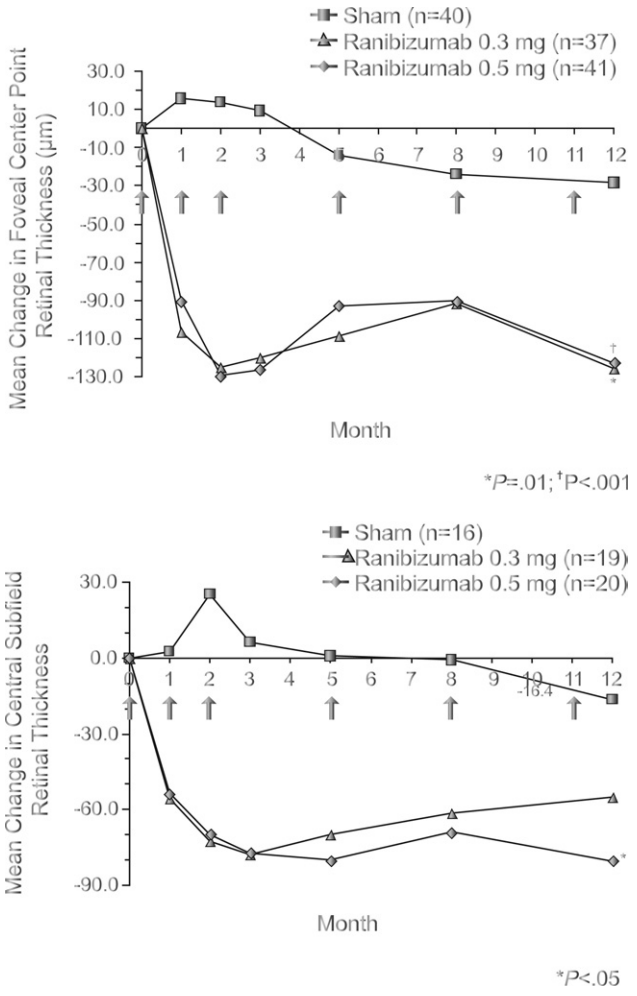

FIGURE 4. Ranibizumab for neovascular AMD. Mean change over time in (Top) foveal center point retinal thickness ($P = .01$ for 0.3 mg ranibizumab and $P < .001$ for 0.5 ranibizumab, vs sham at 12 months) and (Bottom) central subfield retinal thickness ($P < .05$ for 0.5 ranibizumab, vs sham at 12 months). The number of subjects contributing data for central subfield retinal thickness is less than that for foveal center point retinal thickness because calculation of the former requires nine data points on the optical coherence tomography (OCT) scan whereas calculation of the latter requires only six. Therefore, there was a greater likelihood of missing data points (and consequently an inability to calculate thickness) for central subfield retinal thickness than for foveal center point retinal thickness. The arrows indicate that ranibizumab or sham injections occurred at day zero, month one, month two, month five, month eight, and month 11.

lesion size less than 4 DA subgroup, the 0.5 mg ranibizumab group was significantly different from the sham injection group ($P < .05$). The other subgroup comparisons did not achieve statistical significance.

The results for key secondary endpoints related to lesion morphologic characteristics at 12 months are summarized in Table 2. Ranibizumab arrested CNV growth, on average, as indicated by the difference between the ranibizumab and sham groups for change from baseline in total area of CNV (both ranibizumab doses $P < .001$ vs sham). Ranibizumab also reduced the total area of leakage from CNV plus intense progressive RPE staining on average, whereas the sham group exhibited an increase trend (both ranibizumab doses $P < .0001$ vs sham); this pattern was evident at each of the four postbaseline assessments, and was most pronounced at month 12 (Figure 3).

Comparisons between month three and month 12 for the VA endpoints were considered indicative of the efficacy of the quarterly dosing schedule as a maintenance therapy, and therefore several prespecified exploratory analyses were conducted. On average, there was 4.5-letter decline in VA between month three and month 12 for both ranibizumab dose groups. Because neither of the 95% confidence intervals for these values contained zero ([−8.6 to −0.3] and [−7.2 to −1.7] for the 0.3 mg and 0.5 mg groups, respectively), these declines were considered statistically significant. Over the same timeline, VA in the sham group declined by a mean of 7.6 letters. The differences between the ranibizumab dose groups and the sham group in mean change in VA from month three to month 12 were not statistically significant.

Data for comparisons of OCT-assessed anatomical outcomes over time were available from 40, 37, and 41 subjects from the sham, 0.3, and 0.5 mg groups, respectively (Figure 4). On average, both ranibizumab groups showed decreases in retinal thickness over the 12-month period. In ranibizumab-treated subjects, a statistically significant within-group reduction from baseline was seen as early as month one for both foveal center point retinal thickness ($P < .001$, each dose group) and central subfield retinal thickness ($P < .007$, each dose group). At month 12, compared with the sham group, ranibizumab-treated subjects showed significantly greater mean decreases from baseline in foveal center point thickness ($P = 0.01$ for 0.3 mg and $P = .0006$ for 0.5 mg) and, in the 0.5 mg group, central subfield retinal thickness ($P = .04$ for 0.5 mg). There was a maximal decrease in foveal center point thickness at months two and three for both ranibizumab groups, compared with a continued increase in thickness in the sham group during the same period. During the ensuing quarterly dosing interval, at assessments made three months after the previous dose (months five and eight), foveal center point thickness was on average greater than that at months two and three, and also greater than that at month 12, which followed a ranibizumab dose at month 11.

Fluorescein angiographic data for comparisons of change over time were available from 63, 59, and 61 subjects from the sham, 0.3, and 0.5 mg groups, respectively. The leakage from CNV plus RPE staining increased by a mean of approximately 1.4 DA at 12 months in sham-treated subjects while decreasing by a mean of 1.4 DA and 1.3 DA for the 0.3 mg group and the 0.5 mg group at 12 months. During the quarterly dosing interval (months three to 12),

TABLE 3. Ranibizumab for Neovascular Age-Related Macular Degeneration: Summary of Safety During First 12 Months

	Sham Injection (n = 63)	Ranibizumab 0.3 mg (n = 59*)	Ranibizumab 0.5 mg (n = 61)
Key serious ocular adverse events†—no. (%)			
Endophthalmitis, uveitis, retinal detachment, or lens damage	0	0	0
Ocular hemorrhage‡	2 (3.2)	2 (3.4)	0
Macular edema	2 (3.2)	1 (1.7)	0
Most severe ocular inflammation, regardless of cause (slit-lamp examination)†#—no. (%)			
None	59 (95.2)	55 (93.2)	59 (96.7)
Trace	2 (3.2)	1 (1.7)	1 (1.6)
1+	0	2 (3.4)	0
2+	1 (1.6)	1 (1.7)	1 (1.6)
3+ or 4+	0	0	0
Key nonocular adverse events—no. (%)			
Nonocular hemorrhage	3 (4.8)	2 (3.4)	4 (6.6)§
Hypertension	5 (8.1)	4 (6.8)	6 (9.8)
Arterial thromboemobolic events			
Myocardial infarction	0	0	0
Cerebrovascular accident	0	0	0
Ischemic cardiomyopathy	1 (1.6)	0	0
Death	0	0	0

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.

*One subject randomized to the 0.3 mg ranibizumab group withdrew before receiving any study treatment.

†Ocular adverse events in study eye.

‡The two events in the Sham group and 1 of the events in the 0.3 mg ranibizumab group were reported as "retinal hemorrhage." One event in the 0.3 mg ranibizumab group was reported as "eye hemorrhage."

§Includes one event (catheter-site hemorrhage) categorized as serious.

#For slit-lamp examination, the n = 62 for the Sham group.

leakage from CNV plus RPE staining, on average, was greater at months five and eight than that at month three and also greater than that at month 12, which followed the dose at month 11.

Key safety results through month 12 are summarized in Table 3. There was no overall imbalance among the three treatment groups in the proportions of subjects experiencing these key ocular or nonocular adverse events. No cases of endophthalmitis, serious uveitis, rhegmatogenous, or other retinal detachment, retinal tear, vitreous hemorrhage, or lens damage (traumatic cataract) were reported. Serious ocular hemorrhage of any type occurred in two subjects in the sham group (1.6%; both retinal hemorrhages) and two subjects in the 0.3 ranibizumab group (3.4%; one retinal hemorrhage and one reported as "eye hemorrhage"). Serious macular edema was reported in two subjects in the sham group (1.6%) and one subject in the 0.3 mg ranibizumab group (1.7%). Few subjects in any group exhibited intraocular inflammation upon slit-lamp examination, and no cases of 3+ or 4+ inflammation were reported. Cataract event rates were similar across treatment groups, reported in 6.5% of the sham, 5.1% of the 0.3 mg ranibizumab, and 6.6% of the 0.5 mg ranibizumab groups.

As in previous ranibizumab trials, and consistent with intravitreal injection of a small volume of fluid, changes in IOP occurred transiently after injection and were generally mild. Within one hour after injection, IOP was elevated from the preinjection value. On average, postdose IOP was elevated from the predose value by approximately 1.9 mm Hg to 2.3 mm Hg in the ranibizumab groups, compared with approximately 1.4 mm Hg in the sham-injection group. Most of the IOP elevations following the injection were less than 10 mm Hg.

Any postbaseline occurrence of IOP ≥30 mm Hg (pre- or postinjection) was reported in one subject (1.7%) in the 0.3 mg group, five subjects (8.2%) in the 0.5 mg group, and in one subject (1.7%) in the sham group; in only one subject (in the 0.5 mg group; 1.6%) was this elevation reported as a preinjection occurrence.

Assessment of serious or nonserious nonocular adverse events revealed no overall imbalance among groups. No deaths occurred during the first year of treatment. Nonocular adverse events known to be associated with systemic VEGF inhibition were of particular interest, and key events are summarized in Table 3. Hypertension in subjects who were not hypertensive at baseline was reported as an adverse event in 8.1% of sham-treated subjects, 6.8% of

subjects at the 0.3 mg ranibizumab dose, and 8.2% of subjects at the 0.5 mg dose. Routinely measured systolic and diastolic blood pressures were very similar among groups at baseline and at 12 months. No adverse event of proteinuria was reported during the first year in any treatment group. The rates of nonocular hemorrhage were 2.4% and 6.6% for the 0.3 mg and 0.5 mg ranibizumab groups, respectively, compared with 4.8% in the sham group. Only one serious nonocular hemorrhage (hemorrhage at the site of an intravenous catheter in a subject in the 0.5 mg ranibizumab group) was reported, and there were no GI perforations. No arterial thromboembolic events classified using Antiplatelet Trialists' Collaboration (APTC) criteria (i.e., nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, or death due to vascular or unknown cause)[9] were reported in any treatment group. The only serious or nonserious arterial thromboembolic event during the first year was ischemic cardiomyopathy in a sham-treated subject.

Immunoreactivity to ranibizumab was assessed at screening and at month 12 or early termination. During screening, one subject randomized to sham treatment tested positive, possibly due attributable to preexisting anti-Fab antibodies. No ranibizumab subjects tested positive before study treatment, but two subjects in the 0.5 mg ranibizumab group tested positive at month 12. Neither of these two subjects who received ranibizumab experienced any severe or serious adverse event during the study.

DISCUSSION

RESULTS OF THE PIER STUDY INDICATE THAT RANIBIZUMAB administered on a schedule of monthly dosing for three months followed by quarterly dosing provides significant visual acuity benefit to patients with all angiographic subtypes of CNV (i.e., minimally or predominantly classic or occult with no classic component), with a low incidence of serious ocular and nonocular adverse events and an acceptable rate of nonserious adverse events. Both of the ranibizumab dose groups (0.3 mg and 0.5 mg) maintained baseline VA on average at 12 months, and exhibited a clinically meaningful (at least three-line) benefit relative to the sham-injected control group.

Approximately 90% of ranibizumab-treated subjects lost fewer than 15 letters in VA, compared with approximately 50% of sham control subjects. In addition, at 12 months maintenance of visual acuity was accompanied, on average, by a significant reduction in vascular leakage (a more than 2.8-DA mean reduction in leakage), reduced foveal retinal thickness, and inhibition of CNV lesion growth in the ranibizumab groups.

Although quarterly ranibizumab therapy during months three to 12 maintained baseline VA, this regimen was associated on average with a 4.5-letter decline in the maximal VA benefit achieved with monthly induction therapy during months one to three. This loss was accompanied, on average, with an increase in vascular leakage on fluorescein angiography and increases in mean retinal thickness once the quarterly dosing regimen began. This overall increase in mean retinal thickness and increase in leakage suggests that at least some of the subjects needed ranibizumab injections more frequently to control the neovascular leakage. Further subgroup analysis, particularly of individual OCT responses, may support this initial impression. Unfortunately, there are no data available at months four, six, seven, nine, and 10 to allow assessment of duration of action of ranibizumab in individual subjects and the temporal association with retinal thickness. It is possible that the return of retinal edema in at least some subjects contributed to the decline in VA, on average, between months three and 12, in contrast to the patients in the two pivotal ranibizumab trials.[1,2] Also, in the present study there was no benefit demonstrated in the percentage improving by at least 15 letters, whereas in the two pivotal trials a significant improvement was observed. Finally, there were no statistically significant differences between the ranibizumab groups and the sham group in the NEI VFQ-25 subscales, although this may have been attributable to the smaller sample size than in the pivotal studies. Considered together, we conclude that although this regimen provided clinically meaningful and statistically significant benefit to patients, the outcomes were not as strong as those observed with monthly dosing of ranibizumab, suggesting that some patients may require dosing on a more frequent schedule such as that used in the MARINA and ANCHOR studies.[1,2] It is possible that OCT-guided administration of ranibizumab retreatment, as was used with favorable results in a recently reported small, uncontrolled study,[10] may allow greater individualization of ranibizumab dosing intervals, and merits further study.

The overall safety profile of ranibizumab in the PIER study was consistent with that seen during the first year of the MARINA and ANCHOR studies, and indicates that repeated intravitreal injection of ranibizumab is generally well tolerated. Rates of specific ocular and nonocular adverse events that have a hypothesized or documented relationship to ranibizumab, based on either the route of administration (e.g., endophthalmitis) or mechanism of action (e.g., ocular and nonocular hemorrhages; arteriothromboembolic events), were very low or absent in the present study, and intraocular inflammation was infrequent and never above a grade of 2+.

In conclusion, ranibizumab administered monthly for three months and then quarterly provided VA benefit to patients with neovascular AMD and was well tolerated. However, observations from the MARINA and ANCHOR trials suggest that the PIER regimen of dosing every three months after three monthly doses provides less benefit in VA on average than continued monthly dosing. Monthly dosing may be necessary in some patients to achieve maximal treatment benefit from ranibizumab.

THIS STUDY WAS SUPPORTED BY GENENTECH, INC, SOUTH SAN FRANCISCO, CALIFORNIA, AND NOVARTIS PHARMA AG, Basel, Switzerland. Dr Regillo received consulting fees, lecture fees, and grant support from Genentech, Novartis, and OSI/Eyetech. Dr Brown received consulting fees from Genentech, Eyetech/Pfizer, Novartis, and Alcon; lecture fees from Genentech and Eyetech/Pfizer; grant support from Genentech, Alcon, Allergan, Acuity, and Eyetech/Pfizer; and holds Pfizer stock. Dr Abraham received consulting fees from Genentech, QLT/Novartis, Alcon, and Eyetech. Dr Yue is a Genentech employee and Drs Ianchuley, Schneider, and Shams are Genentech employees and stockholders. Involved in conception and design (D.B., P.A., H.Y., T.I., S.S.); analysis and interpretation (C.R., D.B., H.Y., T.I., S.S., N.S.); writing the article (C.R., D.B., P.A., H.Y., T.I., S.S., N.S.); critical revision of the article (C.R., D.B., P.A., H.Y., T.I., S.S., N.S.), final approval of the article (C.R., D.B., P.A., H.Y., T.I., S.S., N.S.); data collection (P.A., H.Y., T.I., N.S.); statistical expertise (H.Y.); literature search (T.I.); and administrative, technical, or logistic support (H.Y.). The Institutional Review Board for each study site approved the study protocol. All subjects provided written informed consent for their participation. All sites were compliant with the U.S. Health Insurance Portability and Accountability Act of 1996. This study is registered at ClinicalTrials.gov (ID No. NCT00090623). The PIER Study Group list is available at AJO.com.

We thank Peter K. Kaiser, MD, Cole Eye Institute, Cleveland, Ohio and William F. Mieler, MD, Department of Ophthalmology, University of Chicago, Chicago, Illinois for assistance in data interpretation and writing of the article, and Darcy Fay, BS, Cynthia Porter, BSN, MBA, and Manpreet Sodhi, BS, Genentech, Inc, Clinical Operations, South San Francisco, California for execution of the study protocol. Genentech provided administrative oversight during conduct of the study, analyzed the data, and provided writing assistance in preparation of the article.

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THE PIER STUDY GROUP

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Biosketch

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SUPPLEMENTAL TABLE A. Eligibility Criteria for PIER Study

Inclusion Criteria
• Age 50 years or older.
• Active primary or recurrent subfoveal lesions with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) in the study eye. "Active" was defined as meeting any of the following criteria: 1) exhibiting a ≥10% increase in lesion size, as determined by comparing a fluorescein angiogram performed within one month preceding day zero, inclusive, with a fluorescein angiogram performed within six months preceding day zero, inclusive; or 2) resulting in a visual acuity loss of >1 Snellen line (or equivalent) and occurring at any time within the prior six months; or 3) subretinal hemorrhage associated with CNV within one month preceding day zero; or 4) ≥50% of the CNV lesion area was composed of classic CNV.
• Lesions with or without a classic CNV component are permissible.
• The total area of CNV (including both classic and occult components) encompassed within the lesion must be 50% or more of the total lesion area.
• The total lesion area must be 12 disk areas or less in size.
• Best-corrected visual acuity, using Early Treatment of Diabetic Retinopathy Study (ETDRS) charts, of 20/40 to 20/320 (Snellen equivalent) in the study eye.
Exclusion Criteria
• Prior treatment with verteporfin photodynamic therapy, external-beam radiation therapy, or transpupillary thermotherapy in the study eye.
• Treatment with verteporfin photodynamic therapy in the nonstudy eye less than seven days preceding day zero.
• Previous participation in a clinical trial (for either eye) involving antiangiogenic drugs (pegaptanib, ranibizumab, anecortave acetate, protein kinase C inhibitors, etc.)
• Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation) in the study eye.
• Previous subfoveal focal laser photocoagulation in the study eye.
• Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within one month preceding day zero.
• History of vitrectomy surgery in the study eye.
• History of submacular surgery or other surgical intervention for AMD in the study eye.
• Previous participation in any studies of investigational drugs within one month preceding day zero (excluding vitamins and minerals).
• Concurrent use of a systemic anti-VEGF agent, including treatment with intravitreal or intravenous bevacizumab.
• Subretinal hemorrhage in the study eye that involves the center of the fovea, if the size of the hemorrhage is either 50% or more of the total lesion area or one or more disk areas in size.
• Fibrosis or atrophy involving the center of the fovea in the study eye.
• CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia.
• Retinal pigment epithelial tear involving the macula in the study eye.
• Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either (a) require medical or surgical intervention during the 24-month study period to prevent or treat visual loss that might result from that condition, or (b) if allowed to progress untreated, could likely contribute to loss of at least two Snellen equivalent lines of best-corrected visual acuity over the 24-month study period.
• Active intraocular inflammation (grade trace or above) in the study eye.
• Current vitreous hemorrhage in the study eye.
• History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4) in the study eye.
• History of idiopathic or autoimmune-associated uveitis in either eye.
• Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
• Aphakia or absence of the posterior capsule in the study eye. Previous violation of the posterior capsule in the study eye was also a reason for exclusion unless it resulted from yttrium aluminum garnet (YAG) posterior capsulotomy in association with prior posterior chamber intraocular lens implantation.
• Spherical equivalent of the refractive error in the study eye demonstrating more than −8 diopters of myopia. For patients who underwent prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye could no exceed −8 diopters of myopia.
• Intraocular surgery (including cataract surgery) in the study eye within two months preceding day zero.
• Uncontrolled glaucoma in the study eye (defined as intraocular pressure of 30 mm Hg or more despite treatment with antiglaucoma medications.
• History of glaucoma filtering surgery in the study eye.
• History of corneal transplant in the study eye.
• Premenopausal women not using adequate contraception.
• History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications.
• Current treatment for active systemic infection.
• History of allergy to fluorescein that is not amenable to treatment.
• Inability to obtain fundus photographs or fluorescein angiogram of sufficient quality to be analyzed and graded by the central reading center.
• Inability to comply with study or follow-up procedures.

SUPPLEMENTAL TABLE B-1. Criteria for Serious (Sight-Threatening) Ocular Adverse Events*

- Adverse event causes a decrease in visual acuity of ≥30 letters (compared with the last assessment of visual acuity prior to the most recent treatment) for more than one hour.
- Adverse event causes a decrease in visual acuity to the level of light perception or worse lasting more than one hour postinjection/sham procedure.
- Adverse event requires surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- Adverse event is associated with severe intraocular inflammation (i.e., 4 + anterior chamber cell/flare or 4 + vitritis).
- In the opinion of the investigator, adverse event may require medical intervention to prevent permanent loss of sight.

*An adverse event meeting any one of these five criteria was considered serious.

SUPPLEMENTAL TABLE B-2. Grading Scales for Flare/Cells*

Flare	
0	No protein is visible in the anterior chamber when viewed by an experienced observer using slit-lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
Trace	Trace amount of protein detectable in the anterior chamber. This protein is visible only with careful scrutiny by an experienced observer using slit-lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
1+	Mild amount of protein detectable in the anterior chamber. The presence of protein in the anterior chamber is immediately apparent to an experienced observer using slit-lamp biomicroscopy and high magnification, but such protein is detected only with careful observation with the naked eye and a small, bright, focal slit-beam of white light.
2– 3+	Moderate amount of protein detectable in the anterior chamber. These grades are similar to 1+ but the opacity would be readily visible to the naked eye of an observer using any source of a focused beam of white light. This is a continuum of moderate opacification, with 2+ being less apparent than 3+.
4+	A large (severe) amount of protein is detectable in the anterior chamber. Similar to 3+, but the density of the protein approaches that of the lens. Additionally, frank fibrin deposition is frequently seen in acute circumstances. It needs to be noted that because fibrin may persist for a period of time after partial or complete restoration of the blood–aqueous barrier, it is possible to have resorbing fibrin present with lower numeric assignations for flare (e.g., 1+ flare with fibrin).
Cells	
0	No cells are seen in any optical section when a large slit-lamp beam is swept across the anterior chamber.
Trace	Rare (1–3) cells are observed when the slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, not every optical section contains circulating cells.
1+	3–10 cells/optical section are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
2+	10–25 cells are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
3+	25–50 cells are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Keratic precipitates or cellular deposits on the anterior lens capsule may be present.
4+	More than 50 cells are seen when the slit-beam of light sweeps across the anterior chamber. When the instrument is held stationary, every optical section contains cells, or hypopyon is noted. As for fibrin deposition, hypopyon may persist for some period of time after the active exudation of cells into the anterior chamber has diminished or ceased entirely, making it possible to have 1+ circulating cells in the anterior chamber with a resolving hypopyon.

*Modified from Hogan MH, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47:155.

SUPPLEMENTAL TABLE B-3. Grading Scale for Vitreous Cells*†

Cells in Retroilluminated Field	Description	Grade
0–1	Clear	0
2–20	Few opacities	Trace
21–50	Scattered opacities	1
51–100	Moderate opacities	2
101–250	Many opacities	3
>251	Dense opacities	4

*Using a Hruby lens.

†Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis: fundamentals and clinical practice. 2nd rev. ed. New York, New York: Mosby, 1996:64.

SUPPLEMENTAL TABLE C. Subject Disposition

Status/Reason for Discontinuation	Sham (n = 63)	Ranibizumab 0.3 mg (n = 60)	Ranibizumab 0.5 mg (n = 61)
Received study drug	62 (98.4%)	59 (98.3%)	61 (100.0%)
Completed month 12*	54 (85.7%)	59 (98.3%)	58 (95.1%)
Discontinued from study on or prior to month 12	8 (12.7%)	1 (1.7%)	2 (3.3%)
Subject's decision	5 (7.9%)	0	2 (3.3%)
Subject noncompliance	1 (1.6%)	1 (1.7%)	0
Subject's condition mandated other therapeutic intervention	2 (3.2%)	0	0
Discontinued treatment prior to month 12†	17 (27.0%)	4 (6.7%)	4 (6.6%)
Adverse event	2 (3.2%)	0	0
Subject's decision	5 (7.9%)	2 (3.3%)	2 (3.3%)
Physician's decision	1 (1.6%)	0	1 (1.6%)
Subject's condition mandated other therapeutic intervention	9 (14.3%)	2 (3.3%)	1 (1.6%)
Analysis population			
Randomized subjects (intent-to-treat efficacy analysis)	63 (100%)	60 (100.0%)	61 (100%)
Randomized subjects in the OCT subset	42 (66.7%)	39 (65.0%)	42 (68.9%)
Safety evaluable subjects	62 (98.4%)	59 (98.3%)	61 (100%)

OCT = optical coherence tomography.

*Defined as having a visual acuity score in the study eye at month 12. Data from subjects who missed the month 12 visit but stayed in the study for the second year were not counted as completed. Hence, the number of subjects who completed and the number who discontinued do not necessarily add to the total number of subjects recruited.

†Some subjects remained in the study after treatment discontinuation.