Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 2

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• PURPOSE: To evaluate efficacy and safety of quarterly (and then monthly) ranibizumab during the 2-year Phase IIIb, multicenter, randomized, double-masked, sham injection–controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal CNV with or without classic CNV secondary to AMD (PIER) study.
• DESIGN: Phase IIIb, multicenter, randomized, double-masked, sham injection–controlled trial in patients with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).
• METHODS: Patients were randomized 1:1:1 to sham injection (n = 63) or 0.3 mg (n = 60) or 0.5 mg (n = 61) intravitreal ranibizumab monthly for 3 months and then quarterly. During study year 2, eligible sham-group patients crossed over to 0.5 mg ranibizumab quarterly. Later in year 2, all eligible randomized patients rolled over to 0.5 mg ranibizumab monthly. Key efficacy and safety outcomes of the 2-year trial are reported.
• RESULTS: At month 24, visual acuity (VA) had decreased an average of 21.4, 2.2, and 2.3 letters from baseline in the sham, 0.3 mg, and 0.5 mg groups ($P < .0001$ for each ranibizumab group vs sham). VA of sham patients who crossed over (and subsequently rolled over) to ranibizumab decreased across time, with an average loss of 3.5 letters 10 months after crossover. VA of 0.3 mg and 0.5 mg group patients who rolled over to monthly ranibizumab increased for an average gain of 2.2 and 4.1 letters, respectively, 4 months after rollover. The ocular safety profile of ranibizumab was favorable and consistent with previous reports.
• CONCLUSIONS: Ranibizumab provided significant VA benefit in patients with AMD-related CNV compared with sham injection. Ranibizumab appeared to provide additional VA benefit to treated patients who rolled over to monthly dosing, but not to patients who began receiving ranibizumab after >14 months of sham injections. (Am J Ophthalmol 2010;150:315–324. © 2010 by Elsevier Inc. All rights reserved.)

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NEOVASCULAR AGE-RELATED MACULAR DEGENERation (AMD) is characterized by new vessel growth and leakage in the choroidal vascular network beneath the macula, with extension and leakage into the subretinal space. Although the pathologic events that precede choroidal neovascularization (CNV) are not clearly understood, disrupting the activity of vascular endothelial growth factor A (VEGF-A), a diffusible cytokine that promotes angiogenesis and vascular permeability, effectively treats CNV secondary to AMD.

Ranibizumab (Lucentis; Genentech, South San Francisco, California, USA) is an intravitreally administered recombinant, humanized, monoclonal antibody antigen-binding fragment that neutralizes all known active forms of VEGF-A. In 2 Phase III pivotal studies—the MARINA[1] study in patients with minimally classic or occult with no classic CNV and the ANCHOR[2,3] study in patients with predominantly classic CNV—monthly intravitreal injections of 0.3 mg or 0.5 mg ranibizumab not only prevented vision loss but also improved visual acuity (VA) compared with sham injections or photodynamic therapy (PDT) with verteporfin.

Subsequently, a Phase IIIb, multicenter, randomized, double-masked, sham injection–controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal CNV with or without classic CNV secondary to AMD (PIER) evaluated adverse events and VA benefit of quarterly dosing in patients with neovascular AMD. The PIER dosing schedule—monthly for 3 months and then quarterly—was selected based on Phase I and II studies, which indicated that the VA benefits of 0.3 mg and 0.5 mg ranibizumab administered intravitreally monthly for 3 months may last up to 90 days.[4]

While ranibizumab administered on the PIER dosing schedule provided significant VA benefit compared to sham injections in patients with neovascular AMD, quarterly dosing with ranibizumab did not provide the VA benefit demonstrated by monthly dosing in the MARINA and ANCHOR studies.[5] In fact, during study year 2, after careful review of available clinical data, including the 12-month data from MARINA and ANCHOR, the PIER protocol was amended to provide all PIER patients the opportunity to receive ranibizumab.

Here, we present VA and safety outcomes over 2 years in the PIER study, showing that the VA benefit of quarterly

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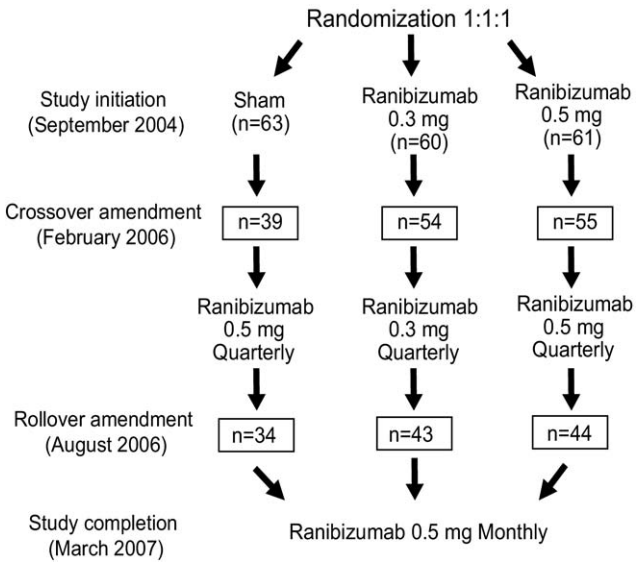

FIGURE 1. Ranibizumab for neovascular age-related macular degeneration trial: PIER randomization, crossover, and rollover scheme. The PIER study was initiated in September 2004 and completed in March 2007. Patients were randomized 1:1:1 to sham injection, 0.3 mg intravitreal ranibizumab, or 0.5 mg intravitreal ranibizumab. A February 2006 protocol amendment allowed sham patients to cross over to receive 0.5 mg intravitreal ranibizumab after completing the month-12 visit. An August 2006 amendment allowed all patients to roll over to receive 0.5 mg intravitreal ranibizumab monthly.

ranibizumab treatment was maintained well into the second year of the study. Furthermore, switching to monthly ranibizumab treatment late in year 2 appeared to provide increased VA benefit to patients who had previously been treated quarterly, while ranibizumab treatment appeared not to provide a VA benefit to control patients who began receiving ranibizumab after a year without treatment.

METHODS

PIER METHODOLOGY, INCLUDING STUDY DESIGN, ELIGIBILity, masking, treatment, assessments, and analyses, has been published in detail.[5] All patients provided informed written consent prior to participation. Briefly, eligible patients were at least 50 years of age with a diagnosis of primary or recurrent subfoveal CNV (predominantly classic, minimally classic, or occult with no classic) secondary to AMD and baseline best-corrected VA of 20/40 to 20/320 Snellen equivalent, measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a distance of 4 meters.

Classic and/or occult CNV comprised ≥50% of the total AMD lesion area, and the total lesion was ≤12 disc areas (DA). If a CNV lesion was minimally classic or occult with no classic component, the treated eye was required to meet protocol-defined criteria for disease progression (ie, a 10% increase in lesion size based on fluorescein angiography [FA] obtained 1 month prior to study initiation [ie, day 0] compared to FA obtained 6 months prior to day 0; ≥5 ETDRS letter [1 Snellen line] VA loss within 6 months prior to day 0; or CNV-associated subretinal hemorrhage 1 month prior to day 0). Patients who had fibrosis or atrophy involving the center of the fovea or subretinal hemorrhage ≥1 DA or ≥50% of total lesion area with foveal involvement were excluded. One eye per patient was studied.

Eligible patients were randomized 1:1:1 to sham injections, 0.3 mg intravitreal ranibizumab, or 0.5 mg intravitreal ranibizumab (Figure 1). Patients were masked to treatment. Randomization was stratified by best-corrected VA (≤54 ETDRS letters, ~20/80 or worse Snellen equivalent vs ≥55 ETDRS letters, ~20/80 or better Snellen equivalent) at day 0, CNV type (minimally classic vs occult with no classic vs predominantly classic), and study center. The protocol mandated that patients receive sham injections or intravitreal injections of their assigned ranibizumab dose once a month for 3 months (day 0, month 1, month 2) and every 3 months thereafter (months 5, 8, 11, 14, 17, 20, and 23), for the duration of the 2-year study. Fluorescein angiography and fundus photography were performed at months 3, 5, 8, 12, and 24 and were evaluated by a central reading center (Fundus Photograph Reading Center, University of Wisconsin, Madison, Wisconsin, USA). Patients underwent complete ocular examination, including VA assessment at each study visit (ie, the first 3 months and then quarterly). The Vision Functioning Questionnaire-25 (VFQ-25) was administered at baseline and at months 3, 8, 12, and 24, prior to patients completing any other study-related procedures. In addition to injection visits, clinic visits were scheduled at months 3, 12, and 24. Subsequent protocol amendments (crossover and rollover amendments described below) increased subject assessments from quarterly to monthly. The monthly assessments were identical to the previous quarterly assessments.

The incidence and severity of ocular and nonocular adverse events (AEs) and changes in vital signs were assessed at all study visits. In accordance with the criteria established by the worldwide Antiplatelet Trialists' Collaboration,[6] arterial thromboembolic events (ATEs), such as vascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, and nonfatal hemorrhagic stroke, were documented.

After careful review of 12-month data from the pivotal MARINA[1] and ANCHOR[2] trials, the study sponsor believed it to be in the best interest of sham group patients to be treated with ranibizumab. Thus, the protocol was amended on February 27, 2006 to provide sham-injection patients the opportunity to cross over to receive 0.5 mg ranibizumab quarterly after completing the month-12 visit (ie, the assessment time point for the primary analysis). Subsequently, after careful review of the 12-month PIER data, the protocol was amended again, on August 21, 2006, to provide all patients remaining in the study the opportunity to roll over to receive 0.5 mg ranibizumab monthly for the remainder of the 2-year study. No patients were

TABLE 1. Ranibizumab for Neovascular Age-Related Macular Degeneration Trial: Patient Demographics and Baseline Ocular Characteristics[a]

	Sham (n = 63)	0.3 mg (n = 60)	0.5 mg (n = 61)
Gender			
Male	20 (31.7)	26 (43.3)	28 (45.9)
Female	43 (68.3)	34 (56.7)	33 (54.1)
Race/ethnicity			
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, years			
50–<65	4 (6.3)	1 (1.7)	4 (6.6)
65–<75	12 (19.0)	12 (20.0)	12 (19.7)
75–<85	36 (57.1)	37 (61.7)	31 (50.8)
≥85	11 (17.5)	10 (16.7)	14 (23.0)
Prior therapy for AMD			
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)	2 (3.3)
Supplements	34 (54.0)	33 (55.0)	28 (45.9)
Years since first diagnosis of neovascular AMD			
n	62	59	61
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 (ETDRS letters)			
n	63	60	61
Mean (SD)	55.1 (13.9)	55.8 (12.2)	53.7 (15.5)
Range	25–76	18–79	13–79
≤ 54, 20/80	25 (39.7)	29 (48.3)	27 (44.3)
≥ 55, 20/80	38 (60.3)	31 (51.7)	34 (55.7)
Visual acuity (approximate Snellen equivalent)			
Median	20/63	20/63	20/80
20/200 or worse	10 (15.9)	3 (5.0)	10 (16.4)
Better than 20/200 but worse than 20/40	42 (66.6)	49 (81.6)	36 (58.9)
20/40 or better	11 (17.5)	8 (13.3)	15 (24.6)
CNV lesion subtype			
n	63	60	61
Predominantly classic	13 (20.6)	8 (13.3)	12 (19.7)
Minimally classic	30 (47.6)	22 (36.7)	19 (31.1)
Occult without classic	20 (31.7)	29 (48.3)	30 (49.2)
Not classified	0	1 (1.7)	0
Total area of lesion (DA)			
n	63	59	61
Mean (SD)	4.34 (3.23)	4.36 (3.27)	4.04 (2.61)
Range	0.1–17.0	0.1–20.3	0.05–10.0
≤4 DA	32 (50.8)	32 (54.2)	31 (50.8)
>4 DA	31(49.2)	27 (45.8)	30 (49.2)
Total area of CNV (DA)			
n	63	59	61
Mean (SD)	3.61 (3.23)	3.77 (3.40)	3.29 (2.27)
Range	0.02–17.0	0.0–20.3	0.03–9.6
Leakage from CNV plus RPE staining (DA)			
Mean (SD)	4.25 (3.55)	4.47 (3.56)	3.99 (2.61)
Range	0.20–19.0	0.0–22.5	0.50–9.70

AMD = age-related macular degeneration; CNV = choroidal neovascularization; DA=disc area; ETDRS = Early Treatment of Diabetic Retinopathy Study; RPE = retinal pigment epithelium; SD = standard deviation.

[a]Values are n (%) except where otherwise noted.

unmasked to their original treatment assignment as a result of the crossover and rollover amendments.

The primary endpoint of PIER was mean change in best-corrected VA at month 12. Key visual outcomes at month 24 were mean change from baseline VA, proportion of patients who lost <15 VA letters from baseline, proportion of patients who gained ≥15 VA letters from baseline, proportion of patients with Snellen equivalent VA of 20/200 or worse, mean change from baseline VFQ-25 near and distance activities and vision-specific dependency subscale scores, mean change from baseline total area of CNV, and total area of CNV leakage plus retinal pigment epithelium (RPE) staining. Safety endpoints were incidence and severity of ocular and nonocular AEs, incidence of positive serum antibodies to ranibizumab, and changes in vital signs.

The intent-to-treat approach was used for visual and anatomic analyses and included all patients as randomized. Missing values were imputed using the last-observation-carried-forward method. All pairwise comparisons between the ranibizumab groups and the sham group were based on statistical models with 2 groups (ranibizumab vs sham) at a time. A type I error management plan was used to adjust for multiplicity of treatment comparisons and visual and anatomic endpoints. Unless otherwise noted, analyses were stratified by CNV type at baseline (minimally classic vs occult with no classic vs predominantly classic), 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-group comparisons of the proportion of patients meeting the endpoint. Analysis-of-variance and analysis-of-covariance models were used to analyze continuous endpoints.

The study sample size was based on the primary endpoint (ie, change from baseline best-corrected VA at month 12). The target sample size of 180 subjects (determined by clinical trial simulation) provided 90% power in the intent-to-treat

TABLE 2. Ranibizumab for Neovascular Age-Related Macular Degeneration Trial: Patient Disposition and Discontinuation During 2 Years in the PIER Study[a]

	Sham (n = 63)	Ranibizumab 0.3 mg (n = 60)	Ranibizumab 0.5 mg (n = 61)
Received assigned treatment	62 (98.4)	59 (98.3)	61 (100.0)
Completed study	46 (73.0)	53 (88.3)	54 (88.5)
Discontinued from study	17 (27.0)	7 (11.7)	7 (11.5)
Patient's decision	8 (12.7)	1 (1.7)	4 (6.6)
Patient noncompliance	1 (1.6)	2 (3.3)	1 (1.6)
Patient's condition mandated other therapeutic intervention	3 (4.8)	0	0
Discontinued treatment	27 (42.9)	11 (18.3)	10 (16.4)
Adverse event	6 (9.5)	4 (6.7)	4 (6.6)
Patient's decision	7 (11.1)	4 (6.7)	4 (6.6)
Physician's decision	2 (3.2)	1 (1.7)	1 (1.6)
Patient's condition mandated other therapeutic intervention	12 (19.0)	2 (3.3)	1 (1.6)
Eligible to participate in crossover	40 (63.5)	—	—
Crossed over and received 0.5 mg ranibizumab	39 (61.9)	—	—
Visit at which patient crossed over to quarterly 0.5 mg ranibizumab			—
Month 14	15 (38.5)	—	—
Month 17	17 (43.6)	—	—
Month 20	7 (17.9)	—	—
Mean (SD) duration of crossover treatment, days	188.3 (75.5)		
Eligible to participate in rollover	35 (55.6)	43 (71.7)	44 (72.1)
Participated in rollover amendment	34 (54.0)	43 (71.7)	44 (72.1)
Visit at which patient rolled over to monthly 0.5 mg ranibizumab			
Month 19	3 (8.8)	3 (7.0)	3 (6.8)
Month 20	14 (41.2)	14 (32.6)	16 (36.4)
Month 21	2 (5.9)	6 (14.0)	4 (9.1)
Month 22	3 (8.8)	7 (16.3)	5 (11.4)
Month 23	12 (35.3)	13 (30.2)	16 (36.4)
Mean (SD) number of rollover injections	2.6 (1.5)	2.6 (1.3)	2.5 (1.3)
Randomized patients (intent-to-treat efficacy analysis)	63 (100.0)	60 (100.0)	61 (100.0)

SD = standard deviation.
[a]Values are n (%) except where otherwise noted.

analysis to detect a 9-letter difference between 1 or both ranibizumab dose groups and the sham-injection group in mean change from baseline VA at month 12, according to the Hochberg-Bonferroni criterion (assumptions based on results of the TAP[7,8] and VIP[9] trials and anticipated proportions of each CNV type).[10] Safety analyses were performed using descriptive statistics and included all treated patients. All analyses were performed with SAS software (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

BETWEEN SEPTEMBER 7, 2004 AND MARCH 16, 2005, 184 patients were randomized 1:1:1 to receive sham injection (n = 63), 0.3 mg ranibizumab (n = 60), or 0.5 mg ranibizumab (n = 61) at 43 US investigative sites. Baseline demographic and ocular characteristics were similar across treatment groups (Table 1). Groups were predominantly white and nearly two-thirds female, with a mean age of 78 years. Mean baseline VA was 53 to 56 letters (Snellen equivalent ~20/63 to 20/80) across groups.

The first diagnosis of neovascular AMD was within the previous year for 87% of patients. Overall, 80% of patients 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 injection group (nearly 50% vs <33% of study eye lesions, respectively). Nearly 50% of the study eyes in each group had lesions ≥4 DA. The mean total area of CNV lesion and CNV leakage plus RPE staining at baseline was similar across groups.

Forty-six of 63 (73%), 53 of 60 (88.3%), and 54 of 61 (88.5%) patients randomized to the sham-injection, 0.3 mg, and 0.5 mg groups, respectively, completed the study through

TABLE 3. Ranibizumab for Neovascular Age-Related Macular Degeneration Trial: Mean Change From Study Eye Baseline Visual Acuity at Months 12 and 24 of the PIER Study

		Ranibizumab	
ETDRS Letters	Sham (n = 63)	0.3 mg (n = 60)	0.5 mg (n = 61)
Month 12			
Mean (SD)	−16.3 (22.3)	−1.6 (15.1)	−0.2 (13.1)
95% CI[a]	−21.9 to −10.7	−5.4 to 2.3	−3.5 to 3.2
P value (vs sham)[b]		.0001	<.0001
Month 24			
Mean (SD)	−21.4 (21.8)	−2.2 (15.6)	−2.3 (14.4)
95% CI[a]	−26.8 to −15.9	−6.3 to 1.8	−6.0 to 1.4
P value (vs sham)[b]		<.0001	<.0001

CI = confidence interval; ETDRS= Early Treatment Diabetic Retinopathy Study; SD = standard deviation.

[a]Derived from t distribution.

[b]Based on pairwise analyses of variance adjusted for stratification of baseline choroidal neovascularization classification (minimally classic vs occult without classic vs predominantly classic) and baseline visual acuity (≤54 vs ≥55 letters).

month 24 (Table 2). By month 24, 48 of 184 (26.1%) patients had discontinued treatment (25 of 184 [13.6%] at month 12), usually because the patient's condition mandated other therapeutic intervention.

At the time of the February 2006 crossover amendment, 40 of 63 (63.5%) patients in the sham-injection group who had not discontinued study treatment were eligible to cross over to receive 0.5 mg ranibizumab quarterly, and 39 (61.9%) of those received at least 1 intravitreal injection, beginning at month 14. At the time of the August 2006 rollover amendment 34 of 63 (54.0%), 43 of 60 (71.7%), and 44 of 61 (72.1%) patients in the sham-injection, 0.3 mg, and 0.5 mg groups, respectively, who had not discontinued study treatment or completed the month-24 visit, rolled over to receive 0.5 mg ranibizumab monthly, beginning month 19. Results are presented according to group assignment at randomization and include post-crossover (sham) and post-rollover (sham, 0.3 mg, 0.5 mg) data.

At month 24, VA had decreased from baseline an average of 21.4 letters in the sham group, 2.2 letters in the 0.3 mg group, and 2.3 letters in the 0.5 mg group ($P < .0001$ each ranibizumab dose vs sham), with about a 19-letter difference between sham-group and treated patients. The group differences at month 24 were similar to those at month 12 (Table 3). At month 24, 47 of 60 (78.2%) patients in the 0.3 mg group and 50 of 61 (82.0%) of patients in the 0.5 mg group had lost <15 letters from baseline VA compared with 26 of 63 (41.3%) sham-injection patients ($P < .0001$ each ranibizumab dose vs sham) (Figure 2); and 21 of 63 (33.3%) patients in the sham group had lost ≥30 VA letters from baseline. Such severe vision loss was uncommon (~3.0%) in patients who were originally randomized to ranibizumab treatment groups. Ranibizumab groups did not differ significantly from the sham group in the proportion of patients who gained ≥15 VA letters: 3 of 63 (4.8%) in the sham-injection group, 9 of 60 (15.0%) in the 0.3 mg group, and 5 of 61 (8.2%) in the 0.5 mg group.

A Snellen equivalent VA of 20/200 or worse was more common in the sham-injection group (55.6%) than in the 0.3 mg (25.0%) and 0.5 mg (27.9%) ranibizumab groups ($P < .0001$ for 0.3 mg vs sham; $P = .0013$ for 0.5 mg vs sham). The 0.3 mg and 0.5 mg ranibizumab groups did not differ significantly from the sham group on the near activities, distance activities, and vision-specific dependency VFQ-25 subscales.

Subgroup analyses of the mean change from baseline VA at month 24 were performed for several baseline characteristics, including age (<75 years vs ≥75 years), gender, race (white vs other), VA (<54 vs ≥54), lesion size (≤4 DA vs >4 DA), presence of occult CNV (yes vs no), and prior laser photocoagulation (yes vs no). The treatment effects of the ranibizumab groups compared with the sham-injection group were consistent with the overall results for all subgroups except race and prior photocoagulation, for which the sample sizes were too small to draw conclusions (data not shown).

At month 24 total area of CNV had increased from baseline an average of 1.90 DA in the sham group, 0.29 DA in the 0.3 mg group, and 0.64 DA in the 0.5 mg group ($P = .0015$ 0.3 mg vs sham, $P = .0021$ 0.5 mg vs sham) (Table 4). The total area of CNV leakage plus RPE staining decreased from baseline an average of 0.78, 1.52, and 1.22 DA in the sham-injection, 0.3 mg, and 0.5 mg groups, respectively ($P \geq .20$ for each ranibizumab group vs sham).

- **CROSSOVER:** Thirty-nine of 40 eligible sham-injection group patients crossed over to 0.5 mg quarterly ranibizumab, beginning month 14 (38.5%), 17 (43.6%), or 20 (17.9%) (Table 2), and received a mean of 4.1 ± 1.7 injections from the time of crossover to study discontinuation or completion. On average, VA of sham-injection patients who crossed over (and subsequently rolled over) to ranibizumab treatment during study year 2 continued to decrease until study completion or discontinuation, with an average loss of 3.5 letters 10 months after crossover (Figure 3). Small sample sizes and variations in treatment time and dose prevented formal statistical analyses of the post-crossover data.

- **ROLLOVER:** Thirty-four, 43, and 44 eligible patients in the sham, 0.3 mg, and 0.5 mg groups, respectively, rolled over to receive monthly 0.5 mg ranibizumab, beginning month 19 (Table 2). Patients in the sham, 0.3 mg, and 0.5 mg groups received an average of 2.6, 2.6, and 2.5 intravitreal injections, respectively, from the time of roll-

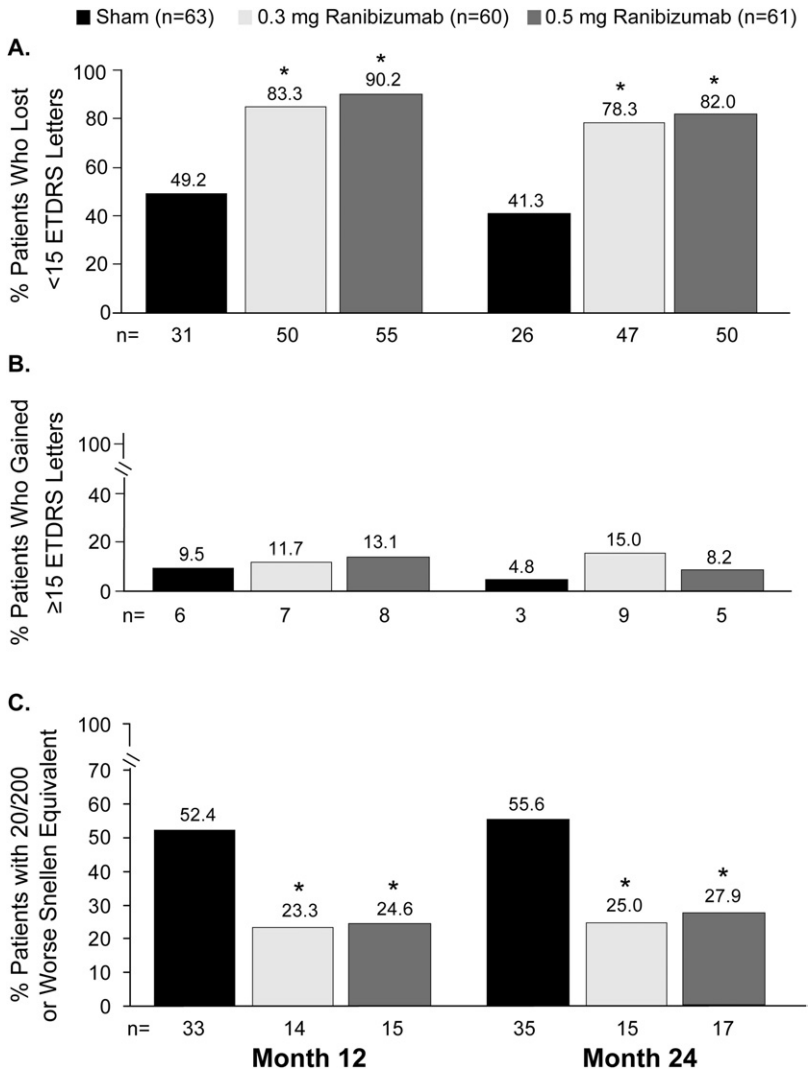

FIGURE 2. Ranibizumab for neovascular age-related macular degeneration trial: visual acuity outcomes at months 12 and 24 of the PIER study. Percentage of patients in each of the 3 treatment groups who (Top) lost <15 ETDRS letters, (Middle) gained ≥15 ETDRS letters, or (Bottom) had 20/200 or worse Snellen equivalent VA at months 12 and 24. Post-crossover and post-rollover data are included. Error bars are ±1 standard error of the mean. Numbers below the bars in each graph are the number of patients for whom visual acuity data were available in the corresponding group. ETDRS = Early Treatment Diabetic Retinopathy Study; *P ≤ .0002 vs sham.

over to study discontinuation or completion. On average, VA of patients in ranibizumab groups who rolled over to monthly treatment with 0.5 mg ranibizumab increased across the first 4 rollover injections, with an average gain of 2.2 and 4.1 letters in the 0.3 mg and 0.5 mg groups 4 months after rollover, respectively (Figure 4). Small sample sizes and group differences (ie, sham-group VA at the time of rollover differed from that of ranibizumab-treated patients) prevented formal statistical comparisons of the post-rollover data.

• **SAFETY:** Key safety results through month 24 are summarized in Table 5. During the 2-year study period, safety was observed for an average of 626.4 (± 197.1), 712.6 (± 43.1), and 689.8 (± 108.0) days for the sham, 0.3 mg, and 0.5 mg groups, respectively. Ocular AEs that occurred at a rate ≥10% in ranibizumab-treated patients compared with pre-crossover sham-injection patients were conjunctival hemorrhage (29% [18/62] of sham-injection patients, 50.8% [30/59] of 0.3 mg patients, 52.5% [32/61] of 0.5 mg patients) and increased intraocular pressure (4.8% [3/62], 23.7% [14/59], and 31.1% [19/61], respectively). No incidents of endophthalmitis were reported. The rate of intraocular inflammation was low, with no notable difference across groups: 2 of 62 (3.2%) in the sham-injection group, 3/59 (5.1%) in the 0.3 mg group, and 3 of 61 (4.9%) in the 0.5 mg group. No serious intraocular inflammation was reported during the study. Five of 62 (8.1%) patients in the pre-crossover sham-injection group, 5 of 59 (8.5%) patients in the 0.3 mg group, and 11 of 61 (18.0%) patients in the 0.5 mg group had cataract, nuclear cataract, or cortical cataract in the study eye.

TABLE 4. Ranibizumab for Neovascular Age-Related Macular Degeneration Trial: Choroidal Neovascularization–Related Changes From Baseline at Months 12 and 24 of the PIER Study

	Sham (n = 63)	Ranibizumab 0.3 mg (n = 59)	Ranibizumab 0.5 mg (n = 61)
Change in total area of CNV (DA)			
Month 12			
Mean (SD)	2.08 (2.66)	0.18 (2.13)	0.43 (1.86)
95% CI[a]	1.41 to 2.75	−0.37 to 0.74	−0.04 to 0.91
P value (vs sham)[b]		.0001	.0002
Month 24			
Mean (SD)	1.90 (2.46)	0.29 (2.73)	0.64 (2.16)
95% CI[a]	1.28 to 2.52	−0.42 to 1.00	0.08 to 1.19
P value (vs sham)[b]		.0015	.0021
Change in total area of CNV leakage + RPE staining (DA)			
Month 12			
Mean (SD)	1.40 (3.77)	−1.41 (2.69)	−1.29 (2.48)
95% CI[a]	0.45 to 2.35	−2.12 to −0.71	−1.93 to −0.66
P value (vs sham)[b]		.0001	.0001
Month 24			
Mean (SD)	−0.78 (4.13)	−1.52 (2.99)	−1.22 (2.74)
95% CI[a]	−1.82 to 0.26	−2.30 to −0.75	−1.92 to −0.52
P value (vs sham)[b]		.273	.199

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

The last-observation-carried-forward method was used to impute missing data. Strata were defined using baseline CNV classification (minimally classic vs occult without classic) and baseline visual acuity score (≤54 vs ≥55 letters).

[a]Derived from t distributions.

[b]Based on pairwise ANCOVA models adjusted for the 2 stratification factors and baseline value of the endpoint.

Nonocular AEs were experienced by 48 of 62 (77.4%) of patients in the pre-crossover sham-injection group, 50 of 59 (84.7%) patients in the 0.3 mg group, and 53 of 61 (86.9) patients in the 0.5 mg group. Nonocular AEs included urinary tract infection, nasopharyngitis, constipation, and upper respiratory tract infection, all of which might be expected in an elderly population.

Nonocular AEs known to be associated with systemic VEGF inhibition were of particular interest. Hypertension AEs occurred in 7 of 62 (11.3%) pre-crossover sham-injection patients, 6 of 59 (10.2%) 0.3 mg patients, and 13 of 61 (21.3%) 0.5 mg patients for 0.5 mg patients (Fisher exact χ^2, 2-sided $P = .13$ for 0.3 mg vs 0.5 mg; $P = .15$ for 0.5 mg vs pre-crossover sham). One of 61 (1.6%) patients in the 0.5 mg group had a serious hypertension AE.

The incidence of nonocular hemorrhage was higher in the 0.3 mg and 0.5 mg groups (4 of 59 [6.8%] and 6 of 61 [9.8%], respectively) compared with the pre- and post-crossover sham-injection group (3 of 62 [4.8%] and 1 of 39 [2.6%], respectively).

The rate of Antiplatelet Trialists' Collaboration ATEs (vascular deaths, nonfatal myocardial infarctions, nonfatal ischemic strokes, and nonfatal hemorrhagic strokes) during the 2-year treatment period was 1.6% (1 of 62 patients) in the pre-crossover sham group, in the post-crossover sham group, 1.7% (1 of 59 patients) in the 0.3 mg group, and 0% in the 0.5 mg group.

DISCUSSION

RANIBIZUMAB, ADMINISTERED MONTHLY FOR 3 MONTHS AND then quarterly, provided a VA benefit to patients with all angiographic subtypes of CNV compared with sham injections. Because ranibizumab-group patients switched from quarterly to monthly ranibizumab treatment beginning at month 19, it was not possible to assess the VA benefits of quarterly dosing for the entire 24-month study. However, the VA differences between sham and ranibizumab group patients that were observed at the primary month-12 analysis were maintained prior to the first rollover treatment, indicating that the VA benefit of quarterly ranibizumab persisted well into the second year of the study.

The finding that VA scores tended to increase after patients in the ranibizumab treatment groups rolled over to receive monthly ranibizumab suggests that, in order to

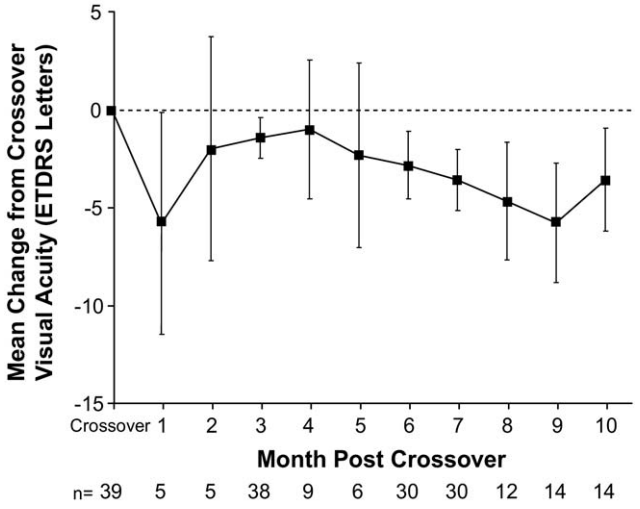

FIGURE 3. Ranibizumab for neovascular age-related macular degeneration trial: mean change in visual acuity for sham-group patients who crossed over to receive quarterly injections of 0.5 mg ranibizumab (and subsequently rolled over to monthly 0.5 mg ranibizumab). Numbers below the x-axis are the number of sham patients for whom visual acuity data were available at the corresponding month post crossover. Error bars are ±1 standard error of the mean. ETDRS = Early Treatment Diabetic Retinopathy Study.

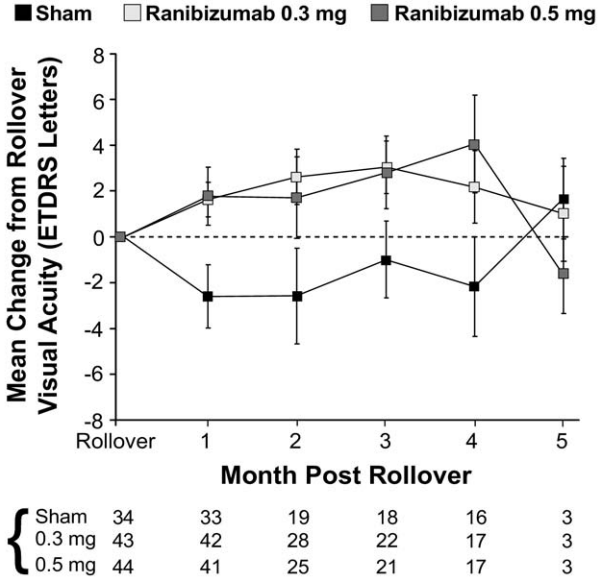

FIGURE 4. Ranibizumab for neovascular age-related macular degeneration trial: mean change in visual acuity for patients who rolled over to receive monthly injections of 0.5 mg ranibizumab. Numbers below the x-axis are the number of patients for whom visual acuity data were available at the corresponding month post rollover. Note the small number of patients in each group who were assessed at month 5 post rollover. Error bars are ±1 standard error of the mean. ETDRS = Early Treatment Diabetic Retinopathy Study.

obtain the greatest benefit from ranibizumab treatment, some patients may require more frequent dosing. This is supported by the finding that the degree of VA benefit obtained with quarterly dosing in the PIER study was not as robust as that obtained with monthly dosing in the ANCHOR and MARINA studies. In those studies, patients who received monthly injections of ranibizumab experienced a gain of 5 to 11 letters from baseline at month 24 compared to a loss of approximately 2 letters with the PIER dosing regimen; and between 25% and 41% of ANCHOR and MARINA patients gained ≥15 letters from baseline at month 24 compared to ≤15% in the PIER study. A current challenge is to determine a dosing regimen that will prove optimal for physicians and patients while realizing the full benefit of ranibizumab (eg, Brown and Regillo, 2007; Fung and associates, 2007).[11,12]

At month 24 (ie, 5 months after patients began rollover to receive 0.5 mg ranibizumab monthly), VA scores tended to increase in the sham group and decrease in the 0.5 mg group, while remaining stable in the 0.3 mg group. The small number of evaluable patients at that time point (ie, n = 3 for each group) prevents interpretation of the observation.

Sham-group patients who began receiving ranibizumab during study year 2 continued to experience a loss of VA relative to baseline. While the extent of any benefit of ranibizumab treatment to sham-group patients was not determinable (since it is not known how sham-injection VA would have changed without crossover/rollover treatment), the implication is that ranibizumab had limited benefit in neovascular AMD patients after ≥12 months without treatment. Given that baseline disease characteristics were similar across all randomized patients, it is likely that sham-group patients experienced disease progression during the first year of the study, while they were not being treated. Although it is unknown whether sham-group VA would have improved with continued ranibizumab treatment or if irreversible damage was incurred during 14 months without treatment, the results emphasize the importance of identifying and treating patients as early as possible to obtain the full benefit of ranibizumab and thwart disease progression and severe vision loss.

The benefits of ranibizumab treatment were reflected in anatomic measures. In general, across the 2-year study, the total CNV lesion area and the total area of CNV leakage plus RPE staining increased by a greater degree in sham-injection patients compared with ranibizumab-treated patients. Notably, although sham-group patients experienced an increase in total area of CNV leakage plus RPE staining relative to baseline at month 12, they had a decrease in CNV leakage plus RPE staining at month 24. The improvement may have been an effect of ranibizumab treatment following crossover, or it may reflect disease progression. For instance, retina damage may have been complete by month 24, resulting in a dry retina (and an absence of leakage). Sufficient data were not available to

TABLE 5. Ranibizumab for Neovascular Age-Related Macular Degeneration Trial: Safety Summary During 2 Years in the PIER Study

Event	Sham		Ranibizumab	
	Before Crossover (n = 62)	After Crossover (n = 39)	0.3 mg (n = 59)	0.5 mg (n = 61)
Key serious ocular adverse events, n (%)				
Endophthalmitis, uveitis, retinal detachment, lens damage	0	0	0	0
Retinal hemorrhage	1 (1.6)	0	1 (1.7)	0
Macular edema	1 (1.6)	0	1 (1.7)	0
Ocular inflammation, regardless of cause (slit-lamp examination)				
None	59 (95.2)	0	55 (93.2)	59 (96.7)
Trace	2 (3.2)	0	1 (1.7)	1 (1.6)
1	0	0	2 (3.4)	0
2	1 (1.6)	0	1 (1.7)	1 (1.6)
≥3	0	0	0	0
Key nonocular adverse events, n (%)				
Nonocular hemorrhage	3 (4.8)	1 (2.6)	4 (6.8)	6 (9.8)
Hypertension	7 (11.3)	0	6 (10.2)	13 (21.3)
Arterial thromboemobolic events	2 (3.2)	2 (5.1)	1 (1.7)	2 (3.3)
Myocardial infarction	1 (1.6)	0	0	0
Cerebrovascular accident	0	1 (2.6)	0	0
Ischemic cardiomyopathy	1 (1.6)	0	0	0
Death	1 (1.6)	1 (2.6)	2 (3.4)	0

evaluate the crossover and rollover effects on anatomic outcomes during study year 2.

The ocular safety profile of ranibizumab was favorable, with no events of endophthalmitis or serious intraocular inflammation. The AEs that occurred more frequently in the ranibizumab groups were those commonly seen with intravitreal injections in general. No new safety issues emerged in the sham-injection group following crossover to ranibizumab treatment. Overall, the groups were similar in the frequency of nonocular adverse events associated with systemic VEGF inhibition, including hypertension, arterial thromboembolic events, nonocular hemorrhage, and proteinuria.

In conclusion, ranibizumab, administered as 3 monthly intravitreal injections of 0.3 mg or 0.5 mg followed by injections every 3 months or more frequently over 24 months, was well tolerated and effectively maintained VA in patients with minimally classic, occult, or predominantly classic neovascular AMD. However, on average, the benefits obtained with quarterly dosing were not as robust as those observed in previous studies with monthly dosing. Furthermore, ranibizumab did not appear to provide a VA benefit after 14 months without treatment. A future goal is to develop treatment regimens that will prove optimal for patients and physicians, while realizing the full benefit of ranibizumab.

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Biosketch

Prema Abraham joined the Black Hills Regional Eye Institute (BHREI), Rapid City, South Dakota, in 1995 and currently serves as Medical Director of the Institute and its retina center. The Institute is affiliated with the University of South Dakota Medical School and is a multi-specialty ophthalmology tertiary care referral center, serving patients from North and South Dakota, Wyoming, Nebraska, and Montana. The 45,000 square feet facility houses refractive surgery and state-of-the-art ambulatory surgery centers. The Institute's retina center provides the latest in diagnostic and therapeutic advances and is a leading research facility for Phase I, II, and III clinical research trials.