Ranibizumab for Diabetic Macular Edema

Results from 2 Phase III Randomized Trials: RISE and RIDE

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Purpose: To evaluate the efficacy and safety of intravitreal ranibizumab in diabetic macular edema (DME) patients.

Design: Two parallel, methodologically identical, phase III, multicenter, double-masked, sham injection–controlled, randomized studies.

Participants: Adults with vision loss from DME (best-corrected visual acuity [BCVA], 20/40–20/320 Snellen equivalent) and central subfield thickness ≥275 μm on time-domain optical coherence tomography (OCT).

Intervention: Monthly intravitreal ranibizumab (0.5 or 0.3 mg) or sham injections. Macular laser was available per-protocol–specified criteria.

Main Outcome Measures: Proportion of patients gaining ≥15 letters in BCVA from baseline at 24 months.

Results: In RISE (NCT00473330), 377 patients were randomized (127 to sham, 125 to 0.3 mg, 125 to 0.5 mg). At 24 months, 18.1% of sham patients gained ≥15 letters versus 44.8% of 0.3-mg ($P<0.0001$; difference vs sham adjusted for randomization stratification factors, 24.3%; 95% confidence interval [CI], 13.8–34.8) and 39.2% of 0.5-mg ranibizumab patients ($P<0.001$; adjusted difference, 20.9%; 95% CI, 10.7–31.1). In RIDE (NCT00473382), 382 patients were randomized (130 to sham, 125 to 0.3 mg, 127 to 0.5 mg). Significantly more ranibizumab-treated patients gained ≥15 letters: 12.3% of sham patients versus 33.6% of 0.3-mg patients ($P<0.0001$; adjusted difference, 20.8%; 95% CI, 11.4–30.2) and 45.7% of 0.5-mg ranibizumab patients ($P<0.0001$; adjusted difference, 33.3%; 95% CI, 23.8–42.8). Significant improvements in macular edema were noted on OCT, and retinopathy was less likely to worsen and more likely to improve in ranibizumab-treated patients. Ranibizumab-treated patients underwent significantly fewer macular laser procedures (mean of 1.8 and 1.6 laser procedures over 24 months in the sham groups vs 0.3–0.8 in ranibizumab groups). Ocular safety was consistent with prior ranibizumab studies; endophthalmitis occurred in 4 ranibizumab patients. The total incidence of deaths from vascular or unknown causes, nonfatal myocardial infarctions, and nonfatal cerebrovascular accidents, which are possible effects from systemic vascular endothelial growth factor inhibition, was 4.9% to 5.5% of sham patients and 2.4% to 8.8% of ranibizumab patients.

Conclusions: Ranibizumab rapidly and sustainably improved vision, reduced the risk of further vision loss, and improved macular edema in patients with DME, with low rates of ocular and nonocular harm.

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Diabetic retinopathy (DR), the most common microvascular complication of diabetes,[1] is the leading cause of new cases of vision loss and blindness among working-aged adults in the United States and most developed countries.[2,3] Diabetic macular edema (DME), swelling of the central retina that causes vision loss, is an advanced complication of DR[4]; the prevalence of DME increases from 0% to 3% in individuals with recent diagnoses of diabetes to 28% to 29% in those with diabetes for ≥20 years.[5] Because the population of people with diabetes is ~285 million worldwide[6] and growing rapidly, vision loss from DR is a significant public health issue, with considerable socioeconomic and quality-of-life impacts.[7]

In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) established macular laser as standard care treatment by demonstrating that patients with clinically significant DME treated with laser experienced a 50% reduction in moderate vision loss over time compared with untreated patients.[8] However, in ETDRS and recent studies, relatively few patients with vision loss experienced significant improvements in best-corrected visual acuity (BCVA) after laser, and improvement

tended to occur slowly.[8–12] A treatment that rapidly and durably improves vision would be an important advance.

Diabetic macular edema results from pathologically increased retinal vascular permeability.[13] Recognition of vascular endothelial growth factor (VEGF) as the primary cytokine mediating this increase[14,15] and observation of increased intraocular VEGF levels in DME[16] led to the hypothesis that VEGF signaling blockade might be beneficial both in restoring normal retinal anatomy and reversing vision loss from macular edema. Ranibizumab is an anti-VEGF antibody fragment, designed for intraocular use, that neutralizes the biologic activity of all known active isoforms of VEGF.[17] Pilot studies demonstrated that intravitreal ranibizumab reduced macular edema and improved visual acuity (VA) in patients with DME.[18] Subsequent studies demonstrated that ranibizumab was superior to laser at 6 months and superior to both intravitreal steroids and laser at 12 months.[9,10,19,20] Herein, we report the results of two 24-month, phase III, randomized studies designed to evaluate long-term treatment with ranibizumab in patients with vision loss from DME.

Methods

Study Design

RISE (registered on ClinicalTrials.gov as NCT00473330) and RIDE (NCT00473382) are parallel phase III multicenter, double-masked, sham injection–controlled, randomized studies conducted at private and university-based retina specialty clinics in the United States and South America (65 principal investigators per study). One objective was to generate confirmatory evidence for regulatory purposes; thus, 2 identically designed studies were carried out. Two ranibizumab doses were chosen for regulatory purposes. Patients were recruited from June 2007 to January 2009, and the 24-month controlled treatment periods ended on November 16, 2010 (RISE), and January 12, 2011 (RIDE). The trials adhered to the tenets of the Declaration of Helsinki, were Health Insurance Portability and Accountability Act–compliant, and protocols were approved by institutional review boards, ethics committees, or as applicable. Patients provided written, informed consent.

Participants

One eye per patient was randomized. Eligible participants were aged ≥18 years with diabetes mellitus (type 1 or 2), decreased vision from DME (study eye BCVA, 20/40–20/320 Snellen equivalent using ETDRS testing), and macular edema (time-domain optical coherence tomography [OCT] central subfield thickness ≥ 275 μm). Key exclusion criteria were prior vitreoretinal surgery, or a recent history (within 3 months of screening) of panretinal or macular laser in the study eye, intraocular corticosteroids, or antiangiogenic drugs. Patients with uncontrolled hypertension, uncontrolled diabetes (glycosylated hemoglobin [HbA1c] > 12%), or recent (within 3 months) cerebrovascular accident (CVA), or myocardial infarction (MI) were excluded.

Randomization, Intervention, and Masking

Eligible patients were randomized[21] to monthly sham injections or intravitreal injections of 0.3 or 0.5 mg of ranibizumab. Beginning at month 3 all patients were evaluated monthly for the need for macular laser according to protocol-specified criteria: Central foveal thickness (CFT) ≥250 μm with a <50-μm change from the prior month, with no prior macular laser in the previous 3 months, and an assessment by the evaluating physician that macular laser

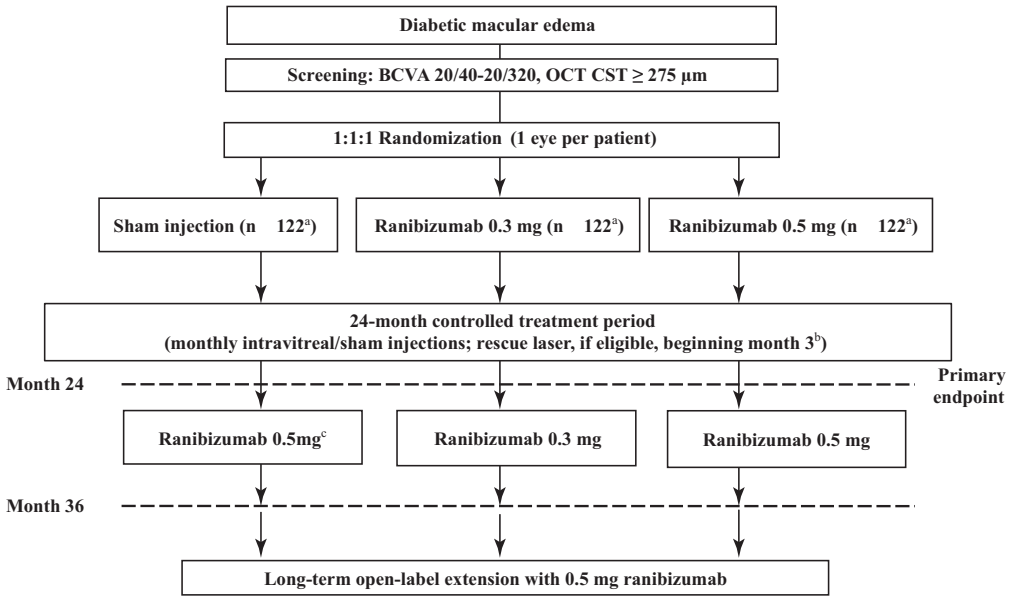

Figure 1. Study design. BCVA = best-corrected visual acuity; CST = central subfield thickness; OCT = optical coherence tomography. [a]Target enrollment, 122 patients per treatment group. [b]Starting at month 3, patients were evaluated monthly for rescue laser based on objective and subjective criteria as described in Methods. [c]After publication of a 12-month trial of ranibizumab, laser, and steroids for diabetic macular edema,[10] and consultation with the data monitoring committee, the studies were amended to allow early crossover (before month 25) to ranibizumab for patients receiving sham with persistent edema and vision loss. One patient in RISE and 3 patients in RIDE crossed over early (before month 25). These patients were analyzed in their original treatment groups per the intent-to-treat principle used for efficacy analyses.

would be beneficial. The goal of laser treatment was to apply photocoagulation in a grid pattern or directly to leaky microaneurysms in areas of retinal thickening and edema, avoiding treatment within the foveal avascular zone. Randomization was stratified by study eye BCVA (≤55 vs >55 ETDRS letters), baseline HbA1c (≤8% vs >8%), prior DME therapy in the study eye (yes vs no), and study site. Dynamic randomization was used to obtain approximately a 1:1:1 ratio among groups (Fig 1). Randomization was done via interactive phone system. The sponsor developed the specifications for the randomization, and a third party programmed and held the randomization algorithm. The studies were unmasked on February 10, 2011 (RISE), and March 22, 2011 (RIDE), when treatment assignments were made available to the study analysis team of the sponsor. Ocular assessments, including the need for macular laser, were made by evaluating ophthalmologists masked to patients' treatment assignments. Study treatments were administered by treating ophthalmologists unmasked to treatment assignments but masked to ranibizumab dose. To improve patient masking, all patients received subconjunctival anesthesia before sham or active injections (performed as previously described).[22] Study site personnel (except treating physicians and assistants), central reading center personnel, and the sponsor and its agents (except drug accountability monitors) were masked to treatment assignment. Treating physicians were masked to the assigned dose of ranibizumab. An independent statistical coordinating center performed the unmasked interim analyses for the data monitoring committee.

Assessments

Evaluations included vital signs, safety assessments, visual function questionnaires, and ocular assessments: BCVA measured with the ETDRS chart (4-m starting distance), contrast sensitivity, intraocular pressure, slit-lamp examination, indirect ophthalmoscopy, OCT, fluorescein angiography (FA), and fundus photography (FP). Study visits were scheduled every 30±7 days. The OCT, FA, and FP images were graded at a central reading center.

Outcomes

The primary efficacy measure was the proportion of patients gaining ≥15 ETDRS letters in BCVA score from baseline at 24 months (corresponding to 3 lines on the eye chart). Secondary outcomes at 24 months were mean change from baseline BCVA score over time, proportion of patients with BCVA Snellen equivalent of ≥20/40, mean change from baseline BCVA score over time in patients with focal edema as assessed on FA, proportion of patients losing <15 letters in BCVA score from baseline, mean change from baseline in OCT CFT over time, proportion of patients with a ≥3-step progression from baseline in ETDRS retinopathy severity on FP, proportion of patients with resolution of leakage on FA, and the mean number of macular laser treatments over time. Certain secondary endpoints were amended after the studies commenced but before unmasking study results, to be more consistent with literature and regulatory guidance received subsequent to initiation of the studies (Appendix 1; available at http://aaojournal.org).

Analysis

Efficacy Analyses. The sample size of 366 patients (122 per treatment group) per study provided 90% experiment-wise power to detect a statistically significant difference in the primary effi-

Table 1. Patient Demographic and Baseline Characteristics

	RISE			RIDE		
		Ranibizumab			*Ranibizumab*	
Characteristic	*Sham (n = 127)*	*0.3 mg (n = 125)*	*0 5 mg (n = 125)*	*Sham (n = 130)*	*0.3 mg (n = 125)*	*0 5 mg (n = 127)*
Mean age (SD), yrs*	61.8 (9.8)	61.7 (8.9)	62.8 (10.0)	63.5 (10.8)	62.7 (11.1)	61.8 (10.1)
Range, yrs	39–85	38–82	21–87	22–91	24–88	29–84
Male, n (%)	74 (58.3)	73 (58.4)	65 (52.0)	66 (50.8)	73 (58.4)	80 (63.0)
Race, n (%)†						
Asian	6 (4.7)	7 (5.6)	7 (5.6)	2 (1.5)	5 (4.0)	5 (3.9)
American Indian or Alaska Native	0	0	0	1 (0.8)	1 (0.8)	2 (1.6)
Black or African American	19 (15.0)	18 (14.4)	14 (11.2)	15 (11.5)	14 (11.2)	13 (10.2)
Native Hawaiian/other/Pacific Islander	1 (0.8)	2 (1.6)	1 (0.8)	0	1 (0.8)	0
White	101 (79.5)	97 (77.6)	97 (77.6)	104 (80.0)	99 (79.2)	105 (82.7)
Not available	0	1 (0.8)	6 (4.8)	8 (6.2)	5 (4.0)	2 (1.6)
Hispanic or Latino ethnicity, n (%)	24 (18.9)	20 (16.0)	25 (20.0)	37 (28.5)	33 (26.4)	31 (24.4)
Mean body mass index (SD)‡	31.4 (7.1)	32.3 (6.8)	32.9 (8.5)	32.3 (8.9)	32.3 (8.6)	31.3 (7.2)
Positive history of smoking, n (%)	60 (48.0)§	64 (51.2)	58 (46.4)	43 (33.6)‖	64 (51.6)‖	57 (45.6)‖
Mean duration of diabetes (SD), yrs*,¶	14.5 (9.9)	15.9 (9.9)	16.3 (8.5)	16.6 (10.6)	16.0 (9.8)	15.3 (10.1)
Mean HbA1c (SD), %**	7.7 (1.5)	7.7 (1.5)	7.7 (1.4)	7.6 (1.4)	7.6 (1.3)	7.6 (1.5)
≤8%, n (%)	80 (65.0)	81 (67.5)	82 (68.3)	84 (67.2)	79 (65.8)	83 (67.5)
>8%, n (%)	43 (35.0)	39 (32.5)	38 (31.7)	41 (32.8)	41 (34.2)	40 (32.5)

HbA1c = glycosylated hemoglobin; SD = standard deviation.
*At randomization.
†Patients who are of >1 race were counted for each category that they indicated.
‡Number of patients: 124, 122, and 124 (RISE) and 128, 125, and 126 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively.
§Number of patients: 125.
‖Number of patients: 128, 124, and 125 in the sham, 0.3-mg, and 0.5-mg groups, respectively.
¶Number of patients: 123, 118, and 118 (RISE) and 122, 119, and 124 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively.
**Number of patients: 123, 120, and 120 (RISE) and 125, 120, and 123 (RIDE) in the sham, 0.3-mg, and 0.5-mg groups, respectively.

Table 2. Study Eye Characteristics at Baseline

Characteristic	RISE			RIDE		
		Ranibizumab			Ranibizumab	
	Sham (n = 127)	0.3 mg (n = 125)	0 5 mg (n = 125)	Sham (n = 130)	0.3 mg (n = 125)	0 5 mg (n = 127)
Mean ETDRS letter score (SD)	57.2 (11.1)	54.7 (12.6)	56.9 (11.6)	57.3 (11.2)	57.5 (11.6)	56.9 (11.8)
Mean approximate Snellen equivalent	20/80+2	20/80	20/80+2	20/80+2	20/80+2	20/80+2
≤20/200, n (%)	10 (7.9)	17 (13.6)	10 (8.0)	10 (7.7)	9 (7.2)	11 (8.7)
>20/200 but <20/40, n (%)	92 (72.4)	91 (72.8)	91 (72.8)	95 (73.1)	92 (73.6)	91 (71.1)
≥20/40, n (%)	25 (19.7)	17 (13.6)	24 (19.2)	25 (19.2)	24 (19.2)	25 (19.7)
Mean CFT (SD), μm	467.3 (152.0)	474.5 (174.8)	463.8 (144.0)	447.4 (154.4)	482.6 (149.3)	463.8 (175.5)
Mean time from first known CSME diagnosis to randomization (SD), yrs*	2.3 (3.0)	2.1 (2.2)	2.1 (2.1)	2.4 (3.2)	1.6 (2.0)	1.9 (2.4)
Active or previously treated PDR present, n (%)†	34 (26.8)	28 (22.4)	32 (25.6)	28 (21.5)	31 (24.8)	34 (26.8)
Previous treatment for CSME, n (%)						
Any	94 (74.0)	94 (75.2)	102 (81.6)	92 (70.8)	86 (68.8)	88 (69.3)
Focal/grid laser	86 (67.7)	86 (68.8)	90 (72.0)	84 (64.6)	72 (57.6)	79 (62.2)
Steroids‡	35 (27.6)	39 (31.2)	50 (40.0)	36 (27.7)	32 (25.6)	37 (29.1)
Other	21 (16.5)	20 (16.0)	21 (16.8)	21 (16.2)	27 (21.6)	25 (19.7)

CFT = central foveal thickness; CSME = clinically significant macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; PDR = proliferative diabetic retinopathy; SD = standard deviation.
*Number of patients: 127, 124, and 123 in the sham, 0.3-mg, and 0.5-mg groups, respectively, in RISE and 126 in the 0.5-mg group in RIDE.
†Active PDR was a study enrollment exclusion criterion.
‡Intraocular or subtenon injection.

cacy measure between 1 or both ranibizumab groups and the control (expecting percentages of 35% for 0.5-mg ranibizumab-treated patients, 25% for 0.3-mg, and 13% for sham patients). The studies were not designed or powered to compare the 2 selected doses of ranibizumab, but rather to compare each ranibizumab dose against the sham comparator (2 doses were used for regulatory purposes). The intent-to-treat principle was used for efficacy analyses, with missing data imputed using the last observation carried forward method. To account for potential differences in baseline characteristics between treatment groups that may affect the outcome measures, efficacy analyses were stratified by the randomization stratification factors baseline BCVA (≤55, >55 letters), baseline HbA1c (≤8%, >8%), and prior therapy for DME (yes or no); reported differences and 95% confidence intervals were also adjusted for these baseline variables. For the primary endpoint and secondary efficacy endpoints based on binary variables, a comparison between each ranibizumab group and the control group was made using the Cochran-Mantel-Haenszel chi-square test stratified (adjusted) by the randomization stratification factors. For secondary efficacy endpoints that were continuous in nature (e.g., mean change from baseline in BCVA score), comparisons were made by fitting either an analysis of variance or analysis of covariance model, adjusting for the randomization stratification factors. For the secondary efficacy endpoint of mean

Table 4. Use of Macular and

Outcomes at Month 24	RISE		
		Ranibizumab	
	Sham (n = 127)	0.3 mg (n = 125)	0.5 mg (n = 125)
Number of macular focal/grid rescue laser treatments, mean (SD)	1.8 (1.8)	0.8 (1.2)	0.8 (1.3)
Difference vs sham (95% CI)†		−1.0 (−1.4 to −0.7)	−1.1 (−1.5 to −0.7)
Test for treatment difference vs sham‡		P<0.0001	P<0.0001
Median	1.0	0	0
Range	0–6	0–7	0–6
Received macular laser treatment, n (%; 95% CI)	94 (74.0; 66.4–81.6)	49 (39.2; 30.6–47.8)	44 (35.2; 26.8–43.6)
Difference vs sham (95% CI)†		−35.0 (−46.4 to −23.7%)	−39.3 (−50.7 to −28.0)
Test for treatment difference vs sham§		P<0.0001	P<0.0001
Proportion of patients who received PRP laser, n (%)‖	14 (11.0)	0	1 (0.8)

CI = confidence interval; PRP = panretinal photocoagulation; SD = standard deviation.
The last-observation-carried-forward method was used to impute missing data. The mean number of macular lasers is reported with no imputation.
*Starting at month 3, patients were evaluated monthly for macular focal/grid laser based on the objective and subjective criteria as described in the
†Difference is adjusted for baseline visual acuity (≤55, >55 Early Treatment Diabetic Retinopathy Study [ETDRS] letters), baseline glycosylated
‡Wilcoxon test stratified by baseline visual acuity (≤55, >55 ETDRS letters), baseline HbA1c (≤8%, >8%), and prior treatment for diabetic macular
§Cochran-Mantel-Haenszel χ^2 (stratified by baseline visual acuity [≤55, >55 ETDRS letters], baseline HbA1c [≤8%, >8%], and prior treatment for
‖Not a prespecified endpoint; no statistical testing performed. Data are reported in context of safety outcomes and laser treatments performed for diabetic

change from baseline in CFT over time up to 24 months, the respective baseline CFT value was included as a continuous variable (covariate) in the analysis of covariance model. The mean number of macular laser treatments during 24 months was compared between each ranibizumab group and sham using a stratified Wilcoxon test. Additional details are in the supplemental material (Appendix 1; available at http://aaojournal.org).

Safety Analyses. Safety was assessed through collection and summary of ocular and nonocular adverse events (AEs), serious AEs (SAEs), ocular assessments, deaths, laboratory results, vital signs, and antibodies to ranibizumab. At each study visit, nondirective questioning was used to elicit AE reports from patients. All AEs and SAEs, whether volunteered by the patient, discovered by study site personnel during questioning, or detected by examination, laboratory testing, or other means, were recorded in the patient record and case report forms. Safety analyses included all patients receiving ≥1 ranibizumab or sham injection. Patients were analyzed according to actual treatment received before optional crossover for patients randomized to the sham group.

All data analyses occurred after all patients completed the month 24 visit or discontinued early. A Data Monitoring Committee (3 ophthalmologists and 1 biostatistician) was established to monitor safety and study conduct by periodically reviewing unmasked data. Each interim safety analysis was allocated a type I error $\alpha = 0.0001$ to account for review of VA data forming the basis of the primary efficacy endpoint.

Results

In total, 759 patients were enrolled and randomized to study treatment (377 in RISE and 382 in RIDE; Fig 2, available at http://aaojournal.org). Randomized groups were generally well-balanced for baseline demographic (Table 1) and study eye characteristics, including history of prior treatment (Table 2); however, in RISE, more patients in the 0.3-mg ranibizumab group had a BCVA <20/200, and more patients in the 0.5-mg ranibizumab group in both studies had previously received intraocular or periocular steroids for DME. The 2-year study period was completed by 83.3% of patients in RISE and by 84.6% in RIDE. The median number of ranibizumab injections was 24 (Table 3, available at http://aaojournal.org). The mean number of macular laser treatments over 24 months was 1.8 and 1.6 in the sham groups and 0.3 to 0.8 in the ranibizumab groups (Table 4). Substantially more sham-treated patients received macular laser under the protocol-specified criteria or underwent panretinal photocoagulation for proliferative DR (PDR; Table 4).

Visual Acuity Outcomes

In both studies, statistically significantly greater numbers of patients randomized to ranibizumab gained ≥15 ETDRS letters from baseline at 24 months. In RISE, 44.8% of patients receiving 0.3 mg ranibizumab and 39.2% of patients receiving 0.5 mg ranibizumab gained ≥15 letters compared with 18.1% of sham-treated patients (Table 5, available at http://aaojournal.org; Fig 3). In RIDE, corresponding proportions were 33.6%, 45.7%, and 12.3%, respectively (Table 5; Fig 3). Ranibizumab treatment led to rapid vision improvements, with statistically significant changes versus sham observed as early as 7 days after the first injection (Fig 4). Mean BCVA in ranibizumab groups continued to improve steadily, with patients experiencing an average benefit over sham (adjusted for baseline variables) of 8.5 to 9.9 ETDRS letters at month 24 (Table 5; Fig 4). Fewer ranibizumab-treated patients experienced significant (≥15 ETDRS letters) vision loss (Tables 5 and 6; Fig 3 and Fig 5 [available at http://aaojournal.org]). More patients in the ranibizumab groups achieved Snellen BCVA of ≥20/40 at month 24 compared with sham ($P<0.0001$ for each ranibizumab group vs sham; Table 5; Fig 3).

The effects of demographic and baseline ocular characteristics on efficacy outcomes were examined in prespecified subgroup analyses. As expected, baseline BCVA impacted efficacy[23]; patients with worse baseline BCVA experienced greater improvements, and patients with better baseline BCVA (and less ability to gain letters) experienced lesser improvements (Table 7, available at http://aaojournal.org). No prespecified subgroup was identified

Panretinal Photocoagulation*

RIDE		
	Ranibizumab	
Sham (n = 130)	*0.3 mg (n = 125)*	*0.5 mg (n = 127)*
1.6 (1.6)	0.7 (1.4)	0.3 (0.7)
	−0.9 (−1.3 to −0.5)	−1.3 (−1.6 to −1.0)
	$P<0.0001$	$P<0.0001$
1.0	0	0
0–7	0–7	0–5
91 (70.0; 62.1–77.9)	45 (36.0; 27.6–44.4)	25 (19.7; 12.8–26.6)
	−32.8 (−44.2 to −21.4)	−49.8 (−60.1 to −39.6)
	$P<0.0001$	$P<0.0001$
16 (12.3)	2 (1.6)	2 (1.6)

methods. Panretinal laser was available as clinically indicated.
hemoglobin (HbA1c; ≤8%, >8%), and prior treatment for DME (yes, no).
edema (DME; yes, no).
DME [yes, no]).
retinopathy during these studies.

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