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 (~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.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

Ophthalmology 2013;120:2013-2022

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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 Henzel[3] 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 disease[5] 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 0.3 mg (N 125)	Ranibizumab 0.5 mg (N 127)	Sham/0.5 mg (N 127)	Ranibizumab 0.3 mg (N 125)	Ranibizumab 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 ranibi zumab 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 rani bizumab therapy, it is notable that the average BCVA improve ments 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 24[7]), 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)

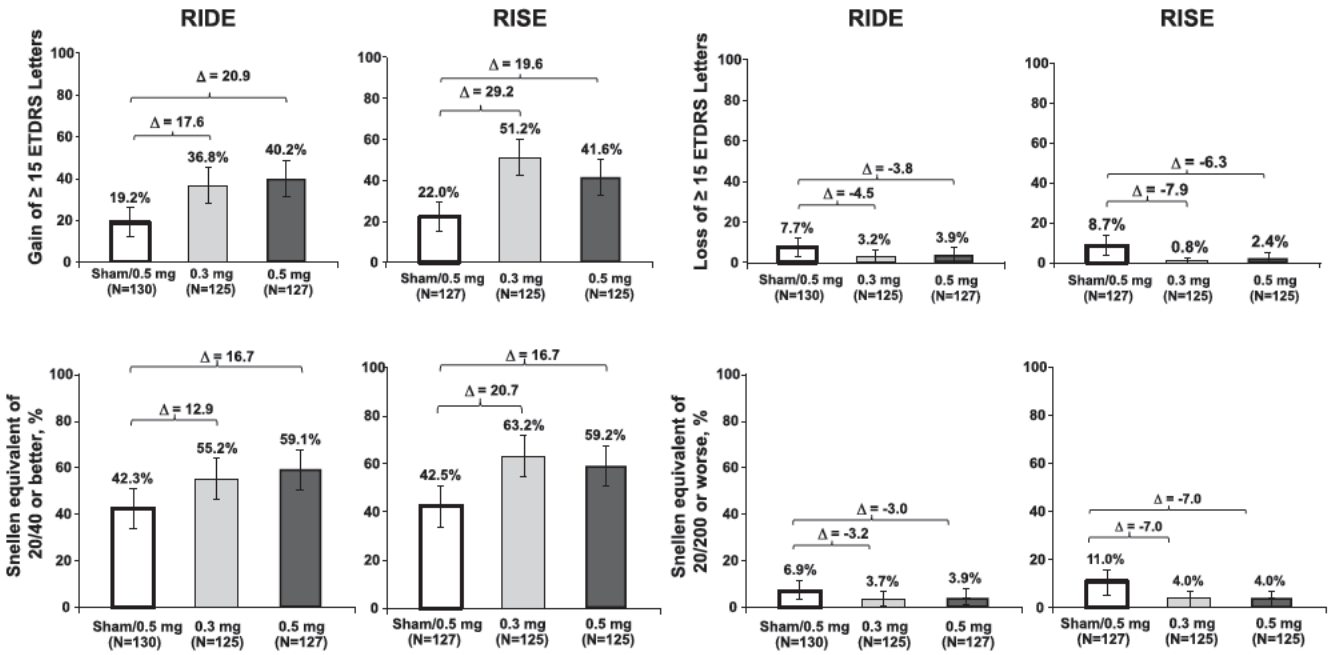

Figure 1. The visual acuity (VA) outcomes at 36 months: percentage of patients who gained ≥15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline VA at 36 months (top left), percentage of patients who lost ≥15 ETDRS letters from baseline VA at 36 months (top right), percentage of patients with vision of the Snellen equivalent of ≥20/40 at 36 months (bottom left), and percentage of patients with vision of the Snellen equivalent of ≤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 rani bizumab, 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		
		Ranibizumab			*Ranibizumab*	
	Sham/0.5 mg (N=130)	0.3 mg (N=125)	0.5 mg (N=127)	Sham/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 ≥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 ≤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 (≤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.

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