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Twenty-four–Month Outcomes of the Ranibizumab for Edema of the Macula in Diabetes – Protocol 3 with High Dose (READ-3) Study

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Purpose: To compare 2.0 mg ranibizumab (RBZ) injections with 0.5 mg RBZ for eyes with center-involved diabetic macular edema (DME).

Design: Randomized, controlled, double-masked (to the dose), interventional, multicenter clinical trial.

Participants: A total of 152 patients (152 eyes) with DME.

Methods: Eligible eyes were randomized in a 1:1 ratio to 0.5 mg (n = 77) or 2.0 mg (n = 75) RBZ. Study eyes received 6 monthly mandatory injections followed by as-needed injections until month 24.

Main Outcome Measures: The primary efficacy end point of the study was mean change in best-corrected visual acuity (BCVA) and central foveal thickness (CFT) at month 6. Secondary outcomes included the mean change in BCVA and CFT at month 24, and incidence and severity of systemic and ocular adverse events through month 24.

Results: A total of 152 eyes were randomized in the study. At month 24, the mean improvement from baseline BCVA was +11.06 letters in the 0.5 mg RBZ group (n = 59) and +6.78 letters in the 2.0 mg RBZ group (n = 54) ($P = 0.02$). The mean numbers of RBZ injections through month 24 were 18.4 and 17.3 in the 0.5 mg and 2.0 mg RBZ groups, respectively ($P = 0.08$). The mean change in CFT was −192.53 μm in the 0.5 mg RBZ group and −170.64 μm in the 2.0 mg RBZ group ($P = 0.41$). By month 24, 3 deaths had occurred in the 0.5 mg RBZ group and 3 deaths had occurred in the 2.0 mg RBZ group; 5 of these 6 deaths occurred secondary to cardiovascular causes, and 1 death occurred as the result of severe pneumonia. All 5 patients with a cardiovascular cause of death had a history of coronary heart disease.

Conclusions: At month 24, there were significant visual and anatomic improvements in both groups, with subjects in the 0.5 mg RBZ group gaining more vision. Visual and anatomic gains achieved at month 6 were largely maintained through month 24. No new safety events were identified. In this study population, 2.0 mg RBZ does not appear to provide additional benefit over 0.5 mg RBZ. *Ophthalmology 2016;■:1–7 © 2016 by the American Academy of Ophthalmology*

The role of vascular endothelial growth factor (VEGF) in the pathogenesis of diabetic macular edema (DME) has been well documented.[1] Several randomized clinical trials have demonstrated the safety and efficacy of anti-VEGF inhibitors such as ranibizumab (RBZ) in eyes with center-involved DME.[2–6] The 0.3-mg dose of RBZ has since been approved by the US Food and Drug Administration (FDA) for DME.

On the basis of data from previous studies, it has been established that monthly follow-up and evaluation with monthly or pro re nata (PRN) treatment with anti-VEGF inhibitors may be required to significantly improve visual acuity (VA) and maintain disease stability in patients with DME.[4,6] Such a regimen may create a treatment burden for both patients and care providers. Therefore, alternative management approaches in patients with DME may be useful.

The Ranibizumab for Edema of the mAcula in Diabetes – Protocol 3 with High Dose (READ-3) Study is a double-masked, randomized, multicenter clinical trial designed to evaluate 2 different doses (0.5 and 2.0 mg) of RBZ in patients with DME. At the month 6 primary end point, patients treated with 0.5 mg and 2.0 mg RBZ showed a mean improvement in best-corrected visual acuity (BCVA) of +9.43 and +7.01 letters, respectively ($P = 0.161$).[7] No significant differences in the visual or anatomic outcomes were reported between the 2 doses of RBZ. After the primary end point, patients were evaluated monthly until month 24, and if re-treatment criteria were met, patients were treated with 0.5 or 2.0 mg RBZ on the basis of their initial study group assignment. We report the 2-year efficacy and safety outcomes for the READ-3 study.

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Methods

The READ-3 Study is a randomized, controlled, parallel clinical trial conducted at 13 sites in the United States through an investigator-initiated investigational new drug application granted by the FDA. The names of the investigators, coordinators, and staff members from all sites who participated in the READ-3 Study are listed in the Acknowledgments. The study adhered to the guidelines of the Declaration of Helsinki and Health Insurance Portability and Accountability Act, and the protocol and consent form were approved by a local institutional review board for selected sites and by a western institutional review board for others. Each subject provided written informed consent. The study was monitored by an independent data and safety monitoring committee that monitored adverse events and data at regular intervals. The study is registered at www.clinicaltrials.gov under the identifier NCT01077401.

Patient Eligibility and Exclusion Criteria

Patients (aged ≥18 years) with type 1 or 2 diabetes and DME were eligible if their BCVA was between 20/40 and 20/320 and met the following criteria: (1) central foveal thickness (CFT) ≥250 μm as measured by time-domain optical coherence tomography (TD-OCT); (2) glycated hemoglobin ≥6% within 12 months before randomization; (3) no other confounding ocular condition that could decrease VA aside from DME; and (4) reasonable expectation that scatter laser photocoagulation would not be required for the next 6 months. Patients were excluded if they had received focal/grid laser treatment within 3 months, intraocular injection of steroid within 3 months, or intraocular injection of a VEGF antagonist within 2 months. If both eyes were eligible, the eye with the greater CFT was enrolled.

Study Protocol

Consenting patients were screened for the study with a medical history, measurement of BCVA by a masked, certified VA examiner using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, slit-lamp examination, measurement of intraocular pressure, dilated funduscopic examination, TD-OCT and spectral-domain optical coherence tomography (SD OCT), fluorescein angiography (FA), and laboratory tests for electrolytes, cell counts, and liver and renal function. Eligible patients were randomized 1:1 (in blocks of 4 using the built-in randomization tool of the electronic data capture system) to receive intravitreal injections of 0.5 mg or 2.0 mg of RBZ. The dose of 0.5 mg RBZ was used in this trial because 0.3 mg RBZ was not yet approved by the FDA for DME at the time of enrollment. Although the 0.3-mg dose gained FDA approval during the study period, the data and safety monitoring committee elected to continue using the 0.5-mg dose for the entire clinical trial duration because both doses have been shown to be efficacious and there are no clear safety concerns associated with the latter dose.[2] Patients in both groups received an injection of RBZ at baseline and at months 1, 2, 3, 4, and 5. Staring at month 6, patients in both groups were evaluated every month and were eligible to receive additional RBZ if CFT was ≥250 μm on TD OCT or there was evidence of any macular fluid on the optical coherence tomography (OCT) scans that the investigator thought was contributing to the decreased vision on TD OCT or SD OCT until month 24; SD OCT also was available at all sites, and institutional review board approval was obtained to use this imaging modality to evaluate DME. Safety evaluations, measurement of BCVA, eye examinations, and OCT scans were performed at all study visits. The procedures for intravitreal injections, OCT, FA, and data collection and management have been described.[5]

Table 1. Baseline Characteristics

	0.5 mg RBZ (n = 77)	2.0 mg RBZ (n = 75)	P Value
Female sex (%)	39.0	49.3	0.26
Race (%)			
White	58.4	52.0	0.64
Asians	5.1	6.6	0.97
Hispanic or Latino	22.1	17.3	0.59
African Americans	7.8	17.3	0.13
Age mean (yrs)	64.8	63.5	0.39
Age range (yrs)	35–87	48–84	
VA mean (ETDRS letters read)	26.30	29.25	0.12
VA range (ETDRS letters read)	0–48	5–61	
VA mean (~Snellen equivalent)	20/80	20/63	
CSF thickness mean (μm)	441.37	432.33	0.86
CSF thickness range (μm)	238–841	247–801	
HbA_{1c} mean	7.5	7.7	0.57
HbA_{1c} range	4.9–13	5.7–13	
Lens status (% pseudophakic)	35.1	29.3	0.45

CSF = central subfield thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; HbA_{1c} = glycated hemoglobin; RBZ = ranibizumab; VA = visual acuity.

Masking

The READ-3 trial was a double-masked study: The patient, physician, and coordinator in contact with the patient did not know which dose of RBZ the patient was receiving. Only the person responsible for dispensing the correct assigned dose of RBZ at each study site was unmasked. The certified VA examiner also was masked to the treatment dose.

Sample Size Calculation

The sample size was selected to allow the study to have an 80% power to detect a difference of 4 or more ETDRS letters between the 2 arms at the primary end point (month 6). The chosen sample size enabled the READ-3 Study to be comparable to other clinical trials, because 80% is the typical power used in many major clinical trials. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Table 2. Previous Treatments

	0.5 mg RBZ (n = 77)	2.0 mg RBZ (n = 75)	P Value
Treatment naïve (%)	53.2	45.3	0.626
Previously treated with RBZ (%)	10.3	6.6	0.596
Previously treated with triamcinolone (%)	22.1	34.6	0.171
Previously treated with bevacizumab (%)	32.4	37.3	0.646

RBZ = ranibizumab.