

# 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.)

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**R**ANIBIZUMAB (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<sup>1</sup> and the ANCHOR Study in patients with predominantly classic CNV<sup>2</sup>—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.<sup>3,4</sup>

## 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 ( $\leq 28$  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  $\geq 50$  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

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  $\geq 50\%$  of the total AMD lesion area; total AMD lesion size  $\leq 12$  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:  $\geq 10\%$  increase in lesion size based on a fluorescein angiogram obtained  $\leq$  one month before day zero, inclusive; vs one obtained  $\leq$  six months before day zero, inclusive; or  $>$  one Snellen line (or equivalent) VA loss within the prior six months; or CNV-associated subretinal hemorrhage  $\leq$  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  $\leq$  one month before day zero); permanent structural damage to the central fovea; or subretinal hemorrhage involving the fovea if  $\geq 1$  DA or  $\geq 50\%$  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  $\leq$  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 ( $\leq 54$  letters [approximately worse than 20/80] vs  $\geq 55$  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.<sup>1,2</sup> 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<sup>1,2</sup>) 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,<sup>1,2</sup> 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, funduscopy, 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  $\leq 15$  letters ( $\approx 3$  lines) from baseline; proportion gaining  $\geq 15$  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  $\leq 30$  letters ( $\approx 6$  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<br>(n = 63) | Ranibizumab 0.3 mg<br>(n = 60) | Ranibizumab 0.5 mg<br>(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 <sup>†</sup>              |                  |                                |                                |
| 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) <sup>‡</sup> |                  |                                |                                |
| 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) <sup>‡</sup> —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 <sup>§</sup>  |                  |                                |                                |
| 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) <sup>§</sup>                                      |                  |                                |                                |
| 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) <sup>§</sup>                    |                  |                                |                                |
| 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.

<sup>†</sup>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.

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

<sup>§</sup>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  $60 \pm 10$  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<sup>5</sup> 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 ( $\leq 54$  vs  $\geq 55$  letters). For binary endpoints, stratified Cochran  $\chi^2$  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  $\alpha$  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<sup>6</sup> and VIP<sup>7</sup> 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<sup>8</sup> (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:  $\geq 20$ -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  $\leq 4$  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  $\approx 78$  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

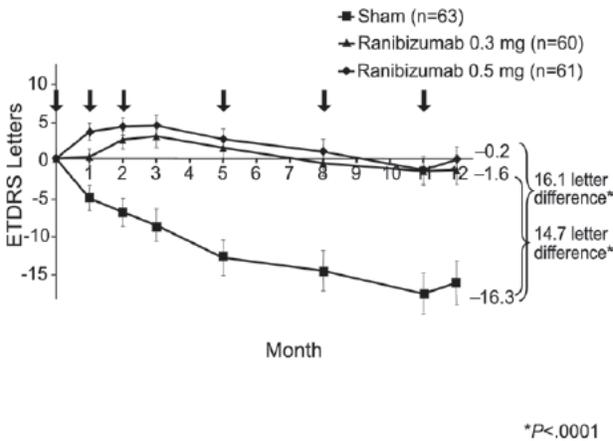


FIGURE 1. Ranibizumab for neovascular age-related macular degeneration (AMD). Mean change from baseline visual acuity, measured as letters read on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, at monthly intervals. At month 12, the 0.3 mg ranibizumab group and the 0.5 mg ranibizumab 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.

less than one-third of study eye lesions, respectively). Nearly half of each group had lesion sizes  $\geq 4$  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

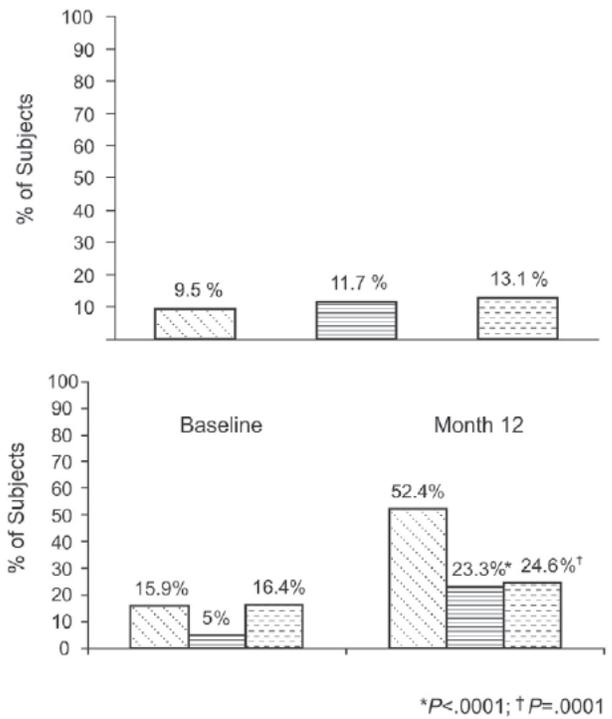
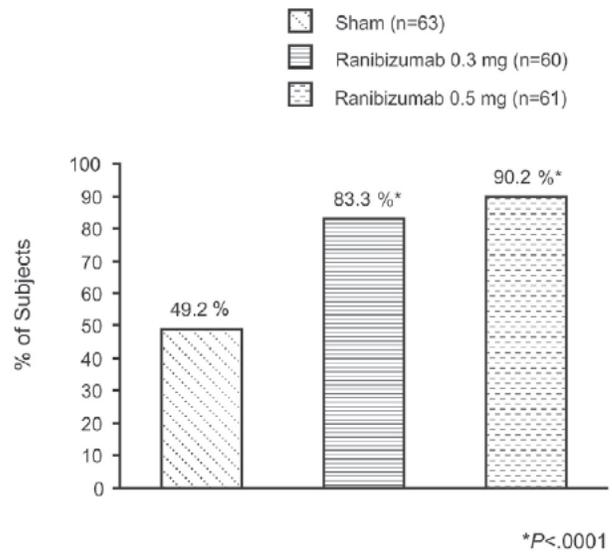


FIGURE 2. Ranibizumab for neovascular AMD. Percentages of the three treatment groups who (Top) at 12 months had lost fewer than 15 letters from baseline visual acuity score, (Middle) at 12 months had gained 15 or more letters from baseline visual acuity score, and (Bottom) had a Snellen equivalent visual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

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

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