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Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE.

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Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two Phase III Trials

RISE and RIDE

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Purpose: To report 36-month outcomes of RIDE (NCT00473382) and RISE (NCT00473330), trials of ranibizumab in diabetic macular edema (DME).

Design: Phase III, randomized, multicenter, double-masked, 3-year trials, sham injection–controlled for 2 years.

Participants: Adults with DME (n=759), baseline best-corrected visual acuity (BCVA) 20/40 to 20/320 Snellen equivalent, and central foveal thickness (CFT) ≥ 275 μm on optical coherence tomography.

Methods: Patients were randomized equally (1 eye per patient) to monthly 0.5 mg or 0.3 mg ranibizumab or sham injection. In the third year, sham patients, while still masked, were eligible to cross over to monthly 0.5 mg ranibizumab. Macular laser was available to all patients starting at month 3; panretinal laser was available as necessary.

Main Outcome Measures: The proportion of patients gaining ≥ 15 Early Treatment Diabetic Retinopathy Study letters in BCVA from baseline at month 24.

Results: Visual acuity (VA) outcomes seen at month 24 in ranibizumab groups were consistent through month 36; the proportions of patients who gained ≥ 15 letters from baseline at month 36 in the sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab groups were 19.2%, 36.8%, and 40.2%, respectively, in RIDE and 22.0%, 51.2%, and 41.6%, respectively, in RISE. In the ranibizumab arms, reductions in CFT seen at 24 months were, on average, sustained through month 36. After crossover to 1 year of treatment with ranibizumab, average VA gains in the sham/0.5 mg group were lower compared with gains seen in the ranibizumab patients after 1 year of treatment (2.8 vs. 10.6 and 11.1 letters). Per-injection rates of endophthalmitis remained low over time ($\sim 0.06\%$ per injection). The incidence of serious adverse events potentially related to systemic vascular endothelial growth factor inhibition was 19.7% in patients who received 0.5 mg ranibizumab compared with 16.8% in the 0.3 mg group.

Conclusions: The strong VA gains and improvement in retinal anatomy achieved with ranibizumab at month 24 were sustained through month 36. Delayed treatment in patients receiving sham treatment did not seem to result in the same extent of VA improvement observed in patients originally randomized to ranibizumab. Ocular and systemic safety was generally consistent with the results seen at month 24.

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In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) established macular laser photocoagulation as the standard of care for diabetic macular edema (DME).¹ Despite widespread use of macular laser for the past quarter-century, its mechanism of action still remains largely unknown. In contrast, Folkman's pioneering work in angiogenesis led to the discovery of precise molecular mechanisms that could be specifically targeted in cancer, macular degeneration, and diabetic retinopathy (DR).² The subsequent cloning of vascular endothelial growth factor

(VEGF) A by Ferrara and Henzel³ and the creation of highly specific VEGF antagonists led to targeted therapy for DME with ranibizumab, a monoclonal antibody fragment (Fab, or antigen-binding fragment) that potently inhibits VEGF.⁴ Randomized prospective clinical trials have demonstrated that intravitreal inhibition of VEGF with ranibizumab, given monthly for up to 24 months or less frequently using a variety of as-needed regimens, results in rapid and sustained improvements in vision and retinal anatomy in patients with DME.^{5–9}

RIDE and RISE are phase III, multicenter, randomized clinical trials that enrolled a total of 759 patients with vision loss from DME (best-corrected visual acuity [BCVA], 20/40–20/320 Snellen equivalent, and documented macular edema with central subfield thickness ≥ 275 μm on time-domain optical coherence tomography [OCT]), with the objective of evaluating the efficacy and safety of intravitreal ranibizumab for DME. The 24-month sham-controlled outcomes, previously published in *Ophthalmology*, demonstrated that the response to intravitreal inhibition of VEGF was rapid and substantial.⁷ Compared with the control treatment of sham injections plus macular laser per protocol-specified criteria, statistically significant improvements in BCVA and reductions in retinal thickness were observed on average as early as 7 days after the first ranibizumab injection; these improvements were maintained to 24 months. Furthermore, in the first 2 years of RIDE and RISE, fewer patients treated with ranibizumab experienced significant vision loss (≥ 15 ETDRS letters), and fewer patients treated with ranibizumab developed proliferative DR.¹⁰ The ocular safety of ranibizumab in patients with DME was consistent with previous phase III studies of ranibizumab in DME, age-related macular degeneration, and retinal vein occlusion.^{5,10–14}

Although sham-controlled for only the first 24 months, the RIDE and RISE studies continued after the primary analysis so that additional questions could be addressed. The study design allowed for patients in the sham control group to cross over and receive monthly 0.5 mg ranibizumab injections in the third year. Patients originally randomized to ranibizumab were maintained in a masked fashion on their originally assigned regimens of monthly 0.3 or 0.5 mg. The additional data provide for evaluation of 3 important clinical questions: (1) Are the results seen after 24 months of ranibizumab treatment maintained over a third year of monthly therapy? (2) What is the effect, if any, of delayed initiation of treatment with ranibizumab in the sham crossover group? (3) Which tested dose of ranibizumab should be recommended over the long term for patients with DME, a population that differs from other populations with retinal disease treated with anti-VEGF therapy in having a higher likelihood of bilateral disease⁵ and an elevated risk of cardiovascular events and mortality?^{15,16} In this report, the ongoing efficacy and safety of monthly injections of 0.3 mg and 0.5 mg ranibizumab for DME through 36 months are presented, and the questions are addressed.

Methods

RIDE (registered on ClinicalTrials.gov as NCT00473382; accessed September 15, 2012) and RISE (registered on ClinicalTrials.gov as NCT00473330; accessed September 15, 2012) are methodologically identical, phase III, randomized, multicenter, double-masked, 3-year trials that were sham injection–controlled for the first 2 years. Adults with decreased vision due to center-involved DME and the presence of macular edema documented on OCT were eligible to enroll. Both trials were designed and conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the Health Insurance Portability and Accountability Act. The study

protocols were approved by institutional review boards, ethics committees, or as applicable. All patients provided written informed consent before enrolling as study participants.

The study methods have been reported in detail elsewhere.⁷ Upon completion of the 24-month sham-controlled treatment period (time point for the primary efficacy outcome), sham patients were eligible to cross over to receive treatment with monthly 0.5 mg ranibizumab. Of note, to preserve study masking, all patients were asked if they wanted to cross over, but only patients randomized to sham injection were actually crossed over by the study management computer system. After a protocol amendment in 2010, sham patients who met predefined vision loss and OCT criteria became eligible for early (before month 25) crossover to active treatment with monthly 0.5 mg ranibizumab starting in mid-2010. Patients with study eyes originally randomized to 0.3 or 0.5 mg ranibizumab continued on the monthly schedule to which they originally had been assigned. All patients remained eligible for per-protocol macular laser beginning at month 3 and throughout the duration of the 36-month treatment period on the basis of pre-specified subjective and objective criteria.

Outcomes

The primary efficacy outcome measure was the proportion of patients who gained ≥ 15 ETDRS letters in BCVA score at month 24 compared with baseline. Secondary outcome measures at month 36 were analogous to the 24-month outcomes and included the proportion of patients who had gained ≥ 15 letters from baseline at month 36, mean change from baseline in BCVA score over time, proportion of patients who lost < 15 letters in BCVA score compared with baseline, proportion of patients with BCVA Snellen equivalent of 20/40 or better, and mean change from baseline in central foveal thickness (CFT) over time, as assessed on OCT by the central reading center. Exploratory outcomes included the proportion of patients with OCT CFT ≤ 250 μm and the proportion of patients progressing to proliferative DR.

Analysis

The statistical methods used to analyze the data have been described in detail elsewhere.⁷ Analyses for efficacy end points were based on the intent-to-treat (ITT) population, with patients grouped according to their assigned treatment. The methods used to analyze the 36-month efficacy were the same as those described for the analysis of the 24-month end points; however, because most patients in the sham group crossed over to receive 0.5 mg ranibizumab monthly in the third year of treatment, analyses of 36-month efficacy data consisted of descriptive statistics by treatment group with limited formal comparisons made post hoc. Comparisons of efficacy at month 36 were between patients actively treated for 3 years (with monthly 0.3 or 0.5 mg ranibizumab) versus patients treated with sham for 2 years followed by treatment for up to 1 year with monthly 0.5 mg ranibizumab. Missing data were imputed by last observation carried forward.

Safety analyses were based on the safety-evaluable population, defined as patients who received at least 1 dose of study drug. Patients were grouped according to the treatment received. Patients randomized to sham who inadvertently received treatment with the active study drug were classified in the active drug treatment group. For the sham group, safety outcomes were summarized during the 24-month sham-controlled period and separately for the sham/0.5 mg group during the 36-month study. The sham/0.5 mg group consists of patients who received sham only and patients who crossed over to receive treatment with monthly 0.5 mg ranibizumab in the third year of treatment.

Table 1. Patient Retention and Drug Exposure through Month 36

Category	RIDE			RISE		
	Sham/0.5 mg (N=130)	Ranibizumab		Sham/0.5 mg (N=127)	Ranibizumab	
		0.3 mg (N=125)	0.5 mg (N=127)		0.3 mg (N=125)	0.5 mg (N=125)
On study at month 24, n (%)	108 (83.1)	105 (84.0)	110 (86.6)	102 (80.3)	105 (84.0)	106 (84.8)
On study at month 36, n (%)	102 (78.5)	98 (78.4)	98 (77.2)	86 (67.7)	98 (78.4)	100 (80.0)
Drug exposure (ranibizumab or sham injections)						
Months	25–36*	1–36	1–36	25–36*	1–36	1–36
No. of patients	101 [†]	125	124	89 [†]	125	125
Total No. of injections	1015	3499	3765	881	3724	3562
Per patient						
Mean (SD)	10.0 (1.8)	28.0 (11.2)	30.4 (9.2)	9.9 (2.3)	29.8 (10.2)	28.5 (10.4)
Median	11	34	34	11	35	34

SD = standard deviation.

*Reflects 1 year of ranibizumab 0.5 mg exposure after crossover.

[†]Number of patients originally randomized to sham who crossed over to ranibizumab 0.5 mg.

Results

Patient Disposition

A total of 594 patients (78.3%) received ranibizumab treatment after month 24. At month 36, the proportion of patients remaining in the study varied from 67.7% to 80.0% across the treatment groups (Table 1). Among the 210 sham patients from both studies remaining in the study at month 24 (of 257 originally randomized to sham), a total of 190 (91%) crossed over to active treatment with monthly 0.5 mg ranibizumab. In the 2 studies, 5 sham patients (2.6%) crossed over early, at month 23. The median number of ranibizumab injections received by the patients in the sham and crossover to 0.5 mg group after crossover (between months 25 and 36) was 11, whereas patients originally randomized to ranibizumab received a median of 34 to 35 injections over their 3-year treatment period (Table 1).

Visual Acuity Outcomes

Continued treatment with ranibizumab through month 36 resulted in maintenance of the efficacy outcomes seen at earlier time points. At the 3-year time point, in RIDE, 36.8% of patients receiving 0.3 mg ranibizumab and 40.2% of patients receiving 0.5 mg ranibizumab had gained ≥ 15 ETDRS letters in BCVA from baseline, compared with 19.2% of patients treated with sham/0.5 mg ($P=0.0026$ for comparison of 0.3 mg with sham/0.5 mg, $P=0.0001$ for comparison of 0.5 mg with sham/0.5 mg in post hoc stratified calculations; Fig 1 and Table 2). In RISE, corresponding proportions were 51.2%, 41.6%, and 22.0%, respectively ($P<0.0001$ for comparison of 0.3 mg with sham/0.5 mg, $P=0.0005$ for comparison of 0.5 mg with sham/0.5 mg in post hoc stratified calculations; Fig 1 and Table 2).

Consistent with the maintenance of efficacy measured in terms of ≥ 15 -letter improvement, the average change in BCVA from baseline achieved at month 24 was sustained through month 36 in patients originally randomized to ranibizumab (Fig 2). In RIDE, the mean number of ETDRS letters change from baseline at month 24 versus change from baseline at month 36 in patients randomized to sham, 0.3 mg, and 0.5 mg ranibizumab was 2.3 versus 4.7, 10.9 versus 10.6, and 12.0 versus 11.4, respectively. In RISE, the corresponding numbers were 2.6 versus 4.3, 12.5 versus 14.2, and 11.9 versus 11.0 (Fig 2). The efficacy of the 0.3-mg and

0.5-mg doses of ranibizumab was similar over 36 months, as demonstrated in efficacy data pooled from RIDE and RISE (Fig 3).

Other measures of BCVA outcome also were consistent with the results previously observed at month 24. At month 36, fewer patients originally randomized to ranibizumab had lost ≥ 15 letters from baseline (0.8%–3.9%), compared with patients originally randomized to sham (7.7, 8.7%; Fig 1). Likewise, more patients treated with ranibizumab from the beginning of the study completed with a Snellen BCVA equivalent of 20/40 or better, and fewer patients originally randomized to ranibizumab completed month 36 with a Snellen BCVA of 20/200 or worse (Fig 1 and Table 2).

At baseline, the mean time from first known DME diagnosis to study enrollment was 2.3 to 2.4 years in patients randomized to sham (comparable to the baseline duration of DME in the groups originally randomized to ranibizumab).⁷ Patients in the sham/0.5 mg group thus had DME for approximately 4.5 years before initiation of ranibizumab treatment. Because the sham crossover group had received only 1 year of ranibizumab treatment, a comparison was made to assess vision gains achieved after the initial 12 months of treatment (Table 3). In pooled data from the 2 studies, the mean number of letters gained after 12 months of monthly ranibizumab was 2.8 letters in the sham/0.5 mg group compared with 10.6 and 11.1 letters in the ranibizumab 0.3 mg and 0.5 mg groups, respectively. However, the conclusions that can be drawn from this observation are limited because the groups were no longer fully comparable.

In evaluating the response of the sham group to delayed ranibizumab therapy, it is notable that the average BCVA improvements in the sham group showed relatively little gain after crossover to 0.5 mg ranibizumab after month 24 (2.5 letters at month 24 and 4.5 letters at month 36 in the pooled RIDE/RISE population; Fig 3). Because the primary analysis was ITT, the mean BCVA values may have been affected by the last observation carried forward method of imputing missing data where values from patients who had discontinued from the sham group and did not receive treatment were carried forward. To better understand the potential improvements associated with ranibizumab use after 2 years of sham treatment (plus laser, when indicated, in 70%–74% of sham patients through month 24⁷), an analysis was performed in the subgroup of patients receiving ≥ 1 study drug injection after month 24. Sham patients who received at least 1 study drug injection after month 24 ($n=190$) gained on average 7.5 (RIDE)

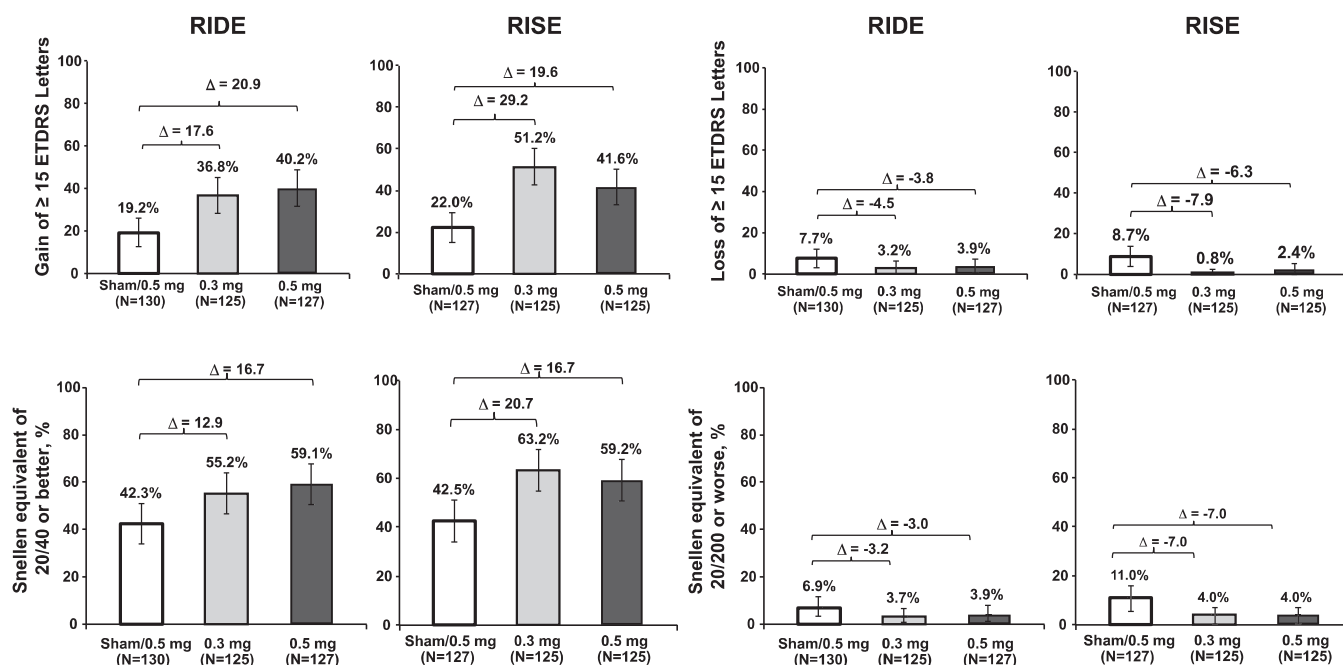


Figure 1. The visual acuity (VA) outcomes at 36 months: percentage of patients who gained ≥ 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline VA at 36 months (top left), percentage of patients who lost ≥ 15 ETDRS letters from baseline VA at 36 months (top right), percentage of patients with vision of the Snellen equivalent of $\geq 20/40$ at 36 months (bottom left), and percentage of patients with vision of the Snellen equivalent of $\leq 20/200$ at 36 months (bottom right). Vertical bars are 95% confidence intervals for the percentage. Differences shown are unadjusted for stratification variables. The last observation carried forward method was used to impute missing data.

and 7.8 (RISE) ETDRS letters from baseline (Fig 4, available at <http://aaojournal.org>). However, this is compared with a 12.1- to 15.6-letters average gain at month 36 in the similar subset of patients originally randomized to ranibizumab who also received at least 1 dose of study drug after month 24 (Fig 3).

Anatomic Outcomes

The mean OCT thickness in the sham group at baseline was 447.4 μm in RIDE and 467.3 μm in RISE, matching that of the originally randomized ranibizumab groups (all >450 μm). All groups at baseline also were well matched with respect to mean duration of DME (1.6–2.4 years) and prior therapy for DME (68.8%–82% in each of the sham, 0.3 mg, and 0.5 mg groups). After 12 months of monthly ranibizumab therapy, the sham/0.5 mg group experienced a reduction (SD) of -98.4 μm (142.8) compared with reductions of -237.9 μm (186.1) and -249.3 μm (194.8) in the 0.3 and 0.5 mg groups, respectively (Table 3).

The average OCT CFT at month 24, after sham treatment but before any ranibizumab exposure, was 292.5 μm in the sham group compared with 463.8 and 478.6 μm at baseline in groups originally randomized to ranibizumab. This may reflect the effect of laser or thinning associated with ongoing retinal cell loss in the diabetic retina. In patients originally randomized to ranibizumab, the significant reductions in CFT from baseline observed at month 24 also were maintained through month 36 (Fig 2). By using the ITT analysis that carried forward the last observation from sham patients who discontinued the study before month 24, OCT reductions after crossover from sham injection to 0.5 mg ranibizumab did not seem to be as great at month 36 as in patients originally randomized to ranibizumab (Fig 2). When considering only the subgroup of patients who received ≥ 1

study drug injection after month 24, observed OCT reductions after sham crossover to ranibizumab were greater than those seen using the ITT analysis, as shown by the steeper decline in the mean OCT CFT curve (Fig 3). Of note, the OCT thicknesses at month 36 were more similar among the groups: the sham/0.5 mg group at month 36 had an average OCT thickness of 194.1 μm , compared with 223.4 μm in the 0.3 mg group and 201.9 μm in the 0.5 mg group.

Consistent with the 24-month outcomes, patients randomized to ranibizumab were more likely to experience improvements in DR severity as measured by the ETDRS retinopathy severity scale and less likely to develop proliferative DR (Table 2). The sham crossover group also demonstrated improvements in DR severity after crossover to ranibizumab therapy (Table 2).

Use of Macular and Panretinal Laser Treatment

Compared with patients who had been randomized to receive ranibizumab, a much greater proportion of sham patients had received macular (19.7%–36% vs. 70% and 74%) or panretinal laser (0%–1.6% vs. 11% and 12.3%) at month 24.⁷ These differences were maintained through 36 months, largely as a result of the difference in laser use during the 24-month sham-controlled portion of the studies. Through 36 months, the proportion of patients in the sham/0.5 mg group who received macular laser at least once over 36 months was 72.3% in RIDE and 74.0% in RISE, compared with 21.3% to 40.8% of patients originally randomized to ranibizumab (Table 2). The proportion of patients in the sham/0.5 mg group who underwent panretinal laser was 13.8% in RIDE and 12.6% in RISE over 36 months compared with 0.0% to 3.2% in patients originally randomized to ranibizumab. The proportions of patients receiving macular laser between months 24 and 36 was

Table 2. Key Efficacy Outcomes at Month 36 in the Intent-to-Treat Population

	RIDE			RISE		
	Sham/0.5 mg (N=130)	Ranibizumab		Sham/0.5 mg (N=127)	Ranibizumab	
		0.3 mg (N=125)	0.5 mg (N=127)		0.3 mg (N=125)	0.5 mg (N=125)
VA Outcomes						
Gaining ≥ 15 ETDRS letters, n (%)	25 (19.2%)	46 (36.8%)	51 (40.2%)	28 (22.0%)	64 (51.2%)	52 (41.6%)
95% CI for percentage	12.5–26.0	28.3–45.3	31.6–48.7	14.8–29.3	42.4–60.0	33.0–50.2
ETDRS letters change from baseline, (SD)	4.7 (13.3)	10.6 (12.9)	11.4 (16.3)	4.3 (14.9)	14.2 (12.8)	11.0 (12.9)
95% CI for mean	2.4–7.0	8.3–12.8	8.6–14.3	1.7–7.0	12.0–16.5	8.8–13.3
Gaining ≥ 10 ETDRS letters, n (%)	43 (33.1%)	71 (56.8%)	80 (63.0%)	49 (38.6%)	87 (69.6%)	72 (57.6%)
95% CI for percentage	25.0–41.2	48.1–65.5	54.6–71.4	30.1–47.0	61.5–77.7	48.9–66.3
Loss of < 15 ETDRS letters, n (%)	120 (92.3%)	121 (96.8%)	122 (96.1%)	116 (91.3%)	124 (99.2%)	122 (97.6%)
95% CI for percentage	87.7–96.9	93.7–99.9	92.7–99.4	86.4–96.2	97.6–100	94.9–100
Snellen $\geq 20/40$, n (%)	55 (42.3%)	69 (55.2%)	75 (59.1%)	54 (42.5%)	79 (63.2%)	74 (59.2%)
95% CI for percentage	33.8–50.8	46.5–63.9	50.5–67.6	33.9–51.1	54.7–71.7	50.6–67.8
Snellen $\leq 20/200$, n (%)	9 (6.9%)	4 (3.2%)	5 (3.9%)	14 (11%)	5 (4.0%)	5 (4.0%)
95% CI for percentage	2.6–11.3	0.1–6.3	0.6–7.3	5.6–16.5	0.6–7.4	0.6–7.4
Anatomic Outcomes						
Mean change in CFT from baseline (SD), μm	–213.2 (193.5)	–261.8 (180.8)	–266.7 (207.8)	–200.1 (215.6)	–261.2 (196.5)	–269.1 (178.9)
95% CI for percentage	–246.8 to –179.6	–293.8 to –229.8	–303.2 to –230.2	–238.0 to –162.3	–296.0 to –226.4	–300.8 to –237.4
≥ 3 -step progression on ETDRS scale, n (%)*	4 (3.2%)	1 (0.9%)	1 (0.8%)	5 (4.3%)	2 (1.7%)	2 (1.7%)
95% CI for percentage	0.1–6.3	0.0–2.5	0.0–2.5	0.6–8.1	0.0–4.1	0.0–4.1
≥ 2 step progression on ETDRS scale, n (%)*	11 (8.9%)	1 (0.9%)	2 (1.7%)	11 (9.6%)	5 (4.3%)	5 (4.3%)
95% CI for percentage	3.9–13.9	0.0–2.5	0.0–4.0	4.2–14.9	0.6–7.9	0.6–8.1
≥ 3 -step improvement on ETDRS scale, n (%)*	5 (4.0%)	17 (14.5%)	18 (15.1%)	3 (2.6%)	18 (15.4%)	13 (11.3%)
95% CI for percentage	0.6–7.5	8.1–20.9	8.7–21.6	0.0–5.5	8.8–21.9	5.5–17.1
≥ 2 -step improvement on ETDRS scale, n (%)*	29 (23.4%)	46 (39.3%)	45 (37.8%)	28 (24.3%)	45 (38.5%)	47 (40.9%)
95% CI for percentage	15.9–30.8	30.5–48.2	29.1–46.5	16.5–32.2	29.6–47.3	31.9–49.9
Progression to PDR by ophthalmoscopy, n (%)	18 (13.8%)	6 (4.8%)	7 (5.5%)	22 (17.3%)	3 (2.4%)	9 (7.2%)
95% CI for percentage	7.9–19.8	1.1–8.5	1.5–9.5	10.7–23.9	0.0–5.1	2.7–11.7
Laser Treatment						
Patients who received macular laser, n (%)	94 (72.3%)	46 (36.8%)	27 (21.3%)	94 (74.0%)	51 (40.8%)	47 (37.6%)
95% CI for percentage	64.6–80.0	28.3–45.3	14.1–28.4	66.4–81.6	32.2–49.4	29.1–46.1%
Patients who received PRP laser, n (%)	18 (13.8%)	4 (3.2%)	3 (2.4%)	16 (12.6%)	0	3 (2.4%)
95% CI for percentage	7.9–19.8	0.1–6.3	0.0–5.0	6.8–18.4	0.0–0.0	0.0–5.1

CFT = central foveal thickness; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; VA = visual acuity.

The last observation carried forward method was used to impute missing data. Stratification variables in stratified analyses: baseline VA (≤ 55 or > 55 letters), baseline hemoglobin A1c ($\leq 8\%$, $> 8\%$), and prior treatment for DME (yes, no).

*N = 124, 117, and 119 (RIDE) and 115, 117, and 115 (RISE) for sham/0.5 mg, 0.3 mg, and 0.5 mg groups, respectively.

5.5% to 9.4% across all treatment groups among patients who received at least 1 dose of study drug after month 24. Likewise, the proportions of patients who had received at least 1 dose of study drug after month 24 and underwent panretinal laser between months 25 and 36 was 0% to 2.2% among all groups.

Safety Outcomes

Safety data collected through month 36 were evaluated to assess whether the longer-term safety profile of ranibizumab

was consistent with that initially observed and to further assess the relative long-term safety of ongoing monthly 0.3 mg and 0.5 mg ranibizumab doses. Because the majority of patients in the sham group crossed over to monthly 0.5 mg ranibizumab dosing after month 24 and received 12 months of exposure compared with 36 months of exposure in the originally randomized groups, comparisons between the groups need to be interpreted with caution because the populations are not directly comparable with respect to the duration of ranibizumab exposure.

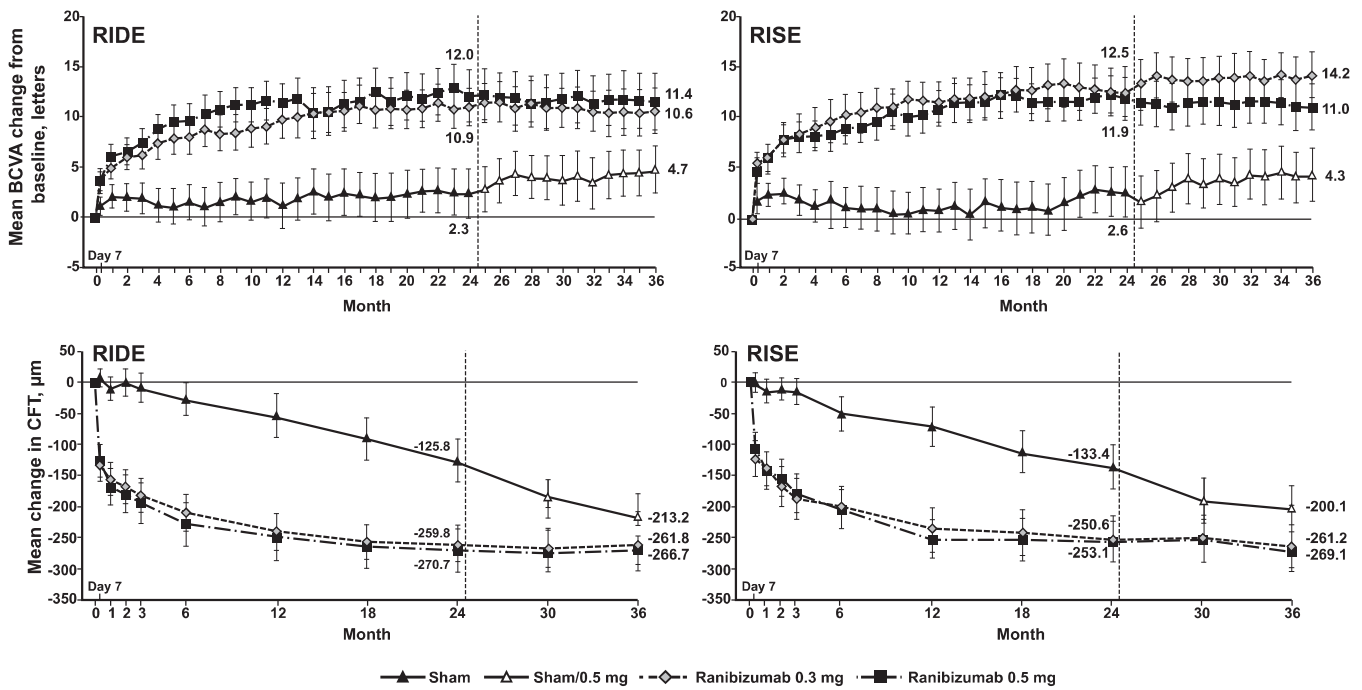


Figure 2. Mean change in best-corrected visual acuity (BCVA) and central foveal thickness (CFT) from baseline over time. Vertical bars are 95% confidence intervals. Missing data were imputed by last observation carried forward.

Ocular Safety

Key study eye ocular safety data are summarized in Table 4 (available at <http://aaojournal.org>). The ocular safety profile was consistent with the sham-controlled safety observations from the 24-month analysis. In particular, rates of procedure-related serious adverse events (SAEs), such as endophthalmitis and traumatic cataract, remained low. The total number of patients in the ranibizumab treatment groups experiencing endophthalmitis or traumatic cataract in the study eye over the 36-month treatment period across both studies was 6 (1.2%) and 4 (0.8%), respectively. The per-injection rate of endophthalmitis was approximately 0.06%, whereas the per-injection rate of traumatic cataract was 0.03% (Table 5, available at <http://aaojournal.org>). Similar proportions of the patients randomized to ranibizumab reported an adverse event (AE) of increased intraocular pressure at months 24 and 36 (Table 4, available at <http://aaojournal.org>). The mean pre-dose intraocular pressure in the study eye at month 36 in the sham and crossover to 0.5 mg, 0.3 mg, and 0.5 mg groups was 15.4 mmHg, 15.5 mmHg, and 14.9 mmHg, respectively.

Systemic Safety

The long-term systemic safety of ranibizumab in DME was evaluated using 2 methods. As in previous studies of intravitreal ranibizumab across several retinal vascular diseases, we first assessed rates of arterial thromboembolic events (ATEs) using the Antiplatelet Trialists' Collaboration (APTC) classification,¹⁷ which is based on a specific and well-defined spectrum of ATE AEs: vascular deaths (including deaths of unknown cause), nonfatal myocardial infarction, and nonfatal stroke (Table 6). Overall APTC-classified AEs occurred in 7.2%, 10.8%, and 10.4% of patients in the sham/0.5 mg, 0.3 mg, and 0.5 mg groups, respectively. Among APTC-classified events occurring over 36 months, deaths of vascular and unknown causes occurred in 2%, 3.6%, and 3.6% of patients in the sham/0.5 mg, 0.3 mg, and 0.5 mg

ranibizumab groups, respectively. The overall incidence of deaths through 36 months, including deaths from nonvascular causes, was 4.4% (11 patients) in the monthly 0.3 mg group, 6.4% (16 patients) in the 0.5 mg group, and 2.8% (7 patients) in the sham/0.5 mg group (Table 7, available at <http://aaojournal.org>). Causes of death, listed in Table 7, were mostly consistent with those typical of patients with advanced complications of diabetes.¹⁸ Rates of stroke over 3 years were higher in the 0.5 mg group (12 [4.8%]) compared with the 0.3 mg group (5 [2.0%]) or sham/0.5 mg group (6 [2.4%]) (Table 6). The incidence of myocardial infarction through month 36 was 18 (7.2%) in the 0.3 mg group and 9 (3.6%) in the 0.5 mg group (Table 6).

Although the APTC classification system provides useful insight into the systemic safety of intraocular anti-VEGF therapy, a more thorough understanding of systemic anti-VEGF safety has developed over the last several years, primarily because of the use of intravenous agents in oncology. As clinical experience with systemic anti-VEGF agents has grown, additional types and categories of systemic AEs potentially associated with the use of systemic anti-VEGF treatment have been identified. These are considered "class" effects related to systemic VEGF inhibition.¹⁹ Categories of these anti-VEGF class-related AEs include hypertension, proteinuria, arterial and venous thromboembolic events, bleeding/hemorrhage (central nervous system and cerebrovascular, non-central nervous system), congestive heart failure, fistulae, gastrointestinal perforation, and wound-healing complications. Categorizing SAEs using this second broader approach demonstrated that the overall incidence of SAEs potentially related to systemic VEGF inhibition was higher in patients who received 0.5 mg ranibizumab compared with 0.3 mg ranibizumab or sham/0.5 mg: 49 of 249 (19.7%) versus 42 of 250 (16.8%) and 33 of 251 (13.1%) (Table 8, available at <http://aaojournal.org>). The incidence of several categories (central nervous system and cerebrovascular hemorrhage, congestive heart failure, hypertension, gastrointestinal perforation, proteinuria, and wound-healing complications) appeared to increase in a dose-dependent fashion in patients with

RIDE and RISE Pooled

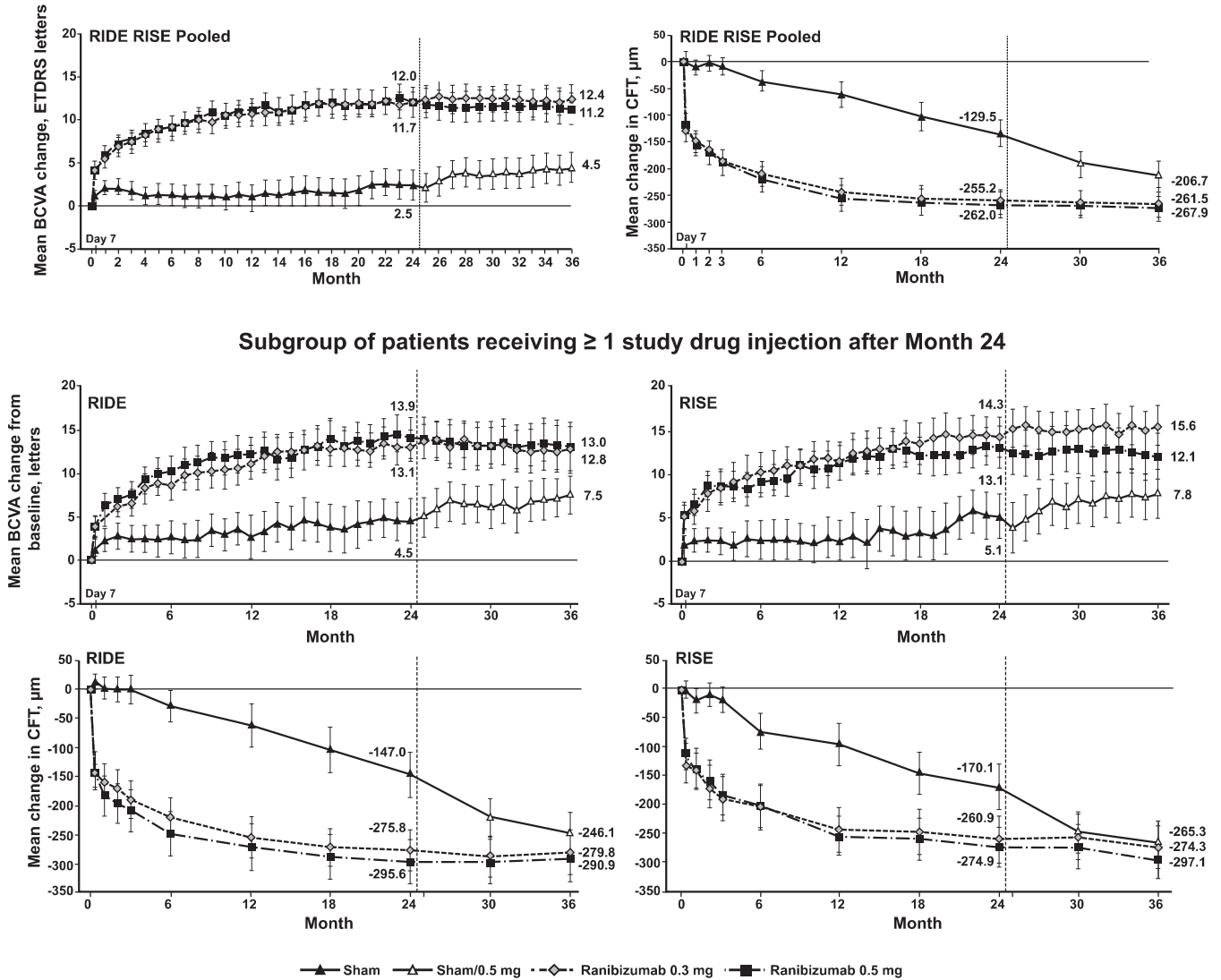


Figure 3. Mean change in best-corrected visual acuity (BCVA) and central foveal thickness (CFT) from baseline over time in the RIDE and RISE pooled population and the subgroup of patients receiving ≥ 1 study drug injection after month 24. Vertical bars are 95% confidence intervals. Missing data were imputed by last observation carried forward. ETDRS = Early Treatment Diabetic Retinopathy Study.

DME treated with intravitreal ranibizumab, although in each of the latter 3 categories, only 1 SAE in the 0.5 mg group was observed.

Discussion

The 36-month results from the RIDE and RISE studies demonstrate that the rapid and sustained efficacy of ranibizumab in patients with DME initially observed at 2 years is maintained over an additional third year of continued monthly treatment. A gain of ≥ 15 letters from baseline was experienced by 36.8% to 51.2% of ranibizumab-treated patients, and the incidence of further vision loss was significantly reduced in ranibizumab-treated eyes. Poor BCVA outcomes (such as BCVA worse than by Snellen $<20/200$) occurred in fewer patients initially treated with ranibizumab, confirming the long-term abilities of ranibizumab to improve

vision and prevent significant vision loss in patients with DME. Reductions in retinal edema on OCT and improvements in DR severity also were maintained through 36 months.

The 36-month results provide important clinical insights into treatment outcomes after a 24-month delay in initiation of ranibizumab therapy in the sham crossover group. The relatively limited improvements in vision in this group, compared with the groups initially treated with ranibizumab, suggest that chronic retinal edema (for an average of 4.5 years before ranibizumab therapy) may result in a certain amount of potential vision gain being irreversibly lost. Retinal atrophy due to chronic edema may provide an explanation for this finding. Although OCT measurements in the sham crossover group after ranibizumab treatment showed a reduction in absolute CFT to a mean value of 190 μm (approximately 20 μm less than that observed after treatment in the

Table 3. Changes in the Study Eye at 12 Months After the First Dose of Ranibizumab for Key Efficacy Outcomes (RIDE and RISE Pooled)

	Sham and Crossover to 0.5 mg (N=191)	Ranibizumab	
		0.3 mg (N=250)	0.5 mg (N=252)
Total No. of ranibizumab injections by first 12-mo ranibizumab treatment, mean (SD)*	10.0 (2.0)	10.6 (2.6)	10.9 (2.2)
BCVA (ETDRS letters)			
Before ranibizumab treatment,† mean (SD)	62.0 (15.3)	56.1 (12.2)	56.9 (11.6)
12-mo after ranibizumab treatment, mean (SD)	64.8 (14.8)	67.8 (15.0)	68.9 (14.1)
Change from before treatment, mean (SD)	2.8 (9.8)	10.6 (10.6)	11.1 (10.1)
Gain of ≥15 letters from before treatment, n (%)	14 (7.3)	81 (32.4)	80 (31.7)
CFT (μm), mean (SD)			
Before ranibizumab treatment†	292.5 (167.2)	478.6 (162.3)	463.8 (160.4)
12-mo after ranibizumab treatment	194.1 (118.2)	223.4 (136.2)	201.9 (107.3)
Change from before treatment	-98.4 (142.8)	-237.9 (186.1)	-249.3 (194.8)

BCVA = best-corrected visual acuity; CFT = central foveal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.

*Actual treatment duration for sham crossover groups is 11 months.

†Month 24 for the sham/0.5 mg group, baseline for the 0.3 mg, and 0.5 mg groups.

groups originally randomized to ranibizumab), the average improvement in BCVA was considerably smaller than that achieved in the originally treated cohorts. This outcome may represent the effect of several potential factors: neural cell loss over time in the diabetic retina, compounded by the effects of chronic edema (including neuronal retinal damage, retinal pigment epithelium pigmentation, and/or subretinal fibrosis), additional structural changes induced by repeated macular laser, and/or the natural history of DR.

In the phase III trials of ranibizumab in the treatment of age-related macular degeneration and retinal vein occlusion, there appeared to be a dose response curve favoring 0.5 mg over 0.3 mg ranibizumab for optimum efficacy. However, in the pooled data from the RIDE and RISE trials, efficacy was equivalent between the 0.3-mg and 0.5-mg doses. The comparative profile of the 2 doses of ranibizumab in DME was assessed using

a structured, systematic approach based on the Benefit Risk Action Team framework (Fig 4A–C, available at <http://aaojournal.org>).^{20,21} These figures help demonstrate that, although concentrations of ranibizumab in the systemic circulation are lower than vitreous concentrations, the use of 0.3 mg may reduce risks potentially related to systemic VEGF suppression while still maintaining optimal efficacy. This may be particularly appropriate in the management of DME because not only do 40% to 50% of patients with DME have bilateral disease requiring contemporaneous treatment,²² but also diabetic patients have an underlying increased risk of mortality and cardiovascular disease, including stroke and silent myocardial ischemia.²³ In light of these considerations, Genentech recommended the 0.3-mg dose; the US Food and Drug Administration ultimately approved use of 0.3 mg ranibizumab for DME on August 10, 2012.

Table 6. Antiplatelet Trialists' Collaboration (APTC) Events through Month 36 (Safety-Evaluable Population)

Category/Event	Sham Months 0–24 (N=250)	Sham/0.5 mg* Months 0–36 (N=251†)	Ranibizumab	
			0.3 mg Months 0–36 (N=250)	0.5 mg Months 0–36 (N=249)
Total APTC-classified events	13 (5.2%)	18 (7.2%)	27 (10.8%)	26 (10.4%)
Deaths				
Vascular	3 (1.2%)	7 (2.8%)	11 (4.4%)	16 (6.4%)
Nonvascular	0	5 (2.0%)	8 (3.2%)	8 (3.2%)
Unknown cause	0	2 (0.8%)	2 (0.8%)	7 (2.8%)
Myocardial infarction				
Fatal	9 (3.6%)	13 (5.2%)	18 (7.2%)	9 (3.6%)
Nonfatal	2 (0.8%)	4 (1.6%)	3 (1.2%)	1 (0.4%)
Stroke (CVA)				
Fatal	7 (2.8%)	9 (3.6%)	15 (6.0%)	8 (3.2%)
Nonfatal	4 (1.6%)	6 (2.4%)	5 (2.0%)	12 (4.8%)
Fatal	1 (0.4%)	2 (0.8%)	1 (0.4%)	3 (1.2%)
Nonfatal	3 (1.2%)	4 (1.6%)	4 (1.6%)	9 (3.6%)

CVA = cerebrovascular accident.

APTC events include vascular deaths, deaths of unknown cause, nonfatal myocardial infarctions, and nonfatal strokes.

*Patients initially randomized to sham including those who crossed over to ranibizumab 0.5 mg during year 3. There is no pure sham control group at month 36, so it is not valid to compare the sham groups with the ranibizumab treatment arms.

†One sham patient received 0.5 mg ranibizumab starting at month 23. This patient was classified in the ranibizumab 0.5 mg group for the 24-month analyses per the prespecified definition of treatment groups for safety analyses. For the 36-month analyses, it was determined that this patient crossed over early and thus was classified in the sham/0.5 mg crossover group.

Study Limitations

As with all clinical trials, certain limitations exist in extrapolating the RIDE and RISE study observations to routine clinical practice. One potential limitation is that some patients discontinued their participation, with 67.7% to 80.0% of patients completing month 36 across the various treatment groups. However, interpretation of the study results did not change when performing sensitivity analyses using a variety of methods for missing data imputation (data not shown). A more important potential limitation is that ranibizumab was administered on a continuous monthly dosing schedule, which may optimize efficacy but not be practical for many patients with DME. However, additional large phase III and phase III-scope studies using 0.5 mg with less than monthly dosing have provided important additional data on the efficacy and safety of ranibizumab in DME.^{5,6,8,24} For example, in the DRCRnet study of ranibizumab, macular laser, or triamcinolone for DME, significant visual acuity benefits were observed with a median of 8 to 9 ranibizumab injections in the first year, 2 to 3 injections in the second year, and 1 to 2 injections in the third year.^{5,9,14} In the RESTORE phase III study of DME, which compared 0.5 mg ranibizumab (with individualized pro re nata dosing) with or without macular laser with laser alone, significant improvements in BCVA and OCT outcomes were observed with ranibizumab with an average of 6.8 to 7.0 injections over 12 months.⁶ Mean BCVA gain was maintained or improved through 36 months.²⁵ These studies also provide insights into the systemic safety of ranibizumab in separate DME populations enrolled and studied contemporaneously with RIDE and RISE. No systemic safety imbalances emerged with 0.5 mg ranibizumab dosed on a less than monthly basis compared with control in the DRCRnet Protocol I or RESTORE studies. In DRCRnet Protocol I, patients in the sham group experienced higher rates of APTC-classified systemic events than patients receiving ranibizumab.¹⁴ In RESTORE, no meaningful differences in the number of ATEs or other systemic events potentially related to VEGF inhibition were observed between the ranibizumab and laser control groups, although patients with a history of stroke or transient ischemic attack were excluded from this study (Abstract PO532. Annual Meeting of the American Academy of Ophthalmology, November 10–13, 2012, Chicago, IL).⁶ Forthcoming data from the open-label extension phase of RIDE and RISE, in which ranibizumab is administered less frequently, will also contribute information on this question.

Another limitation is that it is unknown whether the results with ranibizumab for the management of DME as demonstrated in RIDE and RISE are applicable to other anti-VEGF agents. The various commonly used intravitreal anti-VEGFs have different molecular characteristics, leading to differences in potency, systemic clearance, and systemic VEGF inhibition.²⁵ To help address these questions, a comparative study of 3 anti-VEGF agents for DME is now being recruited by the Diabetic Retinopathy Clinical Research Network (NCT01627249).²⁶

In conclusion, the 36-month results of RIDE and RISE confirm the long-term efficacy and safety of ranibizumab in

DME. These data further highlight the importance of expanding DR screening programs and greater awareness of and adherence to already-recommended national screening guidelines. Recent reports suggest that 93% of patients with DR and 63% of patients with vision-threatening DR were unaware they had DR; 83% with vision-threatening DR had no scheduled follow-up eye examination (Abstract 1287/A37. Association for Research in Vision and Ophthalmology Annual Meeting, May 1–5, 2011, Fort Lauderdale, FL). Prompt treatment with anti-VEGF therapy at the time of initial diagnosis may avoid the considerable visual morbidity associated with chronic DME. Ophthalmologists now have considerable evidence from multiple clinical studies demonstrating that intraocular anti-VEGF therapy with ranibizumab offers a new and substantially better approach to the treatment of DME, one of the leading causes of vision loss in working-aged adults, and thus has set a new standard of care for DME.

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