The RESTORE Study

Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema

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Objective: To demonstrate superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone based on mean average change in best-corrected visual acuity (BCVA) over 12 months in diabetic macular edema (DME).

Design: A 12-month, randomized, double-masked, multicenter, laser-controlled phase III study.

Participants: We included 345 patients aged ≥18 years, with type 1 or 2 diabetes mellitus and visual impairment due to DME.

Methods: Patients were randomized to ranibizumab + sham laser (n = 116), ranibizumab + laser (n = 118), or sham injections + laser (n = 111). Ranibizumab/sham was given for 3 months then pro re nata (PRN); laser/sham laser was given at baseline then PRN (patients had scheduled monthly visits).

Main Outcome Measures: Mean average change in BCVA from baseline to month 1 through 12 and safety.

Results: Ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12 (+6.1 and +5.9 vs +0.8; both $P<0.0001$). At month 12, a significantly greater proportion of patients had a BCVA letter score ≥15 and BCVA letter score level >73 (20/40 Snellen equivalent) with ranibizumab (22.6% and 53%, respectively) and ranibizumab + laser (22.9% and 44.9%) versus laser (8.2% and 23.6%). The mean central retinal thickness was significantly reduced from baseline with ranibizumab (−118.7 μm) and ranibizumab + laser (−128.3 μm) versus laser (−61.3 μm; both $P<0.001$). Health-related quality of life, assessed through National Eye Institute Visual Function Questionnaire (NEI VFQ-25), improved significantly from baseline with ranibizumab alone and combined with laser ($P<0.05$ for composite score and vision-related subscales) versus laser. Patients received ~7 (mean) ranibizumab/sham injections over 12 months. No endophthalmitis cases occurred. Increased intraocular pressure was reported for 1 patient each in the ranibizumab arms. Ranibizumab monotherapy or combined with laser was not associated with an increased risk of cardiovascular or cerebrovascular events in this study.

Conclusions: Ranibizumab monotherapy and combined with laser provided superior visual acuity gain over standard laser in patients with visual impairment due to DME. Visual acuity gains were associated with significant gains in VFQ-25 scores. At 1 year, no differences were detected between the ranibizumab and ranibizumab + laser arms. Ranibizumab monotherapy and combined with laser had a safety profile in DME similar to that in age-related macular degeneration.

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**Group members listed online in Appendix (available at http:///aaojournal.org)*

Diabetic macular edema (DME) is a leading cause of visual impairment in patients with diabetic retinopathy.[1–3] Focal/grid laser photocoagulation (hereafter referred to as laser), the current standard of care in DME, is mostly associated with only vision stabilization. Some recent trials, however, have demonstrated useful vision gain with laser; for example, the Diabetic Retinopathy Clinical Research Network (DRCR.net) study group recently reported a 10-letter gain in 31% patients, whereas 19% of laser-treated patients exhibited progressive visual loss (worsening by ≥2 lines after 2 years follow-up), at a risk of developing scotomas.[4–7]

Vascular endothelial growth factor (VEGF) levels are elevated in the vitreous of eyes with diabetic retinopathy making anti-VEGF treatment an attractive therapeutic modality in DME.[8] Recently, the DRCR.net study group reported that ranibizumab 0.5 mg combined with either prompt or deferred laser therapy was significantly more effective than laser alone in improving vision in patients with DME after 1 year of treatment (best-corrected visual

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acuity [BCVA] letter score of +9 for both ranibizumab groups vs +3 for laser; $P<0.001$).[9] The RESOLVE study (phase II randomized multicenter) demonstrated that ranibizumab monotherapy was well-tolerated and significantly more effective than sham treatment (with rescue laser) in providing rapid and continuous improvements in BCVA over 12 months (mean BCVA letter score change from baseline to month 12, +10.3 for ranibizumab vs −1.4 for sham; $P<0.0001$).[10]

Apart from Ranibizumab for Edema of the mAcula in Diabetes study (READ-2),[11] there have been no other randomized controlled trials that have assessed the efficacy and safety of ranibizumab monotherapy compared with laser monotherapy. Additionally, it is not yet established whether ranibizumab monotherapy is superior or at least equivalent to combined therapy. The 12-month, phase III, randomized, double-masked, multicenter, laser-controlled RESTORE study was designed to assess whether ranibizumab monotherapy or combined with laser was superior to laser alone in patients with visual impairment due to DME. In addition, RESTORE is the first study to assess the impact of ranibizumab treatment on health-related quality of life (HRQoL) outcomes in patients with DME.

Materials and Methods

Study Design

The RESTORE study was a 12-month, double-masked, multicenter, laser-controlled, phase III study where 345 eligible patients from 73 centers (10 European countries, Turkey, Canada, and Australia) were randomized 1:1:1 to 1 of the 3 treatment arms: Intravitreal ranibizumab (0.5 mg) injection + sham laser, adjunctive administration of intravitreal ranibizumab (0.5 mg) injection + active laser, or laser treatment + sham injections for 12 months (for details of randomization and masking, see Appendix 1, available online at http://aaojournal.org). One eye was selected and treated as the study eye. If both eyes were eligible, the eye with the worse visual acuity (VA; assessed at visit 1) was selected for treatment, unless, based on medical reasons, the investigator deemed the other eye more appropriate to receive study treatment. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Approval was obtained from the ethics committee or institutional review board at each contributing center. Patients provided written informed consent before entering the study. The study is registered with clinicaltrials.gov as NCT00687804.

Patients. The study population consisted of 345 male and female patients ≥18 years of age with either type 1 or 2 diabetes mellitus (as per American Diabetes Association or World Health Organization guidelines), glycosylated hemoglobin (HbA1c) ≤10%, and visual impairment due to DME. The key inclusion criteria were (1) stable medication for the management of diabetes within 3 months before randomization and expected to remain stable during the study; (2) visual impairment due to focal or diffuse DME (definition in Table 1) in at least 1 eye that was eligible for laser treatment in the opinion of the investigator; (3) BCVA letter score between 78 and 39, both inclusive, based on Early Treatment Diabetic Retinopathy Study (ETDRS)-like VA testing charts administered at a starting distance of 4 meters (approximate Snellen equivalent 20/32–20/160); and (4) decreased vision due to DME and not other causes, in the investigator's opinion (at visit 1). The key exclusion criteria were (1) concomitant conditions in the study eye that could prevent the improvement in VA on the study treatment in the investigator's opinion; (2) active intraocular inflammation or infection in either eye; (3) uncontrolled glaucoma in either eye (e.g., intraocular pressure [IOP] > 24 mmHg on medication, or from the investigator's

Table 1. Key Baseline Demographic and Disease Characteristics (Randomized Set)

Variable	Ranibizumab 0.5 mg (n = 116)	Ranibizumab 0.5 mg + Laser (n = 118)	Laser (n = 111)
Mean age ± SD (years)	62.9±9.29	64.0±8.15	63.5±8.81
Gender, n (%)			
Men	73 (62.9)	70 (59.3)	58 (52.3)
Women	43 (37.1)	48 (40.7)	53 (47.7)
Diabetes type, n (%)			
Type I	13 (11.2)	15 (12.7)	13 (11.7)
Type II	103 (88.8)	102 (86.4)	97 (87.4)
Not stated	0	1 (0.8)	1 (0.9)
Mean time since first diagnosis of diabetes ± SD (years)	15.23±9.91	14.62±9.84	12.93±9.02
Mean time since first diagnosis of DME ± SD (years)	1.80±1.98	1.99±3.14	1.58±1.96
DME type, n (%)*			
Focal	64 (55.2)	68 (57.6)	53 (47.7)
Diffuse	45 (38.8)	46 (39.0)	52 (46.8)
Missing	7 (6.0)	4 (3.4)	6 (5.4)
Mean VA ± SD (letter score)	64.8±10.11	63.4±9.99	62.4±11.11
Patients with VA letter score >73, n (%)	23 (19.8)	19 (16.1)	17 (15.3)
Mean CRT ± SD (μm)	426.6±118.01	416.4±119.91	412.4±123.95

CRT = central retinal thickness; DME = diabetic macular edema; SD = standard deviation; VA = visual acuity.
*Focal DME: More than 67% of leakage originated from leaking microaneurysms (MAs) in the whole edema area or 30%–67% leakage from MAs in the whole edema area, but >67% of the leakage originated from MAs in the central subfield.
Diffuse DME: Less than 33% of leakage originated from leaking MAs the rest from diffuse leaking capillaries in the whole edema area or 30%–67% leakage comes from MAs, but <33% of the leakage originated from MAs in the central subfield.

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judgment); (4) panretinal laser photocoagulation (within 6 months) or focal/grid laser photocoagulation (within 3 months) before study entry; (5) treatment with antiangiogenic drugs in the study eye within 3 months before randomization; (6) history of stroke; and (7) systolic blood pressure (BP) >160 mmHg or diastolic BP >100 mmHg, untreated hypertension, or change in antihypertensive treatment within 3 months preceding baseline.

Study Objectives. The primary objective of this study was to demonstrate superiority of ranibizumab 0.5 mg as monotherapy or combined with laser therapy over laser alone (the current standard of care) with respect to mean average change in BCVA from baseline over 12 months. Secondary objectives were to evaluate (1) if ranibizumab 0.5 mg as monotherapy or adjunctive to laser was superior to laser alone in the proportion of patients with VA improvement and with BCVA letter score >73 (20/40 Snellen equivalent) at month 12; (2) the time course of mean change in BCVA letter score and central retinal (subfield) thickness (CRT); (3) patient-reported outcomes relative to those associated with laser treatment; and (4) the safety of intravitreal injections of ranibizumab 0.5 mg, as monotherapy or adjunctive to laser therapy relative to laser treatment.

Efficacy and Safety Assessments

Best-Corrected Visual Acuity. We assessed BCVA at every study visit using ETDRS charts at a starting distance of 4 meters. The primary efficacy end point was the mean average change in BCVA letter score from baseline to month 1 through month 12. Secondary efficacy end points included the mean BCVA letter score change from baseline to month 12 and proportion of patients who gained ≥10 and ≥15 letters in BCVA and patients with BCVA letter score >73 at month 12. Mean average change in BCVA from baseline to month 1 through month 12 was chosen as the primary efficacy end point as it accounts for both interpatient and intramonth variability in BCVA and thus gives a more robust estimate of the VA gained by patients over time compared with the mean change of BCVA from baseline to study end.

A subgroup analysis of the primary end point was performed on the basis of demographic and baseline disease characteristics. The key categories assessed were as follows: DME type (focal/diffuse), BCVA letter score (≤60, 61–73, and >73), diabetes type (type 1/type 2), focal and/or grid laser pretreatment (yes/no), CRT (<300, 300–400, and >400 μm), ETDRS retinopathy severity score (10–35, 43 or 47, and 53–85), macular ischemia (yes/no; measured by the presence of capillary loss on fluorescein angiography according to a modified ETDRS grading scale in the center subfield of 1000 μm diameter, where the capillary loss grades "moderate," "severe," or "completely destroyed" were categorized as "yes" ischemia, and the grades "none" or "mild" were classified as "no" ischemia).

Optical Coherence Tomography. Optical coherence tomography (OCT) was performed at every study visit using Stratus OCT (Carl Zeiss, Meditec, Dublin, CA). The images were reviewed by a central reading center to ensure a standardized evaluation. Retinal thickness was determined using individual A-scans along with each of 6 B-scans. End points included mean change in CRT (defined from the central macular area 1000 μm in diameter) over time and the proportion of patients with CRT <275 μm.

Stereoscopic Color Fundus Photography and Fluorescein Angiography. Stereoscopic color fundus photography and fluorescein angiography were performed at baseline, month 6, and month 12. After pupil dilation and before fluorescein dye injection, red-free and ETDRS 7-field color photographic images of the retina of the study eye were taken. Anatomic end points included the proportion of patients with resolution of leakage and cysts at month 12 as assessed by the central reading center and the proportion of patients with a 3-step change in the ETDRS severity score from baseline to month 12 (exploratory end point).

Health-Related Quality of Life. We assessed HRQoL using the visual-specific National Eye Institute Visual Function Questionnaire (NEI VFQ-25), as well as generic health assessment utility tools EuroQoL (EQ-5D), and time trade off (TTO). All questionnaires were scored by patients at baseline and month 12. Additionally, the NEI VFQ-25 was scored at month 3 and the EQ-5D was scored at months 3 and 6. End points included the absolute change in scores, changes in scores over time, and differences in scores between treatment groups.

Drug Exposure. The number of ranibizumab/sham injections and active/sham laser treatments, and the mean duration of treatment-free intervals (ranibizumab/sham injection, active/sham laser) were evaluated over the 12-month assessment period for each of the treatment arms.

Safety Assessments. Safety was assessed by the 12-month incidence of adverse events (AEs) and serious AEs (SAEs), by ophthalmic examinations and IOP measurements, and by changes in vital signs and laboratory parameters over the 12-month assessment period.

Treatment

Ranibizumab/Sham Treatment. Patients received 3 initial consecutive monthly injections of ranibizumab (months 0–2; treatment initiation phase), followed by further treatment according to protocol-defined retreatment criteria between and including months 3 and 11 (continuous/resumed treatment phase; Figure 1, available online at http://aaojournal.org). Intravitreal ranibizumab injections were performed by the investigators' usual routines; both pre- and postinjection topical antibiotics were used. Sham ranibizumab injection involved imitation of an injection procedure using an injection syringe without needle, by applying pressure against the globe.

Retreatment Criteria During Continuous/Resumed Treatment Phase. As of month 3, the protocol required that 1 injection per month was to be continued if stable VA was not reached. Treatment was suspended if either of the following criteria were met: (1) if the investigator's opinion was that no (further) BCVA improvement was attributable to treatment with intravitreal injection at the last 2 consecutive visits, or (2) BCVA letter score ≥ 84 (approximate Snellen equivalent 20/20) was observed at the last 2 consecutive visits. After suspension, injections were resumed pro re nata (PRN [as required]) if there was a decrease in BCVA due to DME progression, confirmed by clinical evaluation and/or OCT or other anatomic and clinical assessments, in the opinion of the investigator. Patients were treated at monthly intervals until stable VA was reached again. Thus, reinitiation of intravitreal injections encompassed ≥2 successive monthly treatments.

Laser/Sham Laser Treatment. The first laser treatment (active or sham depending on treatment group; the ranibizumab + sham laser group did not receive active laser treatment) was administered on day 1. If required, the first laser administration could be split into 2 sessions, 4 weeks apart. Retreatments were given in accordance with ETDRS guidelines at intervals no shorter than 3 months from the previous treatment if deemed necessary by the evaluating investigator. Patients receiving retreatment with active or sham laser continued to be treated with monthly ranibizumab or sham injections as long as the treatment criteria for intravitreal injection were fulfilled. Decisions on retreatment with laser/sham were independent of decisions to administer ranibizumab/sham injections and vice versa. Sham laser was applied under the same procedure used for laser treatment but without switching on the laser beam, and by imitating depression of the laser pedal.

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Statistical Analysis

The primary analysis was performed on the full analysis set (FAS), consisting of all patients who received ≥1 application of the study treatment ([sham] injection and/or [sham] laser) and had ≥1 postbaseline assessment for BCVA. The primary end point was the difference between the average BCVA letter score over all monthly postbaseline assessments from month 1 to month 12 and the baseline BCVA letter score (= average change from baseline).

The analysis of the primary end point used the last observation carried forward approach for the imputation of missing data. Sensitivity analyses of the primary end point were performed using (1) an "as documented" approach in the FAS where the average change from baseline in BCVA was calculated from observed changes only, and (2) a per-protocol set with missing data being handled in the same way as for the FAS.

A sample size of 105 randomized patients per treatment group was considered to have >90% power to detect a 5-letter BCVA score treatment difference in the mean average change in BCVA compared with baseline from month 1 through month 12, assuming a standard deviation (SD) of 10 BCVA letter score with a Bonferroni adjusted 1-sided alpha level of 0.0125 for the 2 comparisons. Hypothesis testing of the superiority of ranibizumab mono and/or ranibizumab/laser combination compared with laser was done in parallel according to the Hochberg procedure controlling the overall 1-sided alpha level at 0.025. The statistical hypothesis testing of the average change from baseline in BCVA was based on the stratified Cochran–Mantel–Haenszel test using the observed values as scores and with stratifications according to DME type (focal, diffuse) and baseline BCVA letter score (≤60, 61–73, >73). Two-sided 95% confidence intervals for the mean average changes in BCVA and for the corresponding pair-wise difference between treatments, were calculated using the least-square means from an analysis of variance model with treatment, DME type, and baseline BCVA category (see above) as factors.

The safety analysis was conducted on the safety set that comprised all patients who received ≥1 application of study treatment and had ≥1 postbaseline safety assessment.

Results

Patient Disposition and Demographics

A total of 345 patients were randomized to receive ranibizumab 0.5 mg (n = 116), ranibizumab 0.5 mg + laser (n = 118), or laser (n = 111). The efficacy analysis was performed on the FAS that comprised 115 (ranibizumab 0.5 mg), 118 (ranibizumab + laser), and 110 (laser) patients (1 patient each from the ranibizumab and laser arm were excluded because they had no postbaseline VA data). The safety analysis was conducted on the safety set comprising 115 (ranibizumab), 120 (ranibizumab + laser), and 110 (laser) patients. Three patients (1 in each treatment arm) received active ranibizumab and active laser in the study eye at baseline without consideration of the randomization, and all 3 of these were analyzed under the ranibizumab + laser arm for the safety set. The patient disposition was comparable across the 3 treatment groups (Fig 2, available online at http://aaojournal.org); 87.9% (ranibizumab), 87.3% (ranibizumab + laser), and 88.3% (laser) of the patients completed the 12-month study period. There were 2 deaths in each of the 3 treatment arms. Baseline demographics and diabetes characteristics were comparable across the 3 treatment arms (Table 1).

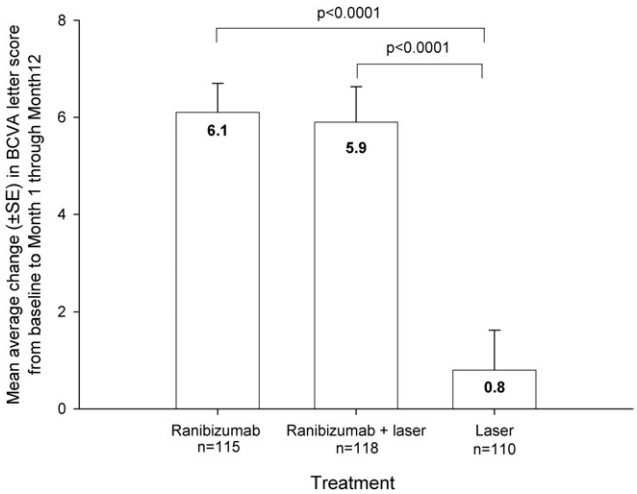

Figure 3. Mean average change in best-corrected visual acuity (BCVA) letter score from baseline to months 1 through 12 (primary end point). SE = standard error.

Efficacy

Best-Corrected Visual Acuity. The mean average change ± SD in the BCVA letter score from baseline to month 1 through month 12 was significantly superior with ranibizumab (6.1 ± 6.4; $P<0.0001$) and ranibizumab + laser (5.9 ± 7.9; $P<0.0001$) than with laser treatment (0.8 ± 8.6), hence the primary end point was achieved (Fig 3; Table 2). There was no difference detected between the 2 ranibizumab treatment arms ($P = 0.61$, Cochran–Mantel–Haenszel test). Similar results were obtained (data not shown) for the primary end point using the "as documented" approach and the per protocol set. The last observation carried forward calculation of the average level of BCVA letter score over all monthly post-baseline assessments from month 1 to month 12 was based on 92.6% (ranibizumab), 92.9% (ranibizumab + laser), and 91.4% (laser) observed monthly BCVA assessments.

The mean change ± SD in BCVA letter score from baseline to month 12 was 6.8 ± 8.3 ($P<0.0001$) in the ranibizumab arm, 6.4 ± 11.8 ($P = 0.0004$) in the ranibizumab + laser arm, and 0.9 ± 11.4 in the laser arm (Table 2). In the ranibizumab and ranibizumab + laser arms, a rapid and clinically relevant improvement in mean BCVA was observed as of the first assessment posttreatment (at month 1), which continued up to month 3 and was sustained at the month 3 level until the last assessment time point at month 12. In the laser arm, mean BCVA stabilized around baseline level and reached a 0.9 letter gain at month 12 (Fig 4A).

At month 12, 53.0% (vs 19.8% at baseline) of patients in the ranibizumab arm and 44.9% (vs 16.1% at baseline) of patients in the ranibizumab + laser arm had a BCVA letter score >73 (20/40 Snellen equivalent) compared with 23.6% (vs 15.3% at baseline) of patients in the laser arm (estimated treatment difference vs laser, 29.4% [95% confidence interval, 17.3–41.5] for ranibizumab and 21.3% [95% confidence interval, 9.3–33.3] for ranibizumab + laser; Table 2; month 3 and 6 data in Table 3, available online at http://aaojournal.org).

A significantly greater proportion of patients gained ≥5 BCVA letters with ranibizumab (65.2% [ranibizumab] and 63.6% [ranibizumab + laser]; $P<0.0001$) versus laser alone (33.6%). Similarly, a significantly greater proportion of patients in either the ranibizumab arm or the ranibizumab + laser arm compared with the laser arm gained a ≥10 BCVA letter score (37.4% and 43.2% vs 15.5%; $P<0.0001$ for both) and a ≥15 BCVA letter score (22.6% [$P = 0.0005$] and 22.9% [$P = 0.0037$] vs 8.2%; Table 2). Con-

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Table 2. Best-Corrected Visual Acuity (BCVA) and Central Retinal Thickness (CRT) Outcome at Month 12 (Full Analysis Set, Last Observation Carried Forward)

	Ranibizumab 0.5 mg (n = 115)	Ranibizumab 0.5 mg + Laser (n = 118)	Laser (n = 110)
Mean average change in BCVA letter score from baseline to month 1–12 (primary end point)*			
Mean ± SD	6.1±6.43	5.9±7.92	0.8±8.56
Median (range)	6.1 (−10.9–25.2)	6.0 (−26.7–27.6)	1.3 (−37.8–26.8)
95% CI for mean**	(4.9, 7.3)	(4.4, 7.3)	(−0.8, 2.4)
Comparison verus laser			
Difference in LS means (vs laser)†	5.4	4.9	
95% CI for difference†	(3.5, 7.4)	(2.8, 7.0)	
P value‡	<0.0001	<0.0001	
Proportion of patients with BCVA letter score >73 at month 12			
n (%)	61 (53.0)	53 (44.9)	26 (23.6)
95% CI for percentage	(43.5, 62.4)	(35.7, 54.3)	(16.1, 32.7)
Difference in percentage (vs laser)	29.4	21.3	
95% CI for difference	(17.3, 41.5)	(9.3, 33.3)	
P value‡	<0.0001	0.0002	
Categorized BCVA letter score outcome at month 12, n (%)			
Gain of ≥5	75 (65.2)	75 (63.6)	37 (33.6)
Gain of ≥10§	43 (37.4)	51 (43.2)	17 (15.5)
Loss of ≥10	4 (3.5)	5 (4.2)	14 (12.7)
Gain of ≥15§	26 (22.6)	27 (22.9)	9 (8.2)
Loss of ≥15	1 (0.9)	4 (3.4)	9 (8.2)
Mean CRT change from baseline to month 12, μm			
Mean ± SD	−118.7±115.07	−128.3±114.34	−61.3±132.29
Median (range)	−103.0 (−514–120)	−116.5 (−487–103)	−60.0 (−451–329)
95% CI for mean**	(−140.1, −97.3)	(−149.3, −107.3)	(−86.5, −36.1)
Comparison verus laser			
Difference in LS means (vs laser)†	−61.5	−70.6	
95% CI for difference†	(−93.8, −29.2)	(−102.1, −39.0)	
P value‡	0.0002	<0.0001	

ANOVA = analysis of variance; CI = confidence intervals; LS = least square; SD = standard deviation.
*Missing VA values imputed using last observation carried forward for 7.39% (ranibizumab), 7.06% (ranibizumab + laser) and 8.56% (laser) patients.
**Two-sided 95% CI are based on the t-distribution.
†Differences in LS means and the 2-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.
‡*P*-values for treatment difference are from the 2-sided stratified Cochran-Mantel-Haenszel test using the row means score.
§Specified gain, or BCVA letter score of ≥84.

versely, a lower proportion of patients lost ≥10 and ≥15 letters in both the ranibizumab arms compared with the laser arm.

The mean average BCVA change from baseline to month 1 through month 12 by some of the key subgroups including patients with/without macular ischemia and those with focal/diffuse DME are presented in Figure 5A–E (Fig 5C–E and Fig 6 [mean average change in BCVA], available online at http://aaojournal.org). Each of the ranibizumab patient subgroups did better on average than those on laser alone in terms of the primary efficacy end point (all categories presented in Table 4 available online at http://aaojournal.org).

Central Retinal Thickness. The mean CRT change from baseline to month 12 decreased significantly for ranibizumab (118.7 μm; $P = 0.0002$) and ranibizumab + laser (128.3 μm; $P<0.0001$) compared with laser (61.3 μm; Fig 4B; Table 2).

At month 12, the proportion of patients with CRT < 275 μm was significantly greater in the ranibizumab monotherapy arm (49.1%; $P = 0.0408$) and the ranibizumab + laser arm (55.1%; $P = 0.0075$) compared with the laser arm (39.1%).

Colour Fundus Photography and Fluorescein Angiography

At month 12, a significantly larger proportion of patients had resolution of leakage in the ranibizumab (19.4%; $P = 0.0002$) and the ranibizumab + laser (13.7%; $P = 0.0114$) arms compared with the laser arm (2.2%).

Health-Related Quality of Life

Visual Functioning Questionnaire. The mean changes in the NEI VFQ-25 composite scores by treatment arms at months 3 and 12 are presented in Figure 7A (available at online http://aaojournal.org). For both ranibizumab arms the composite scores increased from month 3 to 12, whereas it decreased for the laser arm. At month 12, there was a greater improvement in the composite scores in the ranibizumab (5.0; $P = 0.014$) and ranibizumab + laser (5.4; $P = 0.004$) arms compared with the laser arm. At month 12, greater differences from baseline in NEI VFQ-25 subscale scores (general vision, near activities, and distance activities) were observed for ranibizumab and ranibizumab + laser versus laser alone (all $P<0.05$; Fig 7B–D).

At month 12, excellent to good eyesight was reported by 46% and 50% of the patients in the ranibizumab and ranibizumab + laser arm compared with 21% and 23% of the patients at baseline (determined by the individual NEI VFQ-25 question pertaining to patient's perception of eyesight posttreatment). Excellent to good vision was reported by only 24% patients with laser alone at month 12 compared with 22% of the patients at baseline.

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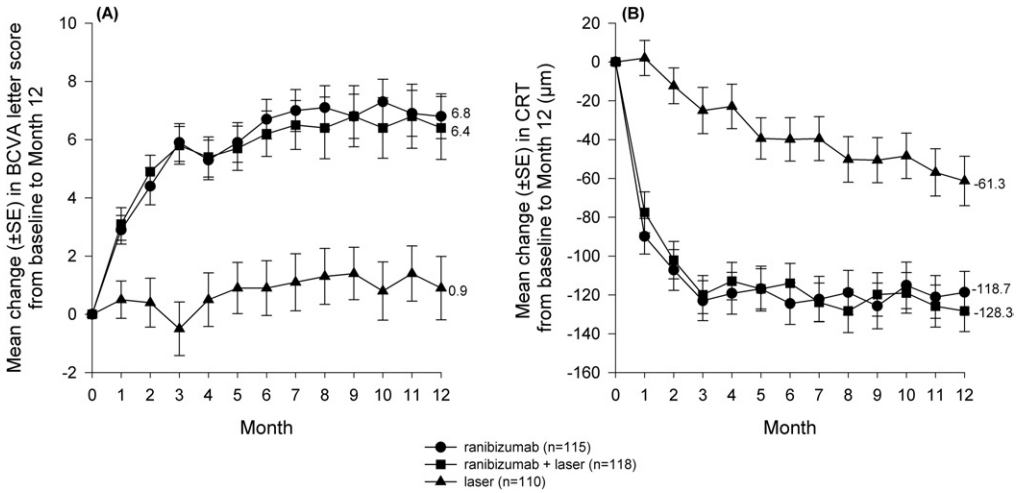

Figure 4. **A**, Mean change in best-corrected visual acuity (BCVA) letter score from baseline to month 12. **B**, Mean change in central retinal thickness (CRT) from baseline to month 12. SE = standard error.

EQ-5D Scores. None of the differences from baseline in the mean EQ-5D visual analog scores between the ranibizumab treatment groups and laser alone were statistically significant at any time point (Fig 8, available online at http://aaojournal.org).

TTO Scores. Patients were asked what proportion of their life expectancy they would be willing to trade off to avoid their current vision impaired health state, the resulting proportion representing the utility of their current health state. An improvement of 0.13 in the utility score was observed for ranibizumab monotherapy (baseline score 0.69), 0.032 for ranibizumab + laser (baseline score 0.73), and 0.023 for laser alone (baseline score 0.73; Fig 9, available online at http://aaojournal.org); these differences were not significant versus laser.

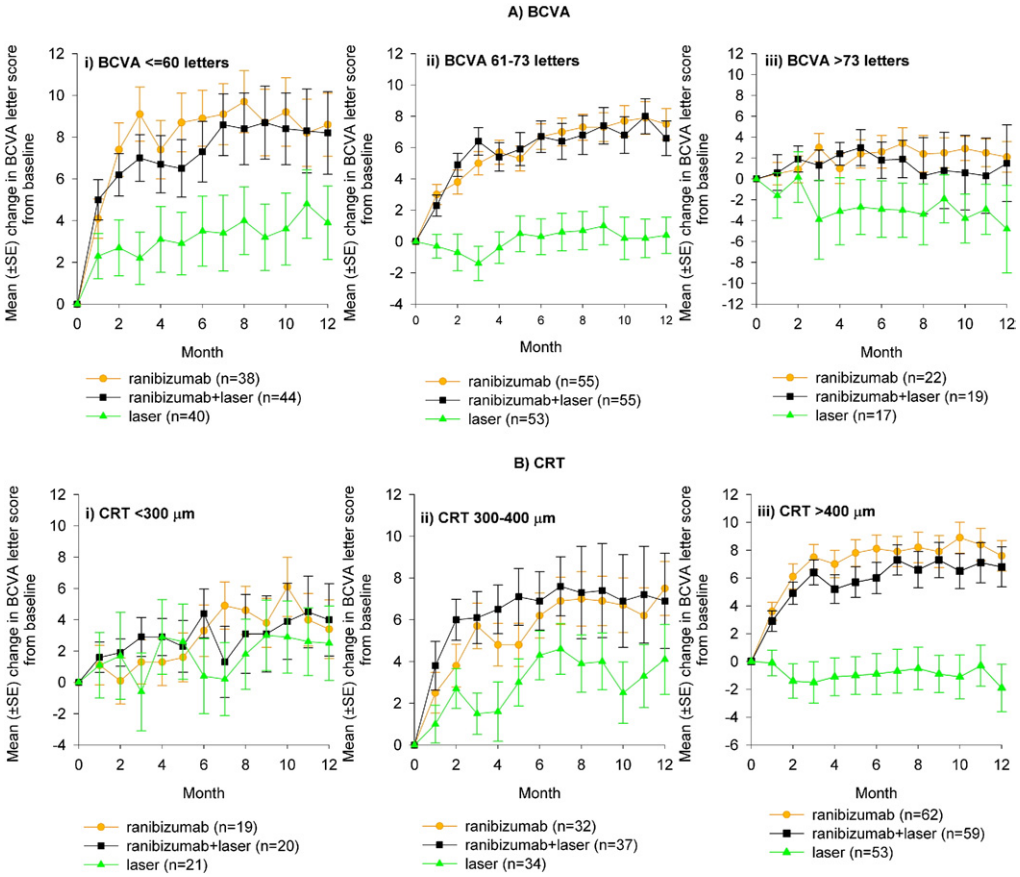

Figure 5. Mean change in best-corrected visual acuity (BCVA) from baseline over 12 months by key baseline characteristics, (A) best-corrected visual acuity and (B) central retinal thickness. BCVA = best-corrected visual acuity; CRT = central retinal thickness; SE = standard error.

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Table 5. Number of Ranibizumab/Sham Injections Received (Safety Set)

	Ranibizumab 0.5 mg (n = 115)	Ranibizumab 0.5 mg + Laser (n = 120)	Laser (n = 110)
Total number of injections	Ranibizumab	Ranibizumab	Sham
Total	800	816	802
Mean ± SD	7.0±2.81	6.8±2.95	7.3±3.22
Median (Range)	7.0 (1–12)	7.0 (2–12)	7.0 (1–12)
Distribution of injections, n (%)			
1–3	16 (13.9)	23 (19.2)	19 (17.3)
4–6	37 (32.2)	34 (28.3)	32 (29.1)
7–9	40 (34.8)	35 (29.2)	22 (20.0)
10–12	22 (19.1)	28 (23.3)	37 (33.6)

SD = standard deviation.

Drug Exposure

Ranibizumab Injections. The mean number of ranibizumab/sham injections received was similar for all treatment groups (6.8–7.3 injections; Table 5). Between months 3 and 11, patients received an average of 4.1 ranibizumab intravitreal injections in the ranibizumab arm, 3.8 in the ranibizumab + laser arm, and 4.5 sham injections in the laser-treated arm.

Treatment-Free Interval for Ranibizumab or Sham Injections. A greater proportion of patients in the ranibizumab (85.2%) and ranibizumab + laser arms (81.7%) had their dose interrupted due to disease improvement compared with the laser arm (68.2%), which received sham injections only (Table 6 available online at http://aaojournal.org). According to the protocol, the first possible time point to stop injections (ranibizumab or sham) because of stability was month 3. At month 3, more patients in the ranibizumab arms (32.2% [ranibizumab] and 30.8% [ranibizumab + laser]) than the laser arm (20.9%) were not treated because of stability of VA.

After treatment interruption, the mean duration of the treatment-free interval was approximately 2 months in both the ranibizumab and the laser arms and approximately 2.5 months in the ranibizumab + laser arm (Table 7 available online at http://aaojournal.org). Fewer patients received monthly treatment in the ranibizumab (8.0%) and ranibizumab + laser (7.6%) arms compared with the laser arm (17.8%). The proportion of patients with a maximum treatment-free interval of ≥3 months was similar across treatment arms (57.9%–61.9%).

Laser Treatment. The mean number of active/sham laser treatments was similar for all treatment groups (1.7–2.1 administrations; Table 8 available online at http://aaojournal.org). From month 3 to month 11, patients received 0.9 sham laser administrations in the ranibizumab arm, 0.7 active laser administrations in the ranibizumab + laser arm, and 1.1 in the laser-treated arm (Table 8, available online at http://aaojournal.org). During this period, 49.6% (ranibizumab) and 44.5% (ranibizumab + laser) of the patients received a sham/active laser treatment compared with 63.9% patients in the laser arm.

Safety

Serious Adverse Events. No ocular SAEs were reported in the ranibizumab arm, whereas there were 2 cases each reported in the ranibizumab + laser (cataract) and laser only (cataract and maculopathy) arms; none suspected to be related to study drug or procedure (Table 9 available online at http://aaojournal.org). There were no cases of endophthalmitis reported in any of the treatment arms (~7 ranibizumab or sham injections over the 12-month treatment period). There were 23 (20%) patients with nonocular SAEs in the ranibizumab arm, 17 (14.2%) in the ranibizumab + laser arm, and 15 (13.6%) in the laser arm (Table 9, available online at http://aaojournal.org). The nonocular SAEs that were suspected by the investigator to be related to a study drug or procedure included intestinal obstruction (0.9%), hypoglycemia (0.9%), pulmonary embolism (1.7%), dyspnea (0.9%), and arterial thrombosis limb (0.9%) in the ranibizumab arm, coronary artery occlusion (0.8%) in the ranibizumab + laser arm. There were 6 deaths reported during the study (2 per treatment arm), none of which were considered to be related to the study drug by the investigator (Table 9, available online at http://aaojournal.org).

Adverse Events. The most frequently occurring ocular and nonocular AEs are summarized in Table 10 (available online at http://aaojournal.org). The most common ocular AE was eye pain in all 3 treatment arms. Eye pain was also the most common ocular AE suspected to be related to study drug (10–12 cases) followed by conjunctival hemorrhage, which was reported in the ranibizumab arms only (8–9 cases). One patient each in the ranibizumab arms experienced IOP increase, which was suspected to be related to study drug or procedure (Table 11 available online at http://aaojournal.org). Nasopharyngitis was the most common nonocular AE observed in all 3 treatment arms. Some of the nonocular AEs that were suspected to be related to study drug or procedure included pulmonary embolism (n = 2), limb arterial thrombosis (n = 1), arthralgia (n = 1), and hypertension (n = 1), all in the ranibizumab arm, coronary artery occlusion (n = 1) in the ranibizumab + laser arm, and hypertension (n = 1) in the sham arm (Table 11). Hypertension, the most common AE potentially related to systemic VEGF inhibition, was comparable in all treatment arms (Table 12). Arterial thromboembolic events were reported by 6 patients in the ranibizumab arm and 1 patient each in the ranibizumab + laser and laser arms. These included 1 case each of myocardial infarction in the ranibizumab and ranibizumab + laser arm, and 1 case of cerebrovascular accident in the ranibizumab arm. At the end of the study, there was no clinically significant difference between treatment arms for either mean BP or IOP, and the values of clinical laboratory evaluations were similar among the study arms (details in Appendix 3, available online at http://aaojournal.org).

Discussion

The results from the RESTORE study demonstrate that treatment with ranibizumab as monotherapy and combined with laser treatment is superior to laser treatment in rapidly improving and sustaining VA in patients with visual im-

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Table 12. Adverse Events Potentially Related to Systemic Vascular Endothelial Growth Factor Inhibition (Safety Set)

Preferred Term, n (%)	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5 mg + Laser N = 120	Laser N = 110
Total	14 (12.2)	7 (5.8)	11 (10.0)
Arterial thromboembolic events	6 (5.2)	1 (0.8)	1 (0.9)
Angina pectoris	2 (1.7)	0	0
Pulmonary embolism	2 (1.7)	0	1 (0.9)
Cerebrovascular accident	1 (0.9)	0	0
Myocardial infarction	1 (0.9)	1 (0.8)	0
Hypertension	9 (7.8)	6 (5.0)	9 (8.2)
Non-ocular hemorrhage	1 (0.9)	0	1 (0.9)
Epistaxis	1 (0.9)	0	1 (0.9)
Proteinuria	1 (0.9)	1 (0.8)	0

pairment due to DME. There were no efficacy differences detected between the ranibizumab and ranibizumab combined with laser treatment arms. A greater proportion of patients treated with ranibizumab gained ≥5, ≥10, and ≥15 BCVA letter scores from baseline compared with the laser-treated patients.

Ranibizumab treatment consistently demonstrated significant and superior VA benefit in all subgroups of DME patients, including patients with focal or diffuse DME and those with or without prior laser as compared with laser treatment alone. The functional improvements in BCVA were accompanied by significant improvements in anatomic end points, CRT on OCT, and resolution of leakage on fluorescein angiography. At month 12, 49.1% (ranibizumab), 55.1% (ranibizumab + laser), and 39.1% (laser) patients had CRT <275 μm, whereas 50.9%, 44.9%, and 60.9%, respectively, had CRT >275 μm.

The efficacy results with ranibizumab treatment from the RESTORE study are consistent with the recently published DRCR.net and RESOLVE studies.[9,10] Results from the DRCR.net study showed that ranibizumab used in conjunction with laser therapy (prompt or deferred) was significantly more effective than laser alone in improving VA in patients with DME after 1 year of treatment (+9 [both] vs +3 BCVA letter score; $P<0.001$).[9] In the DRCR.net study, approximately 30% of the ranibizumab + laser patients gained a ≥15 BCVA letter score from baseline compared with 15% of the laser-treated patients.

The RESOLVE study demonstrated that ranibizumab provided rapid and continuous improvements in BCVA compared with sham over a period of 12 months (mean average change in BCVA letter score from baseline to month 12, +7.8 for ranibizumab vs −0.1 for sham; $P<0.0001$).[10] At month 12, approximately 32% of the ranibizumab-treated patients gained a ≥15 BCVA letter score compared with 10% in the sham control arm.

The observed numerical differences in the BCVA outcome between RESTORE and RESOLVE may be partly attributed to the differences in eligibility criteria and as a consequence to baseline characteristics of the enrolled patients. Additionally, the 2 studies had different retreatment criteria, which led to an average of ~10 ranibizumab injections in the RESOLVE study and ~7 injections in the RESTORE study.

Visual impairment or reduced VA adversely impacts patients' independence (activities like reading, interacting socially, watching TV, driving, etc) and HRQoL.[12–14] The RESTORE trial is the first to assess the impact of ranibizumab treatment on HRQoL, particularly using the NEI VFQ-25 questionnaire. Ranibizumab showed progressive and sustained improvements in HRQoL as assessed by the NEI VFQ25 composite scores. The mean change in VFQ-25 composite scores was significant, with ranibizumab monotherapy and combined with laser (5.0 and 5.4 point) versus laser. These results are consistent with those reported for ranibizumab in the neovascular AMD studies Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA), where a 4- to 6-point improvement in mean NEI VFQ-25 scores represented a clinically meaningful change corresponding with a 15-letter improvement in BCVA.[15] The strongest evidence of HRQoL benefit for ranibizumab compared with laser alone was observed for general vision, near, and distance activities NEI VFQ-25 subscales. Adding to the HRQoL outcomes are the data on the proportion of patients who had a BCVA letter score >73 (20/40 Snellen equivalent, the legal minimum for driving in the United States and the United Kingdom) in the study eye at month 12. In RESTORE, at month 12, 44.9% (ranibizumab + laser) and 53.0% (ranibizumab) patients had a BCVA letter score >73 versus 16.1% and 19.8% patients at baseline, whereas with laser 23.6% patients had a BCVA letter score >73 versus 15.3% at baseline. For the EQ-5D scores, none of the differences between the ranibizumab treatment arms and laser arm at any time point were significant. This is not surprising given that EQ-5D does not contain any vision-related domains, and has known ceiling effects,[16] so the scale may lack sensitivity in detecting changes in DME outcomes.

For the TTO scores, the change in mean utility score of 0.13 with ranibizumab was not statistically different from laser alone at month 12 ($P = 0.10$). Results from the TTO utility measurement indicate a numerical improvement with ranibizumab vs laser alone, and hence a possible impact on the quality-adjusted life years associated with ranibizumab therapy.

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The RESTORE study used retreatment criteria that were designed to enable an individualized treatment regimen based on patients' disease stability. Patients were assessed monthly to observe disease stability/activity and to guide treatment interruption or reinitiation through changes in VA, supported by clinical and anatomic evaluations attributable to the progression of DME. The validity of this approach was confirmed by the efficacy outcome, which showed that the PRN retreatment regimen could maintain the BCVA gained at the end of the treatment initiation phase. Furthermore, this was achieved with an average of 4 injections in the 9-month continuous/resumed treatment phase. However, it is unknown whether or not VA gains would have been greater if monthly treatment had been maintained over 12 months. Ongoing ranibizumab clinical trials, such as the Ranibizumab Injection in Subjects with clinically significant macular Edema with center involvement secondary to diabetes mellitus (RISE, NCT00473330)[17] and the Ranibizumab Injection in subjects with clinically significant macular Edema with center involvement secondary to Diabetes mellitus (RIDE, NCT00473382)[18] where monthly injections are mandated for 24 months will provide data on maximal VA gains in DME with monthly therapy. Overall, a greater proportion of patients interrupted treatment due to disease stability with ranibizumab than laser (85% [ranibizumab] and 82% [ranibizumab + laser] vs 68%), which was expected because the laser arm received sham injections only. Approximately 33% of the ranibizumab-treated patients interrupted treatment for the first time at month 3 due to treatment efficacy. The proportion of patients with a maximum treatment-free interval of ≥3 months was similar across treatment arms (57.9%–61.9%).

The results from the RESTORE study have assessed the treatment effect of ranibizumab monotherapy in DME, as well as the potential benefit of combining it with laser therapy. Over the 1-year study period, the results from RESTORE show that there were no significant efficacy differences detected between the ranibizumab and the ranibizumab combined with laser treatment arms with respect to improvements in BCVA, as well as the number of injections. Overall, the retreatment criteria based on disease stability used in the RESTORE study allowed a reduction in the number of injections compared with the RESOLVE study, through monthly monitoring to assess patients' need for retreatment.

Ranibizumab as monotherapy or combined with laser was well-tolerated in patients with visual impairment due to DME over 12 months. There were no ocular SAEs observed in the ranibizumab arm. There were no incidences of glaucoma reported in any of the treatment arms and only 1 patient in each ranibizumab arm reported increased IOP. Both cases of IOP increase resolved on their own, without treatment, and the investigator considered these events to be related to injection procedure and not to the drug. Ranibizumab treatment was not found to be associated with an increased risk of cerebrovascular or cardiovascular events in DME patients over 12 months; there were no cases of endophthalmitis reported in the study. The pooled analysis of the 2 pivotal studies, RESOLVE and RESTORE, resulted in an incidence rate of 1.4% for endophthalmitis at 1 year, which is consistent with the incidence rate of 1.6% found in the pooled analysis of the pivotal AMD studies, ANCHOR, MARINA, and PIER (A Phase IIIb, multicenter, randomized, double-masked, sham Injection-controlled study of the Efficacy and safety of Ranibizumab; unpublished data, July 21, 2008). The incidence of AEs potentially related to systemic VEGF inhibition (hypertension, proteinuria, and nonocular hemorrhage) were low and did not differ compared with the laser control cohort. Furthermore, ranibizumab treatment did not negatively influence the VA outcome or the progression of macular ischemia, as confirmed by assessing the BCVA at month 12 in the subgroups with or without the presence of ischemia at baseline, as well as by the degree of capillary loss in the central subfield from baseline to month 12 (Appendix 2, available online at http://aaojournal.org). The safety findings from this study are consistent with the safety profile of other studies with ranibizumab treatment in DME[9,10] and neovascular AMD.[19,20]

In summary, data from the 3 randomized clinical trials RESOLVE, DRCR.net and RESTORE involving >1000 patients provide robust evidence for the efficacy and tolerability of ranibizumab in DME.[9,10] Furthermore, the 24-month results from DRCR.net and the recently published READ-2 study have shown that ranibizumab sustains efficacy[9,11] through year 2 of treatment and was well-tolerated.[9] These reports may lead to a shift in treatment paradigm for DME, from laser, to newer approaches using ranibizumab. Results from the 2-year extension of the RESTORE study will add to the data from studies REVEAL (NCT00989989),[21] RIDE,[18] RISE,[17] and RETAIN (NCT01171976),[22] and DRCR.net (4-year follow-up) and are expected to further enhance the evidence for ranibizumab therapy in DME in the coming years.

In conclusion, RESTORE is the first study to demonstrate that ranibizumab monotherapy provides significantly superior benefit over standard-of-care laser in patients with visual impairment due to DME, rapidly improving and sustaining BCVA over the 12-month treatment period. Ranibizumab therapy was administered using an individualized PRN regimen with monthly monitoring and retreatment based on disease stability. During the 12-month study period combining laser with ranibizumab did not seem to provide any advantage compared with ranibizumab monotherapy in terms of improving BCVA and treatment exposure. However, longer follow-up may be required to assess the benefit of combining laser with ranibizumab. Ranibizumab consistently improved BCVA across all the subgroups of patients, including patients with focal or diffuse DME. Ranibizumab treatment was also associated with progressive and sustained improvements in HRQoL compared with laser alone, as assessed by the NEI VFQ-25 scores. Ranibizumab was well-tolerated in patients with visual impairment due to DME with a safety profile similar to the well-established safety profile in neovascular AMD.[19,20]

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Footnotes and Financial Disclosures

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Appendix 4 contains a list of the primary investigators who participated in this study (available online at http://aaojournal.org).

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