Effect of Ranibizumab on the Decision to Drive and Vision Function Relevant to Driving in Patients With Diabetic Macular Edema
Report From RESTORE, RIDE, and RISE Trials

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IMPORTANCE  The potential effect of treatments for diabetic macular edema (DME) on driving should be of value to patients and clinicians, such as ophthalmologists and other physicians, who treat patients with diabetes mellitus.

OBJECTIVE  To determine the effect of ranibizumab on driving and patient-reported vision function relevant to driving among patients with DME.

DESIGN, SETTING, AND PARTICIPANTS  This exploratory post hoc analysis was conducted between October 1, 2011, and July 25, 2015, based on deidentified data from phase 3, multicenter, randomized clinical trials (RIDE, RISE, and RESTORE trials). Individuals assigned randomly to monthly sham, 0.3-mg ranibizumab, or 0.5-mg ranibizumab in RIDE and RISE or to macular laser, macular laser plus 0.5-mg ranibizumab (3-monthly doses, then as needed), or 0.5-mg (3-monthly doses, then as needed) in RESTORE.

MAIN OUTCOMES AND MEASURES  Driving items from the National Eye Institute (NEI) Visual Function Questionnaire–25 (VFQ-25) at baseline through 24 months in RIDE/RISE (pooled) and through 12 months in RESTORE.

RESULTS  A total of 71.2% of 753 patients in RIDE/RISE and 50.4% of 345 patients in RESTORE reported driving at baseline; at least 55% reported still driving at follow-up. Among those not driving at baseline in RIDE/RISE, at 12 months, 7.0% (95% CI, −5.0 to 19.0) more in the 0.3-mg group and 14.4% (95% CI, 1.1 to 27.7) more in the 0.5-mg group vs the sham group reported driving. Among those not driving at baseline in RESTORE, at 12 months, 4.2% (95% CI, −7.7 to 16.1) more in the laser plus 0.5-mg group and 0.9% (95% CI, −10.3 to 12.1) more in the 0.5-mg group vs the laser group reported driving. Although balanced at baseline across treatment groups for RESTORE and RIDE/RISE, the proportion of patients with best-corrected visual acuity typically required for an unrestricted license (20/40 or better in at least 1 eye) appeared greater at month 12 in the ranibizumab groups (77 of 80 [96.3%] for 0.5 mg + laser and 91 of 93 [97.8%] for 0.5 mg) vs laser (71 of 79 [89.9%]) in RESTORE, and at months 12 (112 of 123 [91.1%] and 136 of 137 [99.3%] in 0.3- and 0.5-mg groups, respectively) and 24 (113 of 123 [91.9%] and 135 of 137 [98.5%] in the 0.3- and 0.5-mg groups, respectively) vs sham (121 of 147 [82.3%] and 122 of 147 [83.0%]) in RIDE/RISE.

CONCLUSIONS AND RELEVANCE  These results suggest that 12 months after initiating ranibizumab for vision impairment from center-involved DME, patients not driving at initiation of treatment are more likely to report driving and have driving-eligible visual acuity of 20/40 or better in the better-seeing eye than those treated with sham or laser.

TRIAL REGISTRATION  clinicaltrials.gov Identifier: RESTORE: NCT00687804; RIDE: NCT00473382; and RISE: NCT00473330
Clinical studies have demonstrated the ability of ranibizumab, alone or in combination with laser, compared with observation alone or macular laser alone to reduce the risk for substantial visual acuity (VA) loss and to improve the chance of substantial VA gain in the eyes of patients with diabetic macular edema (DME). However, the VA in 1 eye, as measured in these clinical trials, does not necessarily reflect the full extent of functional impairment caused by DME in both eyes. The decision to drive based on an individual’s vision, or his or her perception of driving ability, is an important measure of one’s capacity for independence and is dependent, in part, on VA. These decisions or perceptions may differ across cultures or environments (eg, cities with public transportation vs rural areas where driving is often the only available mode of transportation).

Therefore, we analyzed several outcomes across clinical sites from 5 continents to evaluate the impact of ranibizumab on driving in patients with DME involving the center of the macula and causing vision impairment, including the following: (1) reporting whether one drives using the National Eye Institute (NEI) Visual Function Questionnaire–25 (VFQ-25) and (2) a best-corrected VA letter score of 70 or greater (approximately equivalent to a VA of 20/40 or better) in at least 1 eye. That level of VA in at least 1 eye is required to obtain an unrestricted individual driver’s license in 45 states in the United States. A VA of 20/40 or better in each eye is necessary to obtain a commercial driver’s license in all but 3 US states. Similarly, in most European countries, drivers must have a binocular VA of 0.5 (20/40 feet, 6/12, or 5.10 m).

Methods

Trials

Detailed methods for the RESTORE (12-Month Core Study to Assess the Efficacy and Safety of Ranibizumab [Intravitreal Injections] in Patients With Visual Impairment Due to Diabetic Macular Edema and a 24 Month Open-label Extension Study), RIDE (Ranibizumab Injection in Subjects With Clinically Significant Macular Edema [ME] With Center Involvement Secondary to Diabetes Mellitus), and RISE (Ranibizumab Injection in Subjects With Clinically Significant Macular Edema [ME] With Center Involvement Secondary to Diabetes Mellitus) trials relevant to VA, as well as NEI VFQ-25 outcomes, have been reported previously. Briefly, these trials were phase 3, multicenter, randomized, double-masked clinical trials. In RESTORE, patients with DME in at least 1 eye that was eligible for laser treatment in the opinion of the investigator and a VA letter score between 78 and 39, inclusive (approximate Snellen equivalent 20/32 to 20/160), were assigned randomly to ranibizumab monotherapy (injections with ranibizumab, 0.5 mg, plus sham laser [n = 116]), ranibizumab combination therapy (ranibizumab, 0.5 mg, plus macular laser [n = 118]), or laser monotherapy (macular laser with sham injection [n = 111]), with follow-up every month up to 1 year. In the ranibizumab arms, treatment was given monthly until stable VA was reached and then as needed at monthly visits if best-corrected VA decreased due to DME progression. After 1 year, all study eyes could receive ranibizumab, therefore, comparisons with the control (laser-only) arm are reported through 1 year.

In RIDE and RISE, patients were assigned randomly to sham injection, 0.3-mg ranibizumab, or 0.5-mg ranibizumab. Macular laser was permitted in any treatment arm starting at the 3-month visit if central foveal thickness was 250 μm or greater with a less than 50-μm change from the prior month with no prior macular laser in the previous 3 months and assessment by the evaluating physician. After 2 years, all study eyes could receive ranibizumab and, therefore, comparisons with the control (sham) arm are reported through 2 years.

In all trials, study treatment was administered to only 1 eligible study eye per patient. The fellow eye was treated according to standard care, which did not include antivascular endothelial growth factor treatment. The study was conducted according to the ethical principles of the Declaration of Helsinki. Approval for these trials, which included approval for the analysis of the data for this report, was obtained from independent ethics committees or institutional review boards for each clinical center in RESTORE and by an institutional review board at each study site in RIDE and RISE before the enrollment of patients. In RIDE and RISE, all study sites complied with the requirements of the Health Insurance Portability and Accountability Act. Written consent was obtained from all participants.

The primary efficacy end point of both RIDE and RISE was the proportion of patients who gained 15 or more letters of VA from baseline at 24 months. The primary efficacy end point of RESTORE was the mean change in best-corrected VA letter score from baseline to month 1 through month 12. The NEI VFQ-25 was a secondary outcome for all 3 trials, and the analyses performed for this study were considered post hoc exploratory outcomes.

NEI VFQ-25

The NEI VFQ-25 evaluates vision-related function and quality of life in several domains assessed on a 100-point scale, with
higher values representing better function. This report focused on an analysis of the driving domain (the driving subscale score, including driving status) assessed by item 15 of the NEI VFQ-25 (“Are you currently driving, at least once in a while?”). The NEI VFQ-25 questionnaire was administered to all patients at baseline and at follow-up months 3 and 12, and, in RIDE and RISE, at 6, 18, and 24 months; validated translations were used in each country. Some of the overall subscale results (but not individual items within that subscale) have been reported previously. Only driving-related questions (i.e., 15, 15a, 15b, 15c, 16, and 16a) were included in these analyses. The driving subscale comprises 15c, 16, and 16a.

Data and Statistical Analyses
A sensitivity analysis confirmed that the magnitude and direction of changes from baseline were similar with or without the last observation carried forward (data not shown). For RIDE and RISE, the baseline characteristics and main outcomes were similar enough to warrant combining the outcomes from those 2 trials for this post hoc analysis (eTable 1 in the Supplement). For all trials, the analysis of individual NEI VFQ-25 driving-related items used observed patient responses; no imputation of missing responses was carried out.

As these were exploratory data, all results were reported as trends and the direction of the data. None of the hypotheses explored were determined a priori so 1- or 2-sided tests for P values were not determined. A 95% CI was provided following numerous results to give an estimate of the variability of the data. As part of a post hoc analysis, study participants were classified into subgroups by VA in the better-seeing eye. A better-seeing study eye was defined as a study eye with baseline VA better than that of the fellow eye by 5 or more letters if baseline VA letter score in both eyes was at least 50 (Snellen equivalent approximately 20/100) or better than that of the fellow eye by 10 or more letters if baseline VA letter score in 1 or both eyes was less than 50. Similarly, a better-seeing fellow eye was defined as a fellow eye with baseline VA better than that of the study eye by 5 or more letters if baseline VA letter score in both eyes was at least 50 or better than that of the study eye by 10 or more letters if baseline VA letter score in 1 or both eyes was less than 50. A better-seeing eye refers to either a better-seeing study eye or a better-seeing fellow eye.

Results

Patient Baseline Characteristics
Selected baseline characteristics of patients that were considered to potentially affect the analyses from the 3 clinical trials for this report appeared similar, with the exceptions of the following: baseline VA of the study eye, which appeared to be between 5 and 10 letters better in RESTORE (depending on the treatment arm); the proportion of patients driving at baseline, which appeared to be greater in RIDE and RISE; and the proportion of patients with VA letter score of 70 or greater (RIDE and RISE) or 68 or greater (RESTORE) (approximate Snellen equivalent 20/40 or better), which appeared to be higher in RESTORE (Table 1). In RIDE, the study eye was the better-seeing eye in 17.1%, 28.0%, and 17.3% of the sham, 0.3-mg ranibizumab, and 0.5-mg ranibizumab groups, respectively. In RISE, the study eye was the better-seeing eye in 12.6%, 16.0%, and 12.9% of the sham, 0.3-mg ranibizumab, and 0.5-mg ranibizumab groups, respectively. In RESTORE, the study eye was the better-seeing eye in 18.2%, 20.3%, and 25.2% of the laser, 0.5-mg ranibizumab plus laser, and 0.5-mg ranibizumab groups, respectively. The baseline NEI VFQ-25 driving subscale score varied between 54.2 and 69.1 across the 3 different treatment arms across the 3 trials.

In pooled RIDE/RISE data, 69.8%, 72.4%, and 71.3% of patients in the sham, 0.3-mg ranibizumab, and 0.5-mg ranibizumab groups, respectively, were driving at baseline (Table 1). In RESTORE, 46.9%, 53.9%, and 50.9% of patients in the laser, 0.5-mg ranibizumab plus laser, and 0.5-mg ranibizumab groups, respectively, were driving at baseline (Table 1). The trials appeared balanced at baseline with respect to factors that could affect the outcomes evaluated, including driving status based on the NEI VFQ-25 (eTable 2 in the Supplement; separate data for RIDE and RISE can be found in eTable 3 in the Supplement).

The proportion of patients who completed the NEI VFQ-25 driving subscale at month 12 was greater in pooled RIDE/RISE (67%-73%) than in RESTORE (54%-57%) (eTable 4 in the Supplement). Separate results for the proportions of patients in RIDE and RISE who completed the driving subscale of the NEI VFQ-25 at months 12 and 24 are shown in eTable 5 in the Supplement. Driving subscale scores appeared greater for ranibizumab treatment groups at 12 months for pooled RIDE/RISE and RESTORE and at 24 months for pooled RIDE/RISE (Figure).

Effect of Ranibizumab on Patient-Reported Driving
More than 86% of patients who reported driving at baseline reported driving at 12 months in RESTORE and at 12 and 24 months in RIDE and RISE, regardless of treatment assignment at baseline (eTable 6 in the Supplement; separate data for RIDE and RISE are presented in eTable 7 in the Supplement). However, among patients who reported not driving at baseline, the difference in the change in proportion of patients in RIDE and RISE who reported driving was greater than sham for both 0.3-mg and 0.5-mg ranibizumab at the 12-month and 24-month visits. Similar differences between the ranibizumab groups and laser group were noted at the 12-month visit in RESTORE (Table 2; separate data for RIDE and RISE are presented in eTable 8 in the Supplement).

Effect of Ranibizumab on VA Status Relevant to Driving
The change in the proportion of patients who had a VA of 20/40 or better in 1 or both eyes at the 12-month visit was generally greater in the ranibizumab groups than in the placebo groups in RESTORE and pooled RIDE/RISE and at the 24-month visit in pooled RIDE/RISE (Table 1; separate data for RIDE and RISE are presented in eTable 9 in the Supplement). Similar outcomes favoring the ranibizumab arms were noted among the subset of patients who had a VA of 20/40 or better in at least 1 eye at baseline and among the subset of patients whose VA was
Discussion

Diabetic macular edema, a major cause of vision impairment, can have a substantial impact on the decision to drive as well as perception of difficulty with driving. Because treatment with ranibizumab results in superior VA outcomes compared with laser or observation alone in eyes with center-involved DME, the potential effect owing to these treatments on the decision to drive and the perception of difficulty with driving should be of value to patients and clinicians, such as ophthalmologists and other physicians, who treat patients with diabetes mellitus. Reports from the RESTORE, RIDE, and RISE $^{6,7}$ NEI VFQ-25 driving subscale data suggested that patients’ perception of their driving difficulty was worse at month 12 in RESTORE and at months 12 and 24 in RIDE and RISE among those assigned to no ranibizumab compared with ranibizumab. Specifically, ranibizumab treatment resulted in patients reporting less difficulty with the following over time relevant to driving: driving during the daytime in familiar places, driving at night, and driving in difficult conditions, such as bad weather, during rush hour, on the freeway, or in city traffic. This report provides further support for these findings.

After receiving ranibizumab therapy compared with sham or macular laser, results from RESTORE, RIDE, and RISE suggest that patients with visual impairment due to center-involved DME were more likely to report that they were driving at 12 or 24 months if they were not driving at the onset of worse than 20/40 in both eyes at baseline (Table 3; separate data for RIDE and RISE are presented in eTable 10 in the Supplement).

### Table 1. Visual Acuity at Baseline, 12 Months, and 24 Months (RIDE and RISE Only) in Patients Driving at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>RIDERISE</th>
<th>RESTORE$^a$</th>
<th>RESTORE$^b$</th>
<th>RESTORE$^c$</th>
<th>RESTORE$^d$</th>
<th>RESTORE$^e$</th>
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<tbody>
<tr>
<td></td>
<td>Sham 0.3 mg</td>
<td>0.5 mg</td>
<td>Laser 0.5 mg</td>
<td>0.5 mg+Laser 0.5 mg</td>
<td>0.5 mg</td>
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<td>Baseline</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driving at baseline</td>
<td>176/252 (69.8)</td>
<td>181/250 (72.4)</td>
<td>179/251 (71.3)</td>
<td>52/111 (46.9)</td>
<td>63/117 (53.8)</td>
<td>59/116 (50.9)</td>
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<tr>
<td>% (95% CI)</td>
<td>NA</td>
<td>2.6 (−5.3 to 10.5)</td>
<td>1.5 (−6.5 to 9.5)</td>
<td>NA</td>
<td>6.9 (−6.1 to 19.9)</td>
<td>4.0 (−9.0 to 17.0)</td>
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<tr>
<td>Letter score ≥70 in 1 or both eyes at baseline$^b$</td>
<td>147/256 (57.4)</td>
<td>123/250 (49.2)</td>
<td>137/251 (54.6)</td>
<td>79/110 (71.8)</td>
<td>80/118 (67.8)</td>
<td>91/115 (80.9)</td>
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<tr>
<td>% (95% CI)</td>
<td>NA</td>
<td>−8.2 (−16.9 to 0.5)</td>
<td>−2.8 (−11.4 to 5.8)</td>
<td>NA</td>
<td>−4.0 (−15.9 to 7.9)</td>
<td>9.1 (−2.0 to 20.2)</td>
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<td>Letter score &lt;70 in both eyes$^c$</td>
<td>109/256 (42.6)</td>
<td>127/250 (50.8)</td>
<td>114/251 (45.4)</td>
<td>31/110 (28.2)</td>
<td>38/118 (32.2)</td>
<td>22/115 (19.1)</td>
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<tr>
<td>% (95% CI)</td>
<td>NA</td>
<td>8.2 (−0.5 to 16.9)</td>
<td>2.8 (−5.8 to 11.4)</td>
<td>NA</td>
<td>4.0 (−7.9 to 15.9)</td>
<td>−9.1 (−20.2 to 2.0)</td>
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<td>12-mo Subgroup</td>
<td></td>
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<td></td>
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<tr>
<td>Letter score ≥70 in 1 or both eyes$^b$</td>
<td>121/147 (82.3)</td>
<td>112/123 (91.1)</td>
<td>136/137 (99.3)</td>
<td>71/79 (89.9)</td>
<td>77/80 (96.3)</td>
<td>91/93 (97.8)</td>
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<tr>
<td>% (95% CI)</td>
<td>NA</td>
<td>8.8 (0.8 to 16.8)</td>
<td>17.0 (10.7 to 23.3)</td>
<td>NA</td>
<td>6.4 (−1.4 to 14.2)</td>
<td>7.9 (0.6 to 15.2)</td>
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<tr>
<td>Letter score &lt;70 in both eyes$^c$</td>
<td>26/147 (17.7)</td>
<td>11/123 (8.9)</td>
<td>1/137 (0.7)</td>
<td>8/79 (10.1)</td>
<td>3/80 (3.7)</td>
<td>2/93 (2.2)</td>
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<tr>
<td>% (95% CI)</td>
<td>NA</td>
<td>−8.8 (−16.8 to −0.8)</td>
<td>−17.0 (−23.3 to −10.7)</td>
<td>NA</td>
<td>−6.4 (−14.2 to 1.4)</td>
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<td>24-mo Subgroup</td>
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<tr>
<td>Letter score ≥70 in 1 or both eyes$^b$</td>
<td>122/147 (83.0)</td>
<td>113/123 (91.9)</td>
<td>135/137 (98.5)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>% (95% CI)</td>
<td>NA</td>
<td>8.9 (1.1 to 16.7)</td>
<td>15.5 (9.1 to 21.9)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Letter score &lt;70 in both eyes$^c$</td>
<td>25/147 (17.0)</td>
<td>10/123 (8.1)</td>
<td>2/137 (1.5)</td>
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<td>NA</td>
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<tr>
<td>% (95% CI)</td>
<td>NA</td>
<td>−8.9 (−16.7 to −1.1)</td>
<td>−15.5 (−21.9 to −9.1)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>

Abbreviation: NA, not applicable.

$^a$ Data for RESTORE are for subgroups with visual acuity letter scores less than 68 or 68 or greater (approximate Snellen equivalent 20/40).

$^b$ Approximate Snellen equivalent 20/40 or better.

$^c$ Approximate Snellen equivalent worse than 20/40.

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Furthermore, ranibizumab treatment as given in RESTORE or RIDE and RISE in patients with DME appeared more likely to result in a VA, when taking into account the VA in both eyes, which would satisfy requirements for an unrestricted driver’s license (assuming best-corrected VA was evaluated) at 12 and 24 months.

This study was limited by its post hoc nature and by the small number of patients in some of the subgroups analyzed. Specifically, RESTORE, RIDE, and RISE were not designed to determine the impact of ranibizumab on driving. Thus, although all patients in RESTORE, RIDE, and RISE were assigned randomly to ranibizumab or control, the subgroup of patients with VA letter score less than 68 (worse than 20/40) in both eyes at baseline was not studied in RISE.

Abbreviation: NA, not applicable.

Data for RESTORE are for patients with VA letter score greater than 68 (approximate Snellen equivalent 20/40 or better) in 1 or both eyes at 12 months among patients with VA letter score less than 68 (worse than 20/40) in both eyes at baseline.
patients who were driving at baseline was not randomized, although the subgroup of patients driving at baseline appeared to be balanced among treatment groups by known factors likely to influence the ability to drive at follow-up.

Other limitations included the lack of adjustment for multiple comparisons. If such adjustments were made, and even without such adjustments, some of the differences, although almost always favoring the ranibizumab treatment arms compared with the control arms, could have been due to chance alone. Also importantly, this study measured patients’ reports as to whether they were driving and solicited the patients’ opinions regarding their driving. As emphasized in a previous review,18 self-reported information on driving, such as that collected by the NEI VFF-25 driving subscale, is not necessarily a strong surrogate for how safe the driver may be or what difficulties the driver may have with driving. Furthermore, just because an individual has best-corrected VA of 20/40 or better following antivascular endothelial growth factor treatment for DME in at least 1 eye does not necessarily mean that the individual is a safer driver or a better-performing driver than an individual who did not receive this treatment and had VA worse than 20/40 in at least 1 eye. Additional work would be needed to determine whether driving skills or driving safety actually were maintained or improved when reporting outcomes as measured in this report. The lower proportion of RESTORE patients driving at baseline, compared with RIDE and RISE, likely reflects the traditionally lower rate of driving among older adults in Europe compared with the United States. However, driving has been shown to be important to older adults in both Europe and the United States and the proportion of older drivers in Europe is increasing.19,20

Conclusions

These results suggest that through at least 24 months, patients with DME treated with ranibizumab are more likely to report that they are driving when they were not driving at the initiation of therapy. As objective support of these patient-reported findings, the results suggest that ranibizumab-treated patients through at least 24 months are more likely to maintain or achieve a Snellen VA equivalent of 20/40 or better with refractive correction in at least 1 eye, the minimum VA required for a driver’s license in most states in the United States and in many other countries. These findings provide further tangible functional support (for payers; clinicians, such as ophthalmologists and other physicians, who treat patients with diabetes mellitus; and patients with diabetes) to the superior VA outcomes reported with ranibizumab compared with sham or macular laser for DME.

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REFERENCES


