Ranibizumab for Macular Edema following Central Retinal Vein Occlusion

Six-Month Primary End Point Results of a Phase III Study

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Purpose: To assess the efficacy and safety of intraocular injections of 0.3 mg or 0.5 mg ranibizumab in patients with macular edema after central retinal vein occlusion (CRVO).

Design: Prospective, randomized, sham injection-controlled, double-masked, multicenter clinical trial.

Participants: A total of 392 patients with macular edema after CRVO.

Methods: Eligible patients were randomized 1:1:1 to receive monthly intraocular injections of 0.3 or 0.5 mg of ranibizumab or sham injections.

Main Outcome Measures: The primary efficacy outcome measure was mean change from baseline best-corrected visual acuity (BCVA) letter score at month 6. Secondary outcomes included other parameters of visual function and central foveal thickness (CFT).

Results: Mean (95% confidence interval [CI]) change from baseline BCVA letter score at month 6 was 12.7 (9.9–15.4) and 14.9 (12.6–17.2) in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, and 0.8 (−2.0 to 3.6) in the sham group ($P<0.0001$ for each ranibizumab group vs. sham). The percentage of patients who gained ≥15 letters in BCVA at month 6 was 46.2% (0.3 mg) and 47.7% (0.5 mg) in the ranibizumab groups and 16.9% in the sham group ($P<0.0001$ for each ranibizumab group vs. sham). At month 6, significantly more ranibizumab-treated patients (0.3 mg = 43.9%; 0.5 mg = 46.9%) had BCVA of ≥ 20/40 compared with sham patients (20.8%; $P<0.0001$ for each ranibizumab group vs. sham), and CFT had decreased by a mean of 434 μm (0.3 mg) and 452 μm (0.5 mg) in the ranibizumab groups and 168 μm in the sham group ($P<0.0001$ for each ranibizumab group vs. sham). The median percent reduction in excess foveal thickness at month 6 was 94.0% and 97.3% in the 0.3 mg and 0.5 mg groups, respectively, and 23.9% in the sham group. The safety profile was consistent with previous phase III ranibizumab trials, and no new safety events were identified in patients with CRVO.

Conclusions: Intraocular injections of 0.3 mg or 0.5 mg ranibizumab provided rapid improvement in 6-month visual acuity and macular edema following CRVO, with low rates of ocular and nonocular safety events.

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**Group members listed online in Appendix 1 (available at http://aaojournal.org).*

Abruptly decreased vision and a "blood and thunder" retina are classic signs of central retinal vein occlusion (CRVO), a retinal vascular disease first described by Leibreich in 1855[1] and Michel in 1878.[2] Dilated tortuous retinal veins, optic disc hyperemia and edema, 360-degree intraretinal hemorrhages, and often massive central edema lead to an abrupt decrease in visual acuity (VA), with rapid presentation and diagnosis of the patient. Unfortunately, despite large natural history studies[3,4] and great therapeutic advances in other ophthalmic diseases over the past 150 years, once the diagnosis of CRVO is made, physicians have had little to offer these patients other than "careful observation," looking for ocular neovascularization or spontaneous improvement.[5] Risk factors and associations with CRVO include systemic vascular disease, ocular disease, hematologic alterations, vasculitis, and medications.[6] During the past 30 years, numerous therapeutic approaches have been advocated for CRVO. When landmark National Eye Institute (NEI)-sponsored clinical trials demonstrated that grid and focal laser photocoagulation were beneficial for the other 2 major retinal vascular diseases (i.e., branch vein occlusion[7] and clinically significant diabetic macular edema[8]), many clinicians began to use laser photocoagulation therapy for macular edema secondary to CRVO, and the therapy seemed to reduce macular edema. In 1994, the NEI-sponsored Central Vein Occlusion Study (CVOS) Group[9] confirmed that mac-

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ular grid photocoagulation decreased macular edema in CRVO, but demonstrated that laser had no beneficial effect on VA compared with observation. Attempts to bypass the vein occlusion or increase venous outflow with surgery (i.e., optic nerve sheath fenestration and radial optic neurotomy)[10] or laser (i.e., laser-induced chorioretinal venous anastomosis)[11] have been described, but none of these procedures have been widely adopted or evaluated in randomized, controlled clinical trials.

Corticosteroids administered orally[12] or intravitreally[13] have been advocated in CRVO to stabilize retinal vessel tight junctions and decrease edema by the indirect antivascular endothelial growth factor (VEGF) effect of corticosteroid. Inflammation may also contribute to the pathology of CRVO, and the corticosteroid anti-inflammatory properties may play a role in altering the disease process.[14] The Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) study, recently sponsored by the NEI, demonstrated an improvement in central retinal thickness and VA in patients receiving injections of a preservative-free triamcinolone preparation up to every 4 months compared with observation alone.[15] Cohorts treated with either 1.0 mg or 4.0 mg intravitreal triamcinolone lost a mean of 1.2 letters over 12 months (compared with −12.1 letters in the observation arm), and only 26.5% and 25.6% of patients treated with 1.0 mg and 4.0 mg triamcinolone, respectively, gained ≥15 letters. Triamcinolone therapy did not halt the development of iris neovascularization in 9.8% of patients in the 1.0 mg group and 4.4% in the 4.0 mg group; and 20% (1.0 mg cohort) and 35% (4.0 mg cohort) required intraocular pressure (IOP)-lowering medications secondary to the corticosteroid effect on IOP, compared with 8% in the observation arm. In addition, although no patients in the observation arm required cataract surgery in 2 years of follow-up, 21 patients in the 4.0 mg group had exacerbation of cataract that required surgery.

Vascular endothelial growth factor is a secreted homodimeric protein that stimulates vascular endothelial cell growth and induces vascular permeability.[16] Vascular endothelial growth factor expression is upregulated by hypoxia and a number of other stimuli, and was noted to be elevated in the ocular fluids of patients with CRVO.[17] Pe'er et al[18] demonstrated upregulation of VEGF mRNA in human CRVO and neovascular glaucoma pathology specimens. mRNA expression was noted in the inner nuclear layer, which would be expected, because the anterior two thirds of the retina derives its circulation from the central retinal artery, which is compromised in CRVO.

Ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) is a humanized, affinity-matured VEGF antibody fragment that binds to and neutralizes all isoforms of VEGF-A and their biologically active degradation products. Ranibizumab was the first anti-VEGF therapy to demonstrate improved visual outcomes in patients with neovascular age-related vascular degeneration[19,20] and was approved by the Food and Drug Administration for that indication. Two small, uncontrolled trials of open-label intravitreal ranibizumab in patients with CRVO[21,22] demonstrated VA improvements of 10 to 18 letters and 90% decreases in central retinal thickness (i.e., macular drying) after 3 monthly injections, with an association between degree of improvement and baseline levels of VEGF. Another uncontrolled trial of 20 patients demonstrated durability of VA and anatomic benefits up to 1 year with intravitreal ranibizumab.[23] These reports suggest that excess production of VEGF in the retina of patients with retinal vein occlusion is a major contributor to macular edema, which leads to vision loss, and they provide a sound rationale for the present phase III trial of efficacy and safety of intravitreal ranibizumab in patients with macular edema secondary to CRVO.

Here we report the month 6 primary and key secondary end points of Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety (CRUISE), a phase III multicenter trial in which patients with macular edema following CRVO were randomized to receive monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab or sham injections.

Materials and Methods

Study Design

The CRUISE was a 6-month phase III, multicenter, randomized, injection-controlled study, with an additional 6 months of follow-up (total 12 months), designed to evaluate efficacy and safety of intraocular injections of ranibizumab in patients with macular edema following CRVO. The study included a 28-day screening period (days −28 to −1); a 6-month treatment period (day 0 to month 6), during which patients received monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab or sham injections; and a 6-month observation period (month 6 to month 12), during which all patients could receive monthly intraocular ranibizumab if they met prespecified functional and anatomic criteria (i.e., Snellen equivalent study eye best-corrected visual acuity [BCVA] ≤20/40 according to the Early Treatment Diabetic Retinopathy Study (ETDRS)[8] chart or mean central subfield thickness ≥250 μm according to optical coherence tomography [OCT]) (Fig 1). The CRUISE is registered at www.clinicaltrials.gov (NCT00485836; accessed December 18, 2009). The protocol was approved by the institutional review board at each study site, and the study was conducted according to the International Conference on Harmonisation E6 Guideline for Good Clinical Practice and any national requirements. All patients provided informed consent before participation in the study. The primary efficacy outcome was the mean change from baseline BCVA in the study eye at month 6.

Screening and Eligibility

Eligibility was determined by the investigating physician at individual studies sites using the criteria listed in Table 1. During the screening visit, patients who provided informed consent provided a medical history and underwent a physical examination, a complete eye examination (including measurement of BCVA), OCT, fluorescein angiography, and laboratory tests. The BCVA was measured by the procedure described in the ETDRS. If the investigating physician judged a patient to be eligible for participation in the study, the patient's OCT was evaluated by certified personnel at the University of Wisconsin Fundus Photograph Reading Center (UWFPRC; Madison, WI), using the Zeiss Stratus and the FastMac protocol (Carl Zeiss Meditec, Inc., Dublin, CA). If that evaluation and all laboratory tests supported inclusion, the patient was scheduled for the day 0 study visit.

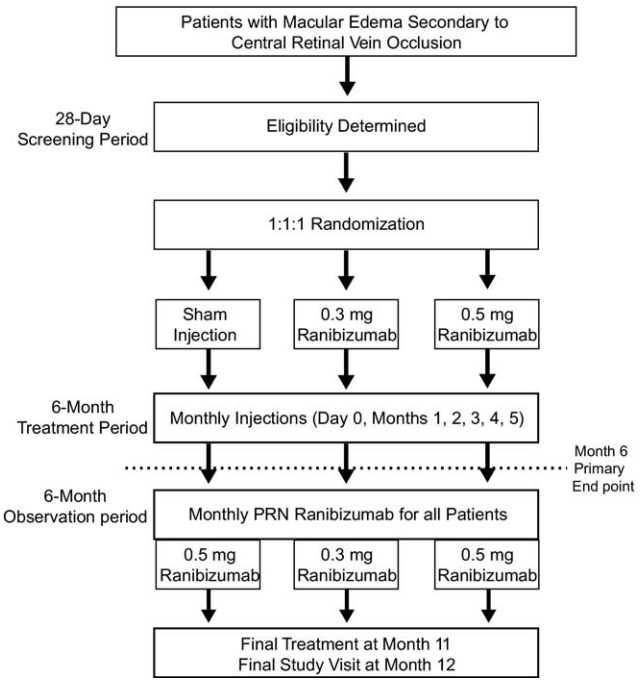

Figure 1. Study design. Eligible patients were randomized 1:1:1 to receive monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections during the 6-month treatment period (day 0, months 1–5). During the 6-month observation period, subjects were eligible to receive monthly intraocular ranibizumab if they had Snellen equivalent study eye BCVA of ≤20/40 according to the ETDRS chart or mean central subfield thickness ≥250 μm according to OCT. PRN = pro re nata.

Randomization

Eligible patients were randomized 1:1:1 to receive monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections, using a dynamic randomization method.[24] Randomization was stratified by baseline BCVA letter score (≤34 [approximate Snellen equivalent <20/200], 35–54 [approximate Snellen equivalent 20/200 to <20/80], ≥55 [approximate Snellen equivalent ≥20/80]) and study center. One eye was chosen as the study eye for each patient. If both eyes were eligible, the eye with the worse BCVA at screening was selected. Patients, certified BCVA examiners, and evaluating physicians were masked to treatment and dose. Injecting physicians, who did not perform examinations or outcome assessments, were masked to dose but not treatment.

Study Visits and Assessments

During the 6-month treatment period, study visits occurred on days 0 and 7 and months 1 to 6. At each visit, patients were given a complete eye examination with OCT assessment of central foveal thickness (CFT). Patients provided a medical history, vital signs were measured (except for day 7), concomitant medication was reviewed, and safety was assessed. Any new sign, symptom, illness, or worsening of any preexisting medical condition was recorded as an adverse event (AE). An AE was classified as a serious AE (SAE) if it led to death, was life threatening, required prolonged hospitalization, resulted in persistent or significant disability, resulted in congenital anomaly/birth defect, or was considered a significant medical event by the investigator. Patients who discontinued the study before the month 12 visit were encouraged to return for an early termination visit 30 days after their last injection or study visit to record AEs and SAEs that had occurred since their last visit and to complete other study assessments. Patient-reported visual function was assessed with the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) at day 0 and months 1, 3, and 6.

Intraocular Injections

Patients received their assigned treatment at day 0 and months 1 to 5 for a maximum of 6 injections. Injection procedures were identical to those previously described.[19,20] Briefly, topical anesthetic drops were given, a lid speculum was inserted, and after subconjunctival injection of 2% lidocaine and cleaning of the injection site with 5% povidone iodine, a 30-gauge needle was inserted through the pars plana, and 0.05 ml of ranibizumab was injected. Patients who were randomized to the sham group were treated similarly to those in the ranibizumab groups, except that a needleless hub of a syringe was placed against the injection site and the plunger of the syringe was depressed to mimic an injection. The ability to count fingers with the study eye was assessed 15 minutes after injection, and IOP was measured within 50 to 70 minutes of an injection.

Outcome Measures

The primary efficacy outcome measure was mean change from baseline BCVA at month 6. Secondary efficacy outcome measures

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria*
≥18 yrs of age with foveal center-involved macular edema secondary to CRVO† diagnosed within 12 mos before study initiation
BCVA 20/40–20/320 Snellen equivalent using the ETDRS charts
Mean central subfield thickness ≥250 μm from 2 OCT measurements (central 1-mm diameter circle with a Stratus OCT3 (Carl Zeiss Meditec, Inc., Dublin, CA) on 2 measurements: 1 at screening confirmed by UWFPRC and 1 on day 0 confirmed by the investigating physician
Key Exclusion Criteria*
Prior episode of RVO
Brisk afferent pupillary defect (i.e., obvious and unequivocal)
>10-letter improvement in BCVA between screening and day 0
History of radial optic neurotomy or sheathotomy
Intraocular corticosteroid use in study eye within 3 mos before day 0
History or presence of wet or dry AMD
Panretinal scatter photocoagulation or sector laser photocoagulation within 3 mos before day 0 or anticipated within 4 mos after day 0
Laser photocoagulation for macular edema within 4 mos before day 0 (for patients who had previously received grid laser photocoagulation, the area of leakage at day 0 must have extended into the fovea (i.e., prior laser treatment was inadequate), and there could be no evidence of laser damage to the fovea
Evidence on examination of any diabetic retinopathy
CVA or MI within 3 mos before day 0
Prior anti-VEGF treatment in study or fellow eye within 3 mos before day 0 or systemic anti-VEGF or pro-VEGF treatment within 6 mos before day 0

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CRVO = central retinal vein occlusion; CVA = cerebrovascular accident; ETDRS = Early Treatment Diabetic Retinopathy Study; MI = myocardial infarction; RVO = retinal vein occlusion; UWFPRC = University of Wisconsin Fundus Photograph Reading Center; VEGF = vascular endothelial growth factor.

*Pertains to study eye, except where noted otherwise.

†CRVO was defined as an eye that had retinal hemorrhage or other biomicroscopic evidence of RVO (e.g., telangiectatic capillary bed) and a dilated (or previously dilated) venous system in ≥3 quadrants of the retina drained by the affected vein.

included mean change from baseline BCVA over time to month 6, percentage of patients who gained ≥15 letters from baseline BCVA at month 6, percentage of patients who lost <15 letters from baseline BCVA at month 6, percentage of patients with CFT ≤250 μm at month 6, and mean change from baseline CFT over time to month 6. Exploratory efficacy outcomes included percentage of patients with Snellen equivalent BCVA 20/200 or worse at month 6, mean change from baseline excess foveal thickness (EFT) over time to month 6, and mean change from baseline NEI VFQ-25 composite score over time to month 6. Additional outcomes included the percentage of patients with Snellen equivalent BCVA of ≥20/40 at month 6. The average normal central subfield thickness is 212 μm, based on measurements of a population of normal patients.[25] Thus, EFT was estimated by subtracting 212 μm from the central subfield thickness. Safety outcomes included the incidence and severity of ocular and nonocular AEs and SAEs.

Optical coherence tomography scans obtained at day 0 and months 1, 2, 3, and 6 during the 6-month treatment period were evaluated by masked graders at the UWFPRC; CFT was recorded as the center point thickness provided by Stratus 3 software (Carl Zeiss Meditec, Inc.), unless there was an error in computer recognition of the outer or inner boundaries of the retina or the center point. If that occurred, the grader determined CFT with a caliper. Software-generated central subfield thickness was recorded at UWFPRC and was used to calculate EFT. Fluorescein angiographs were evaluated by masked graders at the UWFPRC.

Statistical Analysis

Unless otherwise noted, the intent-to-treat approach was used for efficacy analyses and included all patients as randomized. Missing values for efficacy outcomes were imputed using the last-observation-carried-forward method. For each efficacy outcome, 2 pairwise comparisons were made: 0.3 mg ranibizumab versus sham and 0.5 mg ranibizumab versus sham. Unless otherwise noted, efficacy outcome analyses were stratified by baseline BVCA letter score (≤34 vs. 35−54 vs. ≥55). For the primary outcome, the mean change from baseline BCVA at month 6 was compared between each ranibizumab group and the sham injection group using an analysis of variance model stratified by baseline BCVA, with no additional adjustments for covariates, and using the Hochberg–Bonferroni multiple comparison procedure to maintain an overall type I error rate of 0.05. Cochran–Mantel–Haenszel chi-square tests, stratified by baseline BCVA, were used for secondary and exploratory binary end point group comparisons. Analysis of variance or analysis of covariance models were used to analyze the continuous outcome measures. To manage type I error across secondary end points, a type I error rate of 0.05 was allocated for each dose, and a staged hierarchic testing procedure was used with a Hochberg–Bonferroni procedure at each stage. To determine the earliest time point at which statistically significant between-group differences were obtained for mean change from baseline in BCVA, CFT, EFT, and the NEI VFQ-25 composite score, a hierarchic testing procedure for significance at each time point was performed sequentially for each end point, beginning with month 6 and working backward to the time point at which the test for between-group differences resulted in $P>0.05$. Additional analyses were performed to assess the sensitivity of the results to the statistical methods used. The NEI VFQ-25 scores were calculated according to published guidelines. The mean of all of the NEI VFQ-25 subscales was used to calculate the overall composite score (http://www.rand.org/health/surveys_tools.html; accessed December 15, 2009). The incidence of ocular and nonocular AEs and SAEs was summarized by treatment group.

Results

Baseline Characteristics and Patient Disposition

Between July 2007 and December 2008, 392 patients were randomized to intraocular injections of 0.3 mg (n = 132) or 0.5 mg (n = 130) ranibizumab or sham injections (n = 130) at 95 centers in the United States. Patient demographics and baseline ocular characteristics were similar across treatment groups (Table 2). The average age of patients was 68 years, and 57% were male. The mean time from diagnosis of CRVO to screening was 3.3 months (median 2 months for each treatment group), with a duration of ≤3 months in 69% of patients. Mean study eye baseline BCVA letter score was 48.3 (approximate Snellen equivalent 20/100), and mean baseline CFT was 685.2 μm.

Of patients in the 0.3 mg, 0.5 mg, and sham groups, 97.7%, 91.5%, and 88.5%, respectively, completed the study through month 6. The most common reason for study discontinuation was a decision made by the physician or patient to do so. All but 2 of the 392 patients received study drug; for those who did, the mean number of ranibizumab or sham injections received during the 6-month treatment period was 5.7 and was similar across treatment groups. Four patients (3.0%) in the 0.3 mg group, 10 patients (7.7%) in the 0.5 mg group, and 16 patients (12.3%) in the sham group discontinued treatment at or before month 5.

Functional Outcomes at Month 6

Change from Baseline Best-Corrected Visual Acuity. The primary efficacy outcome was mean change from baseline BCVA letter score at month 6. At month 6, patients in the 0.3 mg and 0.5 mg ranibizumab treatment groups had gained a mean (95% confidence interval [CI]) of 12.7 (9.9–15.4) and 14.9 (12.6–17.2) letters, respectively, compared with 0.8 (−2.0 to 3.6) letters in the sham group ($P<0.0001$ for each ranibizumab group vs. sham) (Fig 2; Table 3). The improvement in BCVA letter score after injection of ranibizumab was rapid, with patients having gained an average of 9 letters 7 days after the first injection, and significantly greater than that of the sham group at day 7 and all subsequent monthly assessments. The group differences in BCVA were maintained when analyzed by subgroup (Table 4). The treatment benefit compared with sham for patients diagnosed with CRVO <3 months before study screening was 13.2 letters in both the 0.3 mg and 0.5 mg ranibizumab groups and 10.5 (0.3 mg) and 15.3 (0.5 mg) letters for patients diagnosed with CRVO ≥3 months before screening. Although some of the subgroups were small, the mean change in BCVA at month 6 was greater for patients with worse BCVA and CFT ≥450 μm at baseline.

Percentage of Patients Who Gained ≥15 Early Treatment Diabetic Retinopathy Study Letters. At month 6, 46.2% and 47.7% of patients in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, had gained ≥15 letters from baseline BCVA letter score compared with 16.9% of patients in the sham group ($P<0.0001$ for each ranibizumab group vs. sham). The percentage of patients who gained ≥15 letters increased rapidly after injection of ranibizumab and was 22.0% in the 0.3 mg group and 26.9% in the 0.5 mg group compared with 3.8% in the sham group at day 7. This difference was significant, as were the differences at all subsequent assessments ($P<0.0001$ ranibizumab vs. sham at day 7 and months 1–5).

Percentage of Patients Who Lost <15 Early Treatment Diabetic Retinopathy Study Letters. A large percentage of patients in each treatment group had lost <15 letters from BCVA letter score at month 6: 96.2%, 98.5%, and 84.6%, in the 0.3 mg, 0.5 mg, and sham groups, respectively. A significantly greater percentage of

Table 2. Patient Demographics and Baseline Ocular Characteristics

		Ranibizumab	
	Sham (n = 130)	*0.3 mg (n = 132)*	*0.5 mg (n = 130)*
Age (yrs)			
Mean (SD)	65.4 (13.1)	69.7 (11.6)	67.6 (12.4)
Median	66	71	70
Range	20–91	38–90	40–91
Gender, n (%)			
Male	72 (55.4)	71 (53.8)	80 (61.5)
Female	58 (44.6)	61 (46.2)	50 (38.5)
Race,* n (%)			
White	113 (86.9)	108 (81.8)	108 (83.1)
Black/African American	8 (6.2)	16 (12.1)	10 (7.7)
Other	7 (5.4)	3 (2.3)	7 (5.4)
Unavailable	3 (2.3)	5 (3.8)	5 (3.8)
Study Eye Characteristics			
Months from RVO diagnosis to screening			
Mean (SD)	2.9 (2.9)	3.6 (3.2)	3.3 (3.7)
Median	2	2	2
Range	0–14	0–12	0–27
Distribution, n (%)			
≤3	91 (70.0)	87 (65.9)	94 (72.3)
>3 to ≤ 6	27 (20.8)	18 (13.6)	17 (13.1)
>6 to ≤ 9	4 (3.1)	16 (12.1)	10 (7.7)
>9 to ≤ 12	7 (5.4)	11 (8.3)	6 (4.6)
>12	1 (0.8)	0	3 (2.3)
BCVA			
ETDRS letter score			
Mean (SD)	49.2 (14.7)	47.4 (14.8)	48.1 (14.6)
Range	16–71	9–72	21–73
Distribution, n (%)	—		
<34	26 (20.0)	33 (25.0)	30 (23.1)
35–54	49 (37.7)	46 (34.8)	50 (38.5)
≥55	55 (42.3)	53 (40.2)	50 (38.5)
Approximate Snellen equivalent, median	20/100	20/100	20/100
IOP (mmHg), mean (SD)	15.1 (3.1)	14.9 (3.3)	15.1 (3.4)
IOP-lowering medication, n (%)	13 (10.0)	18 (13.6)	22 (16.9)
Phakic eye,† n (%)	88 (80.7)	84 (75.0)	83 (72.8)
Imaging Data			
CFT (μm),‡ mean (SD)	687.0 (237.6)	679.9 (242.4)	688.7 (253.1)
Total macular volume (mm^3),§ mean (SD)	10.700 (2.303)	10.748 (2.380)	10.308 (2.033)
Total area of retinal hemorrhage, central subfield (DA), calculated,‖ mean (SD)	0.080 (0.113)	0.093 (0.117)	0.093 (0.117)
Area of fluorescein leakage within grid (DA),¶ median	15	15	14
>10 DA of capillary nonperfusion** (%)	0	0	2
Fellow Eye Characteristics			
Fellow eye BCVA (ETDRS letters), mean (SD)	78.9 (18.6)	80.0 (12.5)	78.8 (17.4)
Fellow eye vision compared with study eye, n (%)			
Better	117 (90.0)	123 (93.2)	120 (92.3)
Worse	8 (6.2)	3 (2.3)	7 (5.4)
Same	5 (3.8)	6 (4.5)	3 (2.3)

BCVA = best-corrected visual acuity; CFT = central foveal thickness; DA = disc area; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; RVO = retinal vein occlusion; SD = standard deviation.
*Multiracial patients were counted in each race category that they indicated. No. of patients in Other category may be overestimated. No. assessed in sham, 0.3 mg, and 0.5 mg groups was †109, 112, and 114; ‡129, 131, and 130; §86, 93, and 74; ‖128, 125, and 126; ¶128, 130, and 129; **112, 113, and 109, respectively.

ranibizumab-treated patients lost <15 letters compared with the sham group ($P<0.005$ for each ranibizumab group vs. sham).

Percentage of Patients with Snellen Equivalent Best-Corrected Visual Acuity of ≥20/40. A Snellen equivalent of ≥20/40 is generally sufficient to support reading and driving and is considered an excellent outcome. The percentage of patients who obtained this outcome at month 6 was 43.9% in the 0.3 mg group and 46.9% in the 0.5 mg group compared with 20.8% in the sham group ($P<0.0001$ for each ranibizumab group vs. sham) (Table 5).

Percentage of Patients with Snellen Equivalent Best-Corrected Visual Acuity of ≤ 20/200. Snellen equivalent BCVA

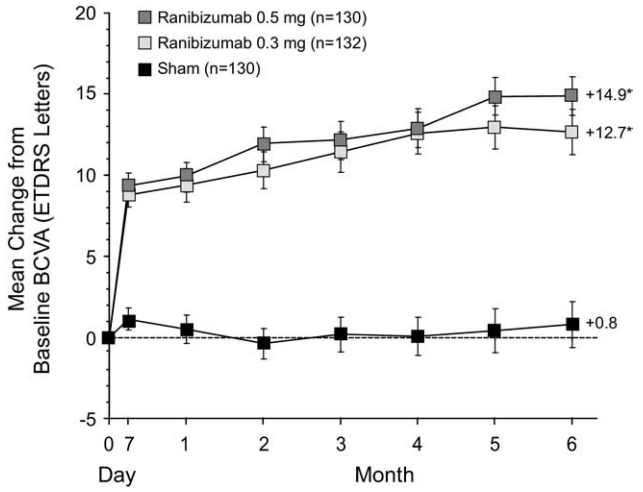

Figure 2. Mean change from study eye baseline BCVA over time to month 6. *$P<0.0001$ versus sham. Earliest statistically significant group difference ($P<0.0001$ vs. sham) was at day 7. Vertical bars are ±1 standard error of the mean. The last-observation-carried-forward method was used to impute missing data. BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.

of ≤20/200 is considered a poor visual outcome. This outcome occurred in the study eye at month 6 in 15.2% (0.3 mg) and 11.5% (0.5 mg) of patients treated with ranibizumab compared with 27.7% of patients in the sham group ($P<0.005$ for each ranibizumab group vs. sham) (Table 5).

Impact on Patient-Reported Outcomes Because of Visual Function

An improvement from baseline in the mean NEI VFQ-25 composite score was observed as early as month 1 in ranibizumab-treated patients. At month 6, the mean (95% CI) change from baseline score was 7.1 (95% CI 5.2–9.0), 6.2 (95% CI 4.3–8.0), and 2.8 (95% CI 0.8–4.7) points in the 0.3 mg (n = 130), 0.5 mg (n = 128), and sham (n = 127) groups, respectively ($P<0.05$ for each ranibizumab group vs. sham) (Fig 3).

Anatomic Outcomes at Month 6

Change from Baseline Central Foveal Thickness. Concomitant with the rapid improvement in BCVA, there was a rapid reduction in CFT after treatment with ranibizumab. At day 7, the mean reduction from baseline CFT was >250 μm in both ranibizumab groups compared with no reduction in the sham group (Fig 4). The difference at day 7 was statistically significant, as were differences at all subsequent graded assessments ($P<0.0001$ for each ranibizumab group vs. sham at each time point). At month 6, the mean (95% CI) change in CFT was −433.7 μm (95% CI −484.9, −382.6) in the 0.3 mg (n = 131) and −452.3 μm (95% CI −497.0, −407.6) in the 0.5 mg (n = 130) ranibizumab groups compared with −167.7 (95% CI −221.5, −114.0) μm in the sham group (n = 129).

Residual Edema. In addition to assessing the absolute reduction in CFT, it is important to determine how much macular edema is eliminated by treatment. The average normal central subfield thickness is 212 μm; thus, foveal thickness >212 μm is excess. At baseline, the mean EFT was 383.2 μm, 390.8 μm, and 373.8 μm in the 0.3 mg, 0.5 mg, and sham groups, respectively. At month 6,

Table 3. Change from Study Eye Baseline Best-Corrected Visual Acuity at Month 6

		Ranibizumab	
	Sham (n = 130)	*0.3 mg (n = 132)*	*0.5 mg (n = 130)*
ETDRS Letter Score			
Mean (SD)	0.8 (16.2)	12.7 (15.9)	14.9 (13.2)
95% CI for mean	−2.0 to 3.6	9.9–15.4	12.6–17.2
Difference in means (vs. sham)	—	11.9	14.1
95% CI for difference		7.9–15.8	10.5–17.7
P value (ranibizumab vs. sham)*		<0.0001	<0.0001
Distribution of change at month 6, n (%)			
Gain			
≥15 letters	22 (16.9)	61 (46.2)	62 (47.7)
10–14 letters	11 (8.5)	21 (15.9)	30 (23.1)
5–9 letters	25 (19.2)	23 (17.4)	15 (11.5)
No change, ±4.0 letters	33 (25.4)	15 (11.4)	14 (10.8)
Loss			
5–9 letters	15 (11.5)	2 (1.5)	6 (4.6)
10–14 letters	4 (3.1)	5 (3.8)	1 (0.8)
≥15 letters	20 (15.4)	5 (3.8)	2 (1.5)
≥15-letter gain, %			
Day 7	3.8	22.0‡	26.9‡
Month 1	5.4	30.3‡	25.4‡
Month 2	5.4	40.2‡	37.7‡
Month 3	8.5	45.5‡	36.9‡
Month 6	16.9	46.2†	47.7†

CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.
*Based on pairwise analysis of variance models adjusting for baseline ETDRS letter score (≤34 vs. 35–54 vs. ≥55). The last-observation-carried-forward method was used to impute missing data.
†$P<0.0001$ versus sham (prespecified secondary endpoint).
‡$P<0.0001$ versus sham (post hoc analyses).

Table 4. Change from Study Eye Baseline Best-Corrected Visual Acuity by Subgroup

Subgroup	No. of Patients Sham/0.3 mg/0.5 mg Ranibizumab	Visual Acuity Outcomes at Month 6 Compared with Baseline					
		Mean Change (95% CI)			Gained ≥15 ETDRS Letters, %		
		Sham	0.3 mg	0.5 mg	Sham	0.3 mg	0.5 mg
Baseline BCVA, ETDRS letter score							
≤34	26/33/30	5.7 (0.3–11.2)	18.7 (13.5–23.9)	18.4 (12.4–24.4)	19.2	48.5	53.3
35–54	49/46/50	2.4 (−2.2 to 7.1)	15.3 (11.4–19.3)	15.7 (12.1–19.4)	28.6	56.5	50.0
≥55	55/53/50	−3.0 (−7.5 to 1.5)	6.5 (1.8–11.2)	11.9 (8.7–15.1)	5.5	35.8	42.0
Baseline CFT, μm							
<450	20/23/19	−1.7 (−12.5 to 9.1)	8.0 (0.0–15.9)	10.2 (5.3–15.0)	25.0	43.5	31.6
≥450	109/108/111	1.2 (−1.6 to 4.0)	13.4 (10.5–16.3)	15.7 (13.2–18.2)	15.6	46.3	50.5
Time from CRVO diagnosis to screening							
<3 mos	80/68/74	1.1 (−2.9 to 5.1)	14.3 (10.3–18.3)	14.3 (11.1–17.5)	18.8	52.9	51.4
≥3 mos	50/64/56	0.4 (−3.4 to 4.1)	10.9 (7.1–14.7)	15.7 (12.4–18.9)	14.0	39.1	42.9

BCVA = best-corrected visual acuity; CI = confidence interval; CFT = central foveal thickness; CRVO = central retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study.
The last-observation-carried-forward method was used to impute missing data.

the mean (95% CI) EFT had decreased to 119.5 (84.9–154.1) μm (0.3 mg, n = 104) and 87.2 (53.9–120.6) μm (0.5 mg, n = 91) in the ranibizumab groups and 300.5 (262.1–338.9) μm in the sham group (n = 97) (Fig 5). The median percent reduction from baseline EFT was 94.0% in the 0.3 mg group, 97.3% in the 0.5 mg group, and 23.9% in the sham group at month 6. Another method of assessing residual edema is to determine the percentage of patients with CFT ≤250 μm at month 6, which was 75.0% (0.3 mg) and 76.9% (0.5 mg) in ranibizumab-treated patients compared with 23.1% in the sham group ($P<0.0001$ for each ranibizumab group vs. sham).

Safety Outcomes through Month 6

All patients who received at least 1 injection of ranibizumab or sham injection were evaluated for safety (sham = 129, 0.3 mg = 132, 0.5 mg = 129) (Table 6). Two key study eye SAEs were reported: 1 vitreous hemorrhage in the sham group and 1 iris neovascularization in the 0.5 mg group. There were no events of endophthalmitis, retinal tear, or retinal detachment during the 6-month treatment period. Adverse events of iris neovascularization and neovascular glaucoma were more common in the sham group than in the ranibizumab groups. Two patients in the 0.3 mg ranibizumab group and 2 patients in the 0.5 mg ranibizumab group were reported to have an AE of cataract.

Some nonocular SAEs are potentially associated with systemic VEGF inhibition and warrant closer scrutiny (Table 7). One patient in each of the 3 groups had a myocardial infarction. One patient in the 0.5 mg group had a transient ischemic attack and angina pectoris; 1 patient in the 0.3 mg group had a retinal artery occlusion; and 1 patient in the sham group had hypertension. Serious arterial thromboembolic events as defined by the Antiplatelet Trialists' Collaboration criteria[26] were balanced, with 1 nonfatal myocardial infarction occurring in each of the 3 groups.

Discussion

Central retinal vein occlusion is a cause of severe irreversible vision loss in older adults, with an incidence of approximately 30 000 eyes in the United States.[27,28] Patients who present with BCVA <20/40 have a poor natural history. The CRUISE was designed to test the safety and efficacy of intraocular ranibizumab (a potent inhibitor of VEGF A) injected monthly in patients with CRVO. Although the

Table 5. Snellen Equivalent Study Eye Best-Corrected Visual Acuity at Baseline and Month 6

Study Eye BCVA (approximate Snellen equivalent), n (%)	Baseline			Month 6*		
		Ranibizumab			Ranibizumab	
	Sham (n = 130)	0.3 mg (n = 132)	0.5 mg (n = 130)	Sham (n = 130)	0.3 mg (n = 132)	0.5 mg (n = 130)
≥20/20	0	0	0	2 (1.5)	8 (6.1)	17 (13.1)
20/25–20/40	12 (9.2)	9 (6.8)	7 (5.4)	25 (19.2)	50 (37.9)	44 (33.8)
20/50–20/63	36 (27.7)	28 (21.2)	38 (29.2)	26 (20.0)	17 (12.9)	21 (16.2)
20/80–20/160	47 (36.2)	54 (40.9)	46 (35.4)	41 (31.5)	37 (28.0)	33 (25.4)
20/200–20/500	35 (26.9)	40 (30.3)	39 (30.0)	31 (23.8)	18 (13.6)	15 (11.5)
<20/500	0	1 (0.8)	0	5 (3.8)	2 (1.5)	0

BCVA = best-corrected visual acuity.
*Last-observation-carried-forward method was used to impute missing data.

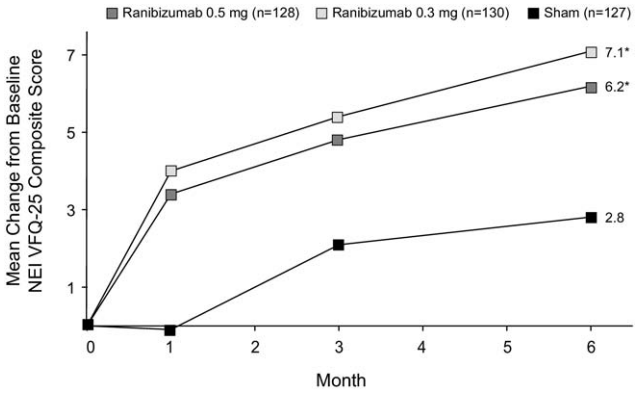

Figure 3. Mean change from baseline NEI VFQ-25 composite score over time to month 6. *$P<0.01$ versus sham (prespecified exploratory end point). The last-observation-carried-forward method was used to impute missing data. NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25.

CVOS[4] and CRUISE were conducted 20 years apart, and the entry criteria for the 2 studies were not identical, the sham group in CRUISE experienced visual outcomes similar to the natural history cohort in the CVOS. At an approximately similar time frame (i.e., 6 months in CRUISE, 4–8 months in CVOS), the CRUISE sham group and the CVOS natural history cohort had a similar net change in VA of approximately 0 letters (± 1 standard deviation). The CVOS subset that presented with a VA of 20/50 to 20/200 had 19% of patients finish with ≥20/40 compared with 20.8% in the CRUISE sham group. In marked distinction, ranibizumab-treated patients in CRUISE had a dramatic improvement in BCVA that was demonstrated as early as day 7, with continued improvements in vision at the primary end point at month 6 when patients in the 0.5 mg group gained approximately 3 lines of BCVA. Patients treated with ranibizumab were twice as likely to have BCVA of ≥20/40 compared with the sham group at month 6.

Of note, the SCORE CRVO natural history cohort actually did much worse (mean loss of 7.8 letters at month 4 and

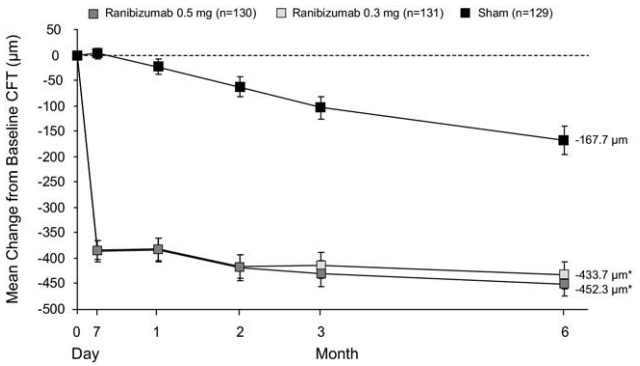

Figure 4. Mean change from study eye baseline CFT over time to month 6. *$P<0.0001$ versus sham. Earliest statistically significant difference at day 7. Vertical bars are ±1 standard error of the mean. The last-observation-carried-forward method was used to impute missing data. Independent review of OCT was performed at the UWFPRC. CFT = central foveal thickness.

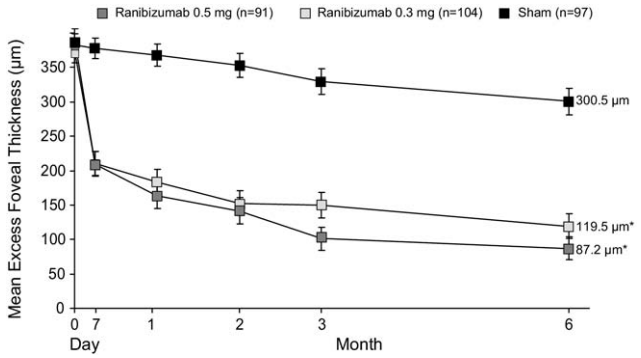

Figure 5. Mean study eye excess foveal thickness over time to month 6. *$P<0.0001$ versus sham (prespecified exploratory end point). $P<0.0001$ ranibizumab vs. sham at day 7 and months 1–3 (post hoc analyses). Vertical bars are ±1 standard error of the mean.

mean loss of 11.7 letters by month 8) than the CRUISE sham group and the CVOS natural history group. This implies that patients recruited for the SCORE CRVO study were, on average, different than those enrolled in CRUISE, and this makes it difficult to compare the results of the 2 trials. Although the mean baseline BCVA of CRUISE patients (ETDRS letter score 48.3) was slightly worse than baseline VA in the SCORE CRVO study (ETDRS letter score 51.0), CRUISE had fewer patients with large areas of capillary dropout than did SCORE CRVO. Servais and Hayreh's extensive natural history studies[29] identified the presence of a relative afferent papillary defect as one of the most sensitive and specific tests for differentiating patients with ischemic CRVO. Exclusion of patients with a positive relative afferent papillary defect from CRUISE may have effectively eliminated patients with extensive capillary dropout and may explain the differences between CRUISE and SCORE patient populations with CRVO.

Table 6. Key Study Eye Adverse Events through Month 6

		Ranibizumab	
	Sham (n = 129)	*0.3 mg (n = 132)*	*0.5 mg (n = 129)*
Adverse Events, n (%)			
Any intraocular inflammation event	5 (3.9)	3 (2.3)	2 (1.6)
Iridocyclitis	0	0	0
Iritis	3 (2.3)	2 (1.5)	2‡ (1.6)
Vitritis	2 (1.6)	1 (0.8)	1‡ (0.8)
Endophthalmitis	0	0	0
Lens damage	0	0	0
Cataract	0	2 (1.5)	2 (1.6)
Iris neovascularization	9 (7.0)	2 (1.5)	1* (0.8)
Neovascular glaucoma	2 (1.6)	0	0
Rhegmatogenous retinal detachment	0	0	0
Retinal tear	0	0	0
Vitreous hemorrhage	9 (7.0)†	5 (3.8)	7 (5.4)

*Reported as serious.
†One vitreous hemorrhage was reported as serious.
‡Same patient had iritis and vitritis.

Table 7. Key Nonocular Serious Adverse Events through Month 6

	Sham (n = 129)	Ranibizumab 0.3 mg (n = 132)	Ranibizumab 0.5 mg (n = 129)
Serious Adverse Events Potentially Related to VEGF Inhibition, n (%)			
Hemorrhagic stroke	0	0	0
Ischemic stroke	0	0	0
Transient ischemic attack	0	0	1* (0.8)
Myocardial infarction	1 (0.8)	1 (0.8)	1 (0.8)
Angina pectoris	0	0	1* (0.8)
Hypertension	1 (0.8)	0	0
Nonocular hemorrhage, other	0	0	0
Proteinuria	0	0	0
APTC ATEs, n (%)			
Vascular death	0	0	0
Nonfatal myocardial infarction	1 (0.8)	1 (0.8)	1 (0.8)
Nonfatal hemorrhagic stroke	0	0	0
Nonfatal ischemic stroke	0	0	0

APTC ATEs = Antiplatelet Trialists' Collaboration arterial thromboembolic events; VEGF = vascular endothelial growth factor.
*Same patient had transient ischemic attack and angina pectoris.

The rapid and significant resolution of macular edema by day 7 in both ranibizumab groups suggests that the majority of retinal edema in CRVO is VEGF mediated. This resolution of edema was apparent in the majority of treated patients and was sustained to month 6 with ongoing anti-VEGF suppression.

Central retinal vein occlusion is thought to occur when a thrombus forms in the central retinal vein of the optic nerve, which drains the retinal circulation. The classic histopathology study of CRVO[30] demonstrated occlusions primarily at the level of the lamina cribrosa. This occlusion of the normal venous outflow of the eye increases venous pressure to a variable degree depending on the degree of occlusion. Previously, CRVOs were classified as "ischemic" or "non-ischemic," but the anatomic improvements in this study imply that the thrombus in the central retinal vein must lead to variable amounts of ischemia in all patients with CRVO and production of VEGF with subsequent macular edema. Increased venous pressure (stasis) and Starling forces do not seem to be a major factor in the pathophysiology of macular edema in CRVO, except for the impedance of arterial flow that results from the venous blockage. It is unlikely that the inciting venous thrombus obstructs all blood flow, because it is rare to have total arterial nonperfusion in cases of CRVO. Indeed, the histopathology sections reported by Green et al[30] demonstrated only partial venous occlusion.

The CRUISE trial demonstrates that monthly intraocular ranibizumab therapy seems to be well tolerated for at least 6 months. No serious ocular AEs of endophthalmitis, traumatic cataract intraocular inflammation, or retina detachment in the study eyes were reported during the 6-month treatment period. Systemic AEs were similar across the 3 treatment groups throughout the 6-month treatment period. Safety was consistent with previous phase III ranibizumab trials in age-related macular degeneration, and no new safety events were identified in patients with CRVO.

Although the 6-month results of the CRUISE trial are laudatory, many questions and gaps remain in the management of patients with macular edema following CRVO. The CRUISE trial included only patients with BCVA <20/40. The natural history arm of the CVOS demonstrated that 29% of patients present with ≥VA 20/40. Thirty-five percent of patients in the CVOS finished with VA <20/40. The CRUISE trial did not address whether ranibizumab treatment is beneficial to patients who present with VA >20/40. It is likely that intraocular ranibizumab would decrease macular edema in all patients with CRVO and potentially lead to faster recovery of vision or better outcomes than the natural history. In addition, the duration of ranibizumab treatment required for patients with macular edema following CRVO and what percentage of patients will require treatment beyond the mandated 6 monthly treatments require further exploration. It is also yet to be determined whether the VA gains demonstrated during the 6-month treatment period will be maintained when patients roll over to criteria-based treatment during the 6-month observation period and whether the low incidence of ocular and systemic side effects will continue. It will also be interesting to learn how much vision can be recovered in patients who were originally randomized to sham therapy, although the lack of a comparator group during the observation period limits the utility of the study for that purpose.

In conclusion, although it is unlikely that ranibizumab alters the original thrombus in the central retinal vein that causes CRVO, monthly intraocular ranibizumab injections reversed both the macular edema and the VA changes in CRVO. Because rapid improvements in macular edema occur with VEGF blockade, and the cause of VEGF production in vascular diseases is known to be induced by hypoxia, the implication is that all CRVOs are ischemic to a relative degree. Monthly ranibizumab therapy improved mean BCVA and increased the proportion of patients gaining ≥15 ETDRS letters. If the functional gains are maintained with longer-term follow-up of the CRUISE cohort, it is likely that this therapy will be considered a "standard of care" for the treatment of macular edema following CRVO.

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Footnotes and Financial Disclosures

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This article contains online-only material. The following should appear online only: CRUISE Investigators (see Appendix 1; available at http://aaojournal.org).

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