

# Ranibizumab for Macular Edema Due to Retinal Vein Occlusions

## Long-term Follow-up in the HORIZON Trial

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**Purpose:** To assess long-term safety and efficacy of intraocular ranibizumab injections in patients with macular edema after retinal vein occlusion (RVO).

**Design:** Open-label extension trial of the 12-month Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) and Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety (CRUISE) trials.

**Participants:** We included 304 patients who completed BRAVO and 304 patients who completed CRUISE.

**Methods:** Patients were seen at least every 3 months and given an intraocular injection of 0.5 mg ranibizumab if they met prespecified retreatment criteria.

**Main Outcome Measures:** Primary outcomes were incidence and severity of ocular and nonocular adverse events (AEs). Key efficacy outcomes included mean change from baseline best-corrected visual acuity (BCVA) letter score by Early Treatment Diabetic Retinopathy Study protocol and central foveal thickness.

**Results:** In patients who completed month 12, the mean number of injections (excluding month 12 injection) in the sham/0.5-, 0.3/0.5-, and 0.5-mg groups was 2.0, 2.4, and 2.1 (branch RVO) and 2.9, 3.8, and 3.5 (central RVO), respectively. The incidence of study eye ocular serious AEs (SAEs) and SAEs potentially related to systemic vascular endothelial growth factor inhibition across treatment arms was 2% to 9% and 1% to 6%, respectively. The mean change from baseline BCVA letter score at month 12 in branch RVO patients was 0.9 (sham/0.5 mg), -2.3 (0.3/0.5 mg), and -0.7 (0.5 mg), respectively. The mean change from baseline BCVA at month 12 in central RVO patients was -4.2 (sham/0.5 mg), -5.2 (0.3/0.5 mg), and -4.1 (0.5 mg), respectively.

**Conclusions:** No new safety events were identified with long-term use of ranibizumab; rates of SAEs potentially related to treatment were consistent with prior ranibizumab trials. Reduced follow-up and fewer ranibizumab injections in the second year of treatment were associated with a decline in vision in central RVO patients, but vision in branch RVO patients remained stable. Results suggest that during the second year of ranibizumab treatment of RVO patients, follow-up and injections should be individualized and, on average, central RVO patients may require more frequent follow-up than every 3 months.

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In patients with central retinal vein occlusion (CRVO), blockage of the major outflow vessel of the eye results in variable changes throughout the entire retina, including hemorrhages, cotton wool patches, reduced perfusion, and edema.<sup>1,2</sup> In branch retinal vein occlusion (BRVO), blockage of 1 of the primary, secondary, or tertiary branches of the central retinal vein results in similar findings as those for CRVO; however, BRVO involves only the portion of the retina drained by the branch vein, which is 50% for the most proximal branch and less than that for more distal branches. Thus, CRVO and BRVO have many similarities, but CRVOs tend to be more severe.

Although the precise pathogenesis for the occlusions is not completely understood, recent studies have helped to clarify consequences of the occlusions on a molecular level.

The retinal vein occlusions (RVOs) result in retinal ischemia and release of large amounts of vascular endothelial growth factor (VEGF), which is a major contributor to macular edema.<sup>3,4</sup> Ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), a Fab fragment that specifically binds all isoforms of VEGF-A, has been shown to markedly reduce macular edema. Two large, multicenter, double-masked trials—the Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO)<sup>5</sup> and Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety (CRUISE)<sup>6</sup>—examined the efficacy and safety of intravitreal ranibizumab in patients with either BRVO (BRAVO) or CRVO (CRUISE). At the 6-month primary endpoint of

BRAVO, the mean gain from baseline in best-corrected visual acuity (BCVA) letter score was 16.6 and 18.3 in the 0.3- and 0.5-mg ranibizumab groups, compared with 7.3 letters in the sham group.<sup>5</sup> After the initial 6 months, BRVO patients were evaluated every month. If BCVA was  $\leq 20/40$  or central subfield thickness was  $\geq 250 \mu\text{m}$ , patients in the ranibizumab groups received an injection of their assigned dose, and patients in the sham group received 0.5 mg ranibizumab. At month 12 in the BRAVO trial, the mean improvement from baseline BCVA letter score was 16.4 (0.3 mg) and 18.3 (0.5 mg) in the 2 ranibizumab groups and 12.1 in the sham/0.5-mg group.<sup>7</sup> In patients with CRVO, after an intraocular injection of 0.3 or 0.5 mg ranibizumab every month for 6 months, the mean improvement from baseline in BCVA letter score was 12.7 and 14.9, respectively, compared with 0.8 in the sham/0.5-mg group.<sup>6</sup> At month 12 in the CRUISE trial, the mean improvement from baseline BCVA letter score was 13.9 in the 2 ranibizumab groups and 7.3 in the sham/0.5-mg group.<sup>8</sup> These data demonstrate that intraocular injections of ranibizumab provide benefits to patients with BRVO or CRVO over the course of 12 months.

The HORIZON trial (ClinicalTrials.gov identifier: NCT00379795) was designed to obtain additional information about the effects of ranibizumab in 2 patient cohorts. Cohort 1 included patients with neovascular age-related macular degeneration who had completed the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration,<sup>9</sup> the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration,<sup>10</sup> or the RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety<sup>11</sup> studies. Cohort 2 included patients with macular edema after RVO who had completed the BRAVO and CRUISE studies. Herein, we have presented the safety and efficacy outcomes of the RVO cohort from the HORIZON study.

## Materials and Methods

### Study Design and Patient Population

HORIZON (ClinicalTrials.gov identifier: NCT00379795) was an open-label, single-arm, multicenter extension trial that was conducted in accordance with the Declaration of Helsinki, applicable US Food and Drug Administration (FDA) regulations, and the Health Insurance Portability and Accountability Act. The study protocol was approved by the respective institutional review boards before study initiation, and all participating patients provided informed consent. Patients with RVO were eligible for HORIZON if they completed BRAVO or CRUISE and did not meet any of the following exclusion criteria: (1) Intraocular surgery within 1 month of study entry, (2) use of intravitreal bevacizumab in either eye, (3) concurrent use of systemic anti-VEGF agents, (4) use of any non-FDA-approved treatments for RVO in the study eye, or (5) macular edema in the study eye due to causes other than RVO, such as diabetic retinopathy.

Eligible patients who gave informed consent were evaluated at least every 3 months, or more frequently if needed, with measurement of BCVA using the Early Treatment Diabetic Retinopathy

Study protocol; a complete eye examination; measurement of vital signs; review of medical history, including concurrent medications and medical procedures; and optical coherence tomography (OCT) using Stratus OCT III (Carl Zeiss Meditec, Inc., Dublin, CA; software version 4.0 or higher). Fluorescein angiography (FA) was performed at baseline and months 12 and 24. At each study visit, patients were eligible to receive an intravitreal injection of 0.5 mg ranibizumab if mean center subfield thickness was  $\geq 250 \mu\text{m}$  or if there was evidence of persistent or recurrent macular edema deemed to be affecting the patient's visual acuity based on the investigator's evaluation. Patients with BRVO were eligible for rescue grid laser therapy if BCVA was  $\leq 20/40$  caused by macular edema. Follow-up during this extension trial was planned for up to 24 months or until 30 days after the FDA approved ranibizumab treatment for RVO.

### Outcome Measures

The primary outcome measures were the incidence and severity of ocular and nonocular adverse events (AEs). Secondary outcomes included the mean change from baseline in BCVA measured in Early Treatment Diabetic Retinopathy Study letter score at 6, 12, 18, and 24 months; the mean change from baseline in central foveal thickness (CFT) by OCT at 6 and 12 months; and the percentage of patients with CFT  $\leq 250 \mu\text{m}$  at 12 months. Exploratory analyses included the percentage of patients gaining or losing  $\geq 15$  BCVA letters from baseline and the percentages of patients with Snellen equivalent BCVA  $\geq 20/40$  or  $\leq 20/200$  at 6, 12, 18, and 24 months.

The OCT scans, fundus photographs, and FAs were evaluated by graders at the University of Wisconsin Fundus Photograph Reading Center (Madison, WI). The CFT was recorded as the center point thickness provided by Stratus software unless there was an error in computer recognition of the outer or inner boundaries of the retina or the center point. If the latter occurred, the grader determined CFT with a caliper.

### Statistical Analysis

Safety analyses included all subjects who received  $\geq 1$  ranibizumab injection at any time during either the initial study or this extension study (ranibizumab-treated patients). Efficacy analyses included all enrolled patients. Analyses of efficacy and safety were based on available cases without imputation for missing values. Efficacy and safety results were summarized descriptively, and no formal statistical tests were performed in this study.

The change from extension baseline in BCVA and CFT was calculated using the day 0 value of the extension study as baseline. In addition, the change from the baseline value of the applicable previous study was calculated for BCVA and CFT. The definition of baseline for a previous study was according to the protocol for that study. The proportion of patients gaining  $\geq 15$  letters, losing  $\leq 15$  letters in BCVA compared with the initial study baseline, and the proportion of patients with Snellen equivalent BCVA  $\geq 20/40$  or  $\leq 20/200$  were summarized at months 6 and 12.

## Results

### Patient Characteristics and Disposition

The RVO cohort of HORIZON enrolled 608 patients (Fig 1, available at <http://aaojournal.org>). Approximately 85% of patients who completed BRAVO (n = 304; sham/0.5 mg = 97; 0.3/0.5 mg [defined as patients who received 0.3 mg in BRAVO or CRUISE and received 0.5 mg during HORIZON] = 103; 0.5 mg = 104)

Table 1. Patient Demographics and Baseline Study Eye Characteristics

	Patients from BRAVO			Patients from CRUISE		
	Sham/0.5 mg (n = 97)	Ranibizumab		Sham/0.5 mg (n = 98)	Ranibizumab	
		0.3/0.5 mg (n = 103)	0.5 mg (n = 104)		0.3/0.5 mg (n = 107)	0.5 mg (n = 99)
Age, yrs, mean (SD)	66.2 (12.2)	67.7 (11.3)	68.3 (12.3)	66.0 (12.5)	71.0 (11.3)	68.2 (11.6)
Male, n (%)	54 (55.7)	46 (44.7)	58 (55.8)	57 (58.2)	55 (51.4)	60 (60.6)
Race, n (%)						
White	82 (84.5)	86 (83.5)	84 (80.8)	85 (86.7)	89 (83.2)	86 (86.9)
Black or African American	8 (8.2)	7 (6.8)	10 (9.6)	7 (7.1)	11 (10.3)	9 (9.1)
Asian	3 (3.1)	1 (1.0)	4 (3.8)	3 (3.1)	2 (1.9)	3 (3.0)
Not available/other	5 (5.2)	9 (8.7)	6 (5.8)	4 (4.1)	5 (4.7)	3 (3.0)
Visual acuity (no. of letters [0–100])						
Mean (SD)	68.1 (15.6)	73.6 (11.7)	72.2 (13.8)	59.8 (18.4)	62.5 (16.2)	64.7 (16.7)
Range	14–94	22–91	28–99	15–90	14–95	4–94
≤34, n (%)	4 (4.1)	2 (1.9)	2 (1.9)	9 (9.4)	6 (5.7)	4 (4.1)
35 to 54, n (%)	16 (16.5)	5 (4.9)	10 (9.6)	24 (25.0)	27 (25.5)	20 (20.4)
≥55, n (%)	77 (79.4)	96 (93.2)	92 (88.5)	63 (65.6)	73 (68.9)	74 (75.5)
Visual acuity (Snellen equivalent), n (%)						
≤20/200	5 (5.2)	2 (1.9)	3 (2.9)	14 (14.6)	11 (10.4)	8 (8.2)
>20/200 but <20/40	34 (35.1)	26 (25.2)	28 (26.9)	43 (44.8)	47 (44.3)	40 (40.8)
≥20/40	58 (59.8)	75 (72.8)	73 (70.2)	39 (40.6)	48 (45.3)	50 (51.0)
CFT (μm), mean (SD)	196.7 (107.4)	208.5 (144.9)	187.0 (80.8)	200.3 (132.7)	223.8 (162.3)	202.6 (123.7)

BRAVO = Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; CRUISE = Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety; SD = standard deviation.

and 87% of patients who completed CRUISE (n = 304; sham/0.5 mg = 98; 0.3/0.5 mg = 107; 0.5 mg = 99) participated in HORIZON. Patient demographics and baseline characteristics for the study eye by initial treatment group in BRAVO or CRUISE are shown in Table 1.

During the study, ranibizumab was approved by the FDA for treatment of RVO, and according to the protocol all patients were discontinued from the study by 30 days after the approval date (Table 2, available at <http://aaojournal.org>). As a result, the duration of follow-up varied considerably among patients enrolled in HORIZON, with a mean of 14±4.7 months (range, 1–24 months). About 63% of patients had a 12-month study visit; therefore, the efficacy analyses presented focus on the 12-month time point. Data were available for 205 patients with BRVO (sham/0.5 mg = 66; 0.3/0.5 mg = 66; 0.5 mg = 73) and for 181 patients with CRVO (sham/0.5 mg = 60; 0.3/0.5 mg = 70; 0.5 mg = 51) at 12 months.

Safety analyses included all patients over the entire study duration (up to 24 months).

Among patients with BRVO who completed month 12, the mean number of injections (excluding the month 12 injection) was 2.0, 2.4, and 2.1 in the sham/0.5-mg, the 0.3/0.5-mg, and 0.5-mg groups, respectively (Table 3). For patients with CRVO, the mean number of ranibizumab injections (excluding the month 12 injection) was 2.9, 3.8, and 3.5 in the sham/0.5-mg, the 0.3/0.5-mg, and 0.5-mg groups, respectively. The majority of BRAVO patients had 0 to 3 ranibizumab injections during the first 12 months of HORIZON, and the majority of CRVO patients had to 1 to 6 ranibizumab injections (Fig 2, available at <http://aaojournal.org>).

Approximately 9% (18/205) of BRVO patients who completed month 12 of HORIZON received rescue grid laser therapy during HORIZON (Table 4); 17 patients received 1 laser treatment and 1 patient received 2 laser treatments.

Table 3. Number of Ranibizumab Injections in First 12 Months of HORIZON (Excluding Injection at Month 12)

	Patients from BRAVO*			Patients from CRUISE*		
	Sham/0.5 mg	Ranibizumab		Sham/0.5 mg	Ranibizumab	
		0.3/0.5 mg	0.5 mg		0.3/0.5 mg	0.5 mg
Patients, n*	66	66	73	60	70	51
Mean (SD)	2.0 (2.2)	2.4 (2.1)	2.1 (2.6)	2.9 (2.7)	3.8 (2.8)	3.5 (2.7)
Median	1	2	1	3	4	4
Range	0–9	0–7	0–11	0–12	0–10	0–11

BRAVO = Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; CRUISE = Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety; SD = standard deviation.

\*Data are summarized for patients who completed the month 12 study visit of HORIZON.

Table 4. Rescue Grid Laser Use in BRAVO Patients Who Completed 12 Months of HORIZON RVO\*

	Sham/0.5 mg (n = 66)	Ranibizumab	
		0.3/0.5 mg (n = 66)	0.5 mg (n = 73)
None in BRAVO and HORIZON	20 (30)	34 (52)	43 (59)
Patients who received ≥1 rescue treatment, n (%)			
BRAVO only	43 (65)	26 (39)	21 (29)
HORIZON only	0	2 (3)	4 (5)
BRAVO and HORIZON	3 (5)	4 (6)	5 (7)

BRAVO = Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; RVO = retinal vein occlusion.

\*Data are summarized for patients from BRAVO who enrolled in and completed 12 months of HORIZON RVO.

**Safety Outcomes**

**Ocular.** Over the total duration of HORIZON, the most commonly reported ocular AEs in the study eye were retinal hemorrhage (11.8%, 24.3%, and 21.2% of BRAVO patients in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg groups, respectively; 18.8%, 19.6%, and 27.3% of CRUISE patients in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg groups, respectively); conjunctival hemorrhage (15.1%, 20.4%, and 14.4% of BRAVO patients in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg groups, respectively; 15.6%, 15.0%, and 16.2% of CRUISE patients in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg groups, respectively). The frequency of ocular serious AEs (SAEs) in the study eye was low (Table 5, available at <http://aaojournal.org>). Two cases of endophthalmitis were reported in the study eye in CRVO patients in the 0.3/0.5-mg ranibizumab group, exhibiting the small risk of infection inherent

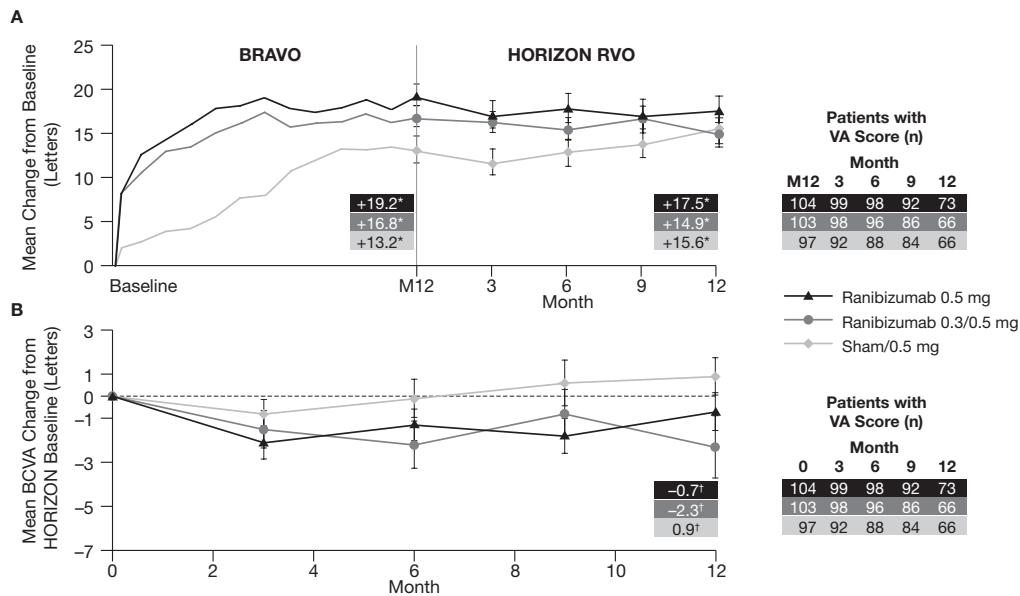
in any treatment involving repeated intraocular injections. Serious intraocular inflammation AEs did not occur in any of the groups. The overall rate of serious cataract AEs was low and no cases of traumatic cataract (lens damage) were reported. Increased intraocular pressure was reported in 2 BRVO patients, 1 each in the 0.3/0.5-mg and 0.5-mg groups, and in 1 CRVO patient in the 0.3/0.5-mg group. Other ocular SAEs seemed to be part of the natural history of RVOs and were not attributable to ranibizumab or the injection procedure.

**Nonocular.** The most common nonocular AEs were hypertension and nasopharyngitis (Table 6, available at <http://aaojournal.org>). A total of 11 deaths were reported during this study. No imbalance was observed for AEs potentially related to systemic VEGF inhibition. Arterial thromboembolic events, as categorized by the Antiplatelet Trialists' Collaboration<sup>12</sup> were reported in 6 patients enrolled from BRAVO (2.0%) and 10 patients enrolled from CRUISE (3.3%). No imbalance in changes in vital signs was observed. Nonocular SAEs were rare and similar to those seen in other trials investigating intraocular ranibizumab for other disease indications.

**Functional Outcomes at Month 12**

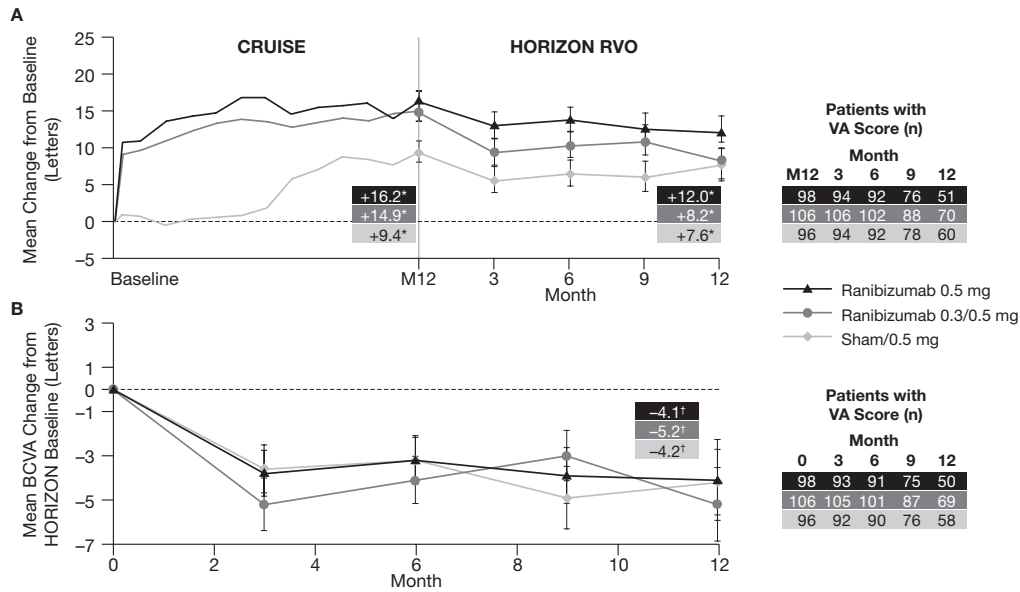
**Change from Baseline BCVA.** At HORIZON baseline, the mean change from BRAVO baseline in BCVA letter score was 13.2, 16.8, and 19.2 in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg treatment groups, respectively. At month 12 of HORIZON, the mean change from BRAVO baseline in BCVA letter score was 15.6, 14.9, and 17.5 in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg treatment groups, respectively (Fig 3A). The BCVA remained stable in BRVO patients over the first 12 months of HORIZON; the mean change in BCVA letter score at 12 months from HORIZON baseline was 0.9, -2.3, and -0.7 in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg treatment groups, respectively (Fig 3B).

At HORIZON baseline, the mean change from CRUISE baseline BCVA letter score was 9.4, 14.9, and 16.2 in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg treatment groups, respectively. At month



**Figure 3.** Mean change in visual acuity (VA) up to month 12 of HORIZON in BRAVO patients from (A) BRAVO baseline and (B) HORIZON RVO baseline. Vertical bars are ±1 SEM. \*Includes patients with data available at that time point and BRAVO baseline. †Includes patients with data available at HORIZON baseline and month 12. BCVA = best-corrected visual acuity; BRAVO = Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; RVO = retinal vein occlusion; SEM = standard error of the mean.





**Figure 4.** Mean change in visual acuity (VA) up to month 12 of HORIZON in CRUISE patients from (A) CRUISE baseline and (B) HORIZON RVO baseline. Vertical bars are  $\pm 1$  SEM. \*Includes patients with data available at that time point and CRUISE baseline. †Includes patients with data available at HORIZON baseline and month 12. BCVA = best-corrected visual acuity; CRUISE = Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety; RVO = retinal vein occlusion; SEM = standard error of the mean.

12 of HORIZON, the mean change from CRUISE baseline BCVA letter score was 7.6, 8.2, and 12.0 in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg treatment groups, respectively (Fig 4A). The BCVA decreased in ranibizumab patients with CRVO over the first 12 months of HORIZON; the mean change in BCVA letter score at 12 months from HORIZON baseline was  $-4.2$ ,  $-5.2$ , and  $-4.1$  in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg treatment groups, respectively (Fig 4B).

**Percentage of Patients Who Had BCVA Letter Score Gain or Loss of  $\geq 15$  Letters.** At month 12 of HORIZON, the percentage of BRVO patients who had an improvement of  $\geq 15$  letters from BRAVO baseline was 51.5% (sham/0.5 mg), 50.0% (0.3/0.5 mg), and 60.3% (0.5 mg), whereas the percentage of BRVO patients who lost  $\geq 15$  letters from BRAVO baseline was 1.5% (sham/0.5 mg), 1.5% (0.3/0.5mg), and 1.4% (0.5 mg; Fig 5A, available at <http://aojournal.org>). In CRVO patients, at month 12 of HORIZON, the percentage of patients who had an improvement of  $\geq 15$  letters from CRUISE baseline was 38.3% (sham/0.5 mg), 38.6% (0.3/0.5 mg), and 45.1% (0.5 mg); the percentage of CRVO patients who lost  $\geq 15$  letters from CRUISE baseline was 13.3% (sham/0.5 mg), 12.9% (0.3/0.5 mg), and 5.9% (0.5 mg; Fig 5B available at <http://aojournal.org>).

**Percentage of Patients with Snellen Equivalent BCVA  $\geq 20/40$ .** A Snellen equivalent BCVA score of  $\geq 20/40$  is generally considered a clinically relevant outcome, because it is sufficient to support reading and is a minimum visual acuity requirement for driving in the majority of states in the United States.<sup>5,13</sup> In patients with BRVO, the percentage of patients with Snellen equivalent BCVA  $\geq 20/40$  at month 12 of HORIZON was 69.7% (sham/0.5 mg), 65.2% (0.3/0.5 mg), and 61.6% (0.5 mg). In patients with CRVO, the percentage of patients with Snellen equivalent BCVA  $\geq 20/40$  at month 12 of HORIZON was 33.3% (sham/0.5 mg), 37.1% (0.3/0.5 mg), and 41.2% (0.5 mg).

**Percentage of Patients with Snellen Equivalent BCVA  $\leq 20/200$ .** Snellen equivalent BCVA  $\leq 20/200$  is a poor visual outcome and is defined as legal blindness.<sup>14</sup> This outcome occurred at month 12 in HORIZON RVO in 3.0% (sham/0.5 mg),

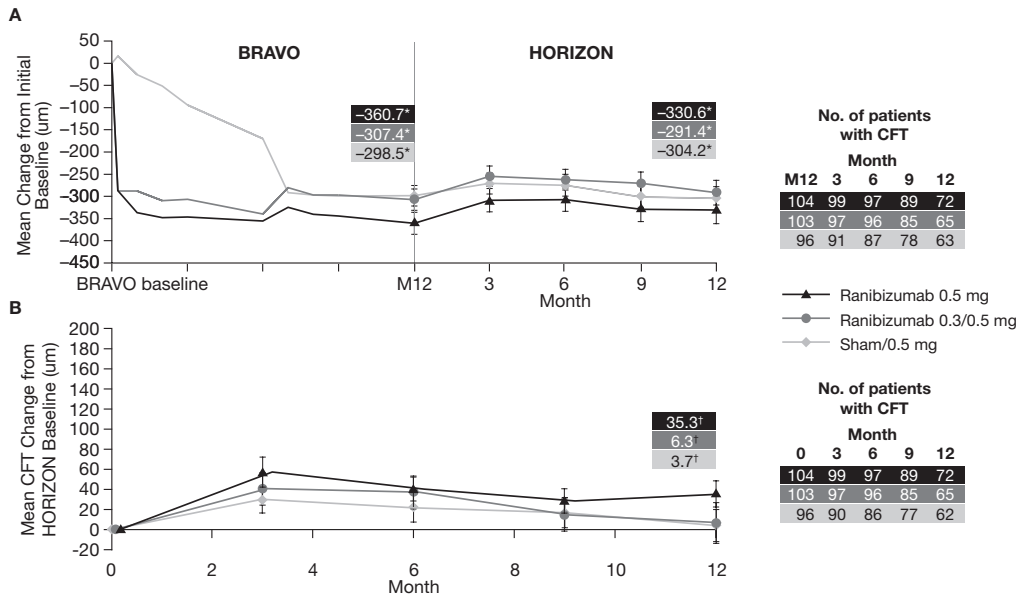
1.5% (0.3/0.5 mg), and 2.7% (0.5 mg) in BRVO patients and in 21.7% (sham/0.5 mg), 17.1% (0.3/0.5 mg), and 5.9% (0.5 mg) in CRVO patients.

### Anatomical Outcomes at Month 12

**Changes in CFT.** At HORIZON baseline, the mean reduction in CFT from BRAVO baseline was 307.4 and 360.7  $\mu\text{m}$  in the 0.3/0.5-mg and 0.5-mg ranibizumab groups compared with a reduction of 298.5  $\mu\text{m}$  in the sham/0.5-mg group. At month 12 in HORIZON, the mean reduction from BRAVO baseline was 291.4 and 330.6 in the 0.3/0.5-mg and 0.5-mg treatment groups, and 304.2 in the sham/0.5-mg group (Fig 6A). Mean CFT increases from HORIZON RVO baseline were minimal in BRVO patients; the mean changes in CFT were 3.7, 6.3, and 35.3  $\mu\text{m}$  in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg treatment groups, respectively (Fig 6B).

At HORIZON baseline, the mean reduction in CFT from CRUISE baseline was 459.5  $\mu\text{m}$  and 484.6  $\mu\text{m}$  in the 0.3/0.5-mg and 0.5-mg treatment groups compared with 481.4  $\mu\text{m}$  in the sham/0.5-mg group. At month 12 in HORIZON, the mean reduction from CRUISE baseline was 370.9 and 412.2 in the 0.3/0.5-mg and 0.5-mg treatment groups and 418.7 in the sham/0.5-mg group (Fig 7A). However, from HORIZON baseline, mean CFT increased by 79.7, 88.3, and 68.4  $\mu\text{m}$  in the sham/0.5-mg, 0.3/0.5-mg, and 0.5-mg treatment groups, respectively, at month 12 (Fig 7B).

**Residual Edema.** In addition to assessing the absolute reduction in CFT, it is important to determine how much macular edema a treatment eliminates. One way to assess residual edema is to determine the percentage of patients with CFT  $\leq 250$   $\mu\text{m}$ .<sup>15</sup> At month 12 of HORIZON, the percentage of BRVO patients with CFT  $\leq 250$   $\mu\text{m}$  was 79.4% (sham/0.5 mg), 78.5% (0.3/0.5 mg), and 75.0% (0.5 mg). At month 12 of HORIZON, the percentage of CRVO patients with CFT  $\leq 250$   $\mu\text{m}$  was 70.2% (sham/0.5 mg), 58.0% (0.3/0.5 mg), and 56.9% (0.5 mg).

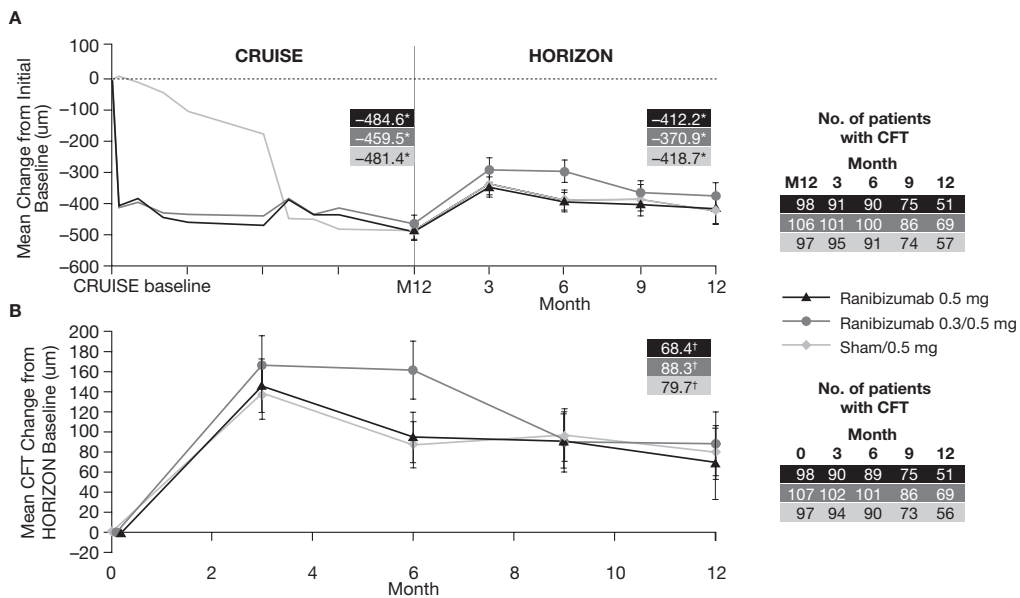


**Figure 6.** Mean change in central foveal thickness (CFT) up to month 12 of HORIZON in BRAVO\* patients from (A) BRAVO baseline and (B) HORIZON RVO baseline. Vertical bars are  $\pm 1$  SEM. \*Includes patients with data available at that time point and BRAVO baseline. †Includes patients with data available at HORIZON baseline and month 12. BRAVO = Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; SEM = standard error of the mean.

## Discussion

Overall, this study found that long-term use of intravitreal injections of 0.5 mg ranibizumab administered on an as-needed basis were well-tolerated in patients with macular edema secondary to RVO. These results are consistent with previous findings.<sup>5,6</sup> No new safety events were identified.

Among patients who have had a BRVO or CRVO for <12 months, on average, injections of ranibizumab every month for 6 months resulted in marked improvement in BCVA and macular edema compared with sham injections.<sup>5,6</sup> Benefits were maintained over the subsequent 6 months if ranibizumab was injected only if CFT  $\geq 250 \mu\text{m}$  or BCVA  $\leq 20/40$ .<sup>7,8</sup>



**Figure 7.** Mean change in central foveal thickness (CFT) up to month 12 of HORIZON in CRUISE patients from (A) CRUISE baseline and (B) HORIZON RVO baseline. Vertical bars are  $\pm 1$  SEM. \*Includes patients with data available at that time point and CRUISE baseline. †Includes patients with data available at HORIZON baseline and month 12. CRUISE = Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety; RVO = retinal vein occlusion; SEM = standard error of the mean.

The present study reports additional follow-up for a second year during which patient visits were required every 3 months; however, patients could be seen more frequently and treated every 30 days if needed. This less stringent requirement for study visits resulted in fewer injections compared with the initial trials. The reduction in frequency of ranibizumab injections during the second year of follow-up had little effect on patients with BRVO. In the BRVO ranibizumab-treated groups, mean BCVA gains achieved at month 12 of the BRAVO study were reduced by letter score values of 2.0 (0.3/0.5 mg) and 1.7 (0.5 mg) and increased by 2.4 in the sham/0.5-mg group, whereas mean CFT was increased by 16  $\mu\text{m}$  (0.3/0.5 mg) and 30  $\mu\text{m}$  (0.5 mg) in the ranibizumab groups and reduced by 6  $\mu\text{m}$  in the sham/0.5-mg group. In contrast, the reduced frequency of ranibizumab injections in the second year was observed in conjunction with worsening of outcome measures in CRVO patients. Mean BCVA gains achieved at month 12 of the CRUISE study were reduced by letter score values of 6.2 (0.3/0.5 mg), 4.0 (0.5 mg), and 2.3 (sham/0.5 mg), whereas mean CFT was increased by 89  $\mu\text{m}$  (0.3/0.5 mg), 72  $\mu\text{m}$  (0.5 mg), and 63  $\mu\text{m}$  (sham/0.5 mg).

A large number of patients with BRVO stabilized and cemented their gains after 12 months of intensive ranibizumab treatment. Despite the reduced frequency of injections in the second year, the percent of BRVO patients who gained  $\geq 15$  letters from initial study baseline remained relatively stable after 1 year of follow-up (57.3%, 61.3%, and 48.5% at month 12 in BRAVO to 50.0%, 60.3%, and 51.5% at month 12 in HORIZON for the 0.3/0.5-mg, 0.5-mg, and sham/0.5-mg groups, respectively). However, in patients with CRVO, many who had made substantial gains during 1 year of intensive ranibizumab treatment were not stabilized and required further ranibizumab treatment. Reductions in the percent of CRVO patients who gained  $\geq 15$  letters from initial study baseline were observed with the decrease in frequency of injections in the second year in the ranibizumab groups (47.2% and 59.2% at month 12 in CRUISE to 38.6% and 45.1% at month 12 in HORIZON for the 0.3/0.5-mg and 0.5-mg groups, respectively), whereas there was little change in the sham/0.5-mg group (37.5% to 38.3%).

These data are consistent with a pilot trial by Campochiaro et al,<sup>3</sup> in which patients with BRVO or CRVO received injections of ranibizumab every month for 3 months and subsequently were seen every 2 months and given a ranibizumab injection for persistent or recurrent edema. At 2 years, patients with BRVO maintained the visual gains achieved after 3 monthly injections, whereas patients with CRVO were not able to maintain their gains with repeat injections only as frequently as every 2 months. However, although this general rule applies to a group of patients with CRVO or BRVO, substantial variability occurs in each group. In the pilot trial, some patients with CRVO were free of edema and did not require any injection in the second year, some required intermittent injections, and some required injections at every visit. Similarly, in the present study, the range of injections in patients with CRVO was 0 to 12.

A likely explanation for the difference between patients with BRVO and those with CRVO in HORIZON is that patients with CRVO tend to have a greater amount of retinal ischemia. The mean level of VEGF in aqueous humor is substantially higher for patients with CRVO than those with BRVO<sup>16</sup> and iris neovascularization occurs more commonly in patients with CRVO than in patients with BRVO.

Although we have focused on the need for continued aggressive follow-up and treatment with ranibizumab during the second year of management of patients with CRVO, the results of HORIZON are encouraging. It is clear from these results that treatment with ranibizumab for up to 2 years provides benefit in patients with RVO with no identified retinal toxicity. The take-home message for clinical practice is that there is considerable variability among patients with RVO. Some stabilize after an injection of ranibizumab every month for 6 months and require few injections thereafter, whereas many (CRVO more than BRVO) require frequent follow-up and continued injections to control edema. Thus far, using frequent injections for  $\geq 2$  years in patients who require them has not shown notable disadvantages. Patients who received 0.5 mg in CRUISE maintained benefits somewhat better during HORIZON compared with patients who received 0.3 mg ranibizumab in CRUISE, even though both groups received 0.5 mg ranibizumab during the extension phase. Similarly, compared with the other 2 groups, a smaller percentage of patients in the 0.5-mg ranibizumab group lost  $\geq 15$  letters. This may be a chance occurrence, but it may mean that there are benefits to more aggressive treatment early on (higher dose or more frequent injections) that reduce the need for injections over the long-term. Currently, the role of the 2-mg ranibizumab dose in the management of macular edema after RVO is being investigated.

The use of grid laser treatment in some patients with BRVO may have contributed to the greater stability seen in BRVO patients compared with CRVO patients by decreasing production of VEGF. The percentage of BRVO patients enrolled in HORIZON that received grid laser treatment during BRAVO was 43% (0.3/0.5 mg), 36% (0.5 mg), and 67% (sham/0.5 mg). During HORIZON, the percentage was 13% (0.3/0.5 mg), 11% (0.5 mg), and 9% (sham/0.5 mg). Thus, a large proportion of patients with BRVO received grid laser treatment, with the majority of treatments occurring during BRAVO. Another strategy to reduce production of VEGF and reduce the need for prolonged injections of ranibizumab is scatter photocoagulation to peripheral areas of reduced perfusion. Currently, this strategy is being investigated for BRVO and CRVO in the Ranibizumab Dose Comparison and the Role of LASER in RETINAL Vein Occlusions study (NCT01003106).

A potential limitation of this study is the open-label, nonrandomized design. Also, because study termination resulted from the FDA approval of ranibizumab for RVO, 12-month data were not available for all patients in HORIZON and very few patients were followed for the full 24 months.

It is clear that anti-VEGF treatment is the foundation for treatment of patients with macular edema after RVO, but important questions remain. Can the loss of visual benefit

during periods of recurrent edema potentially associated with reduced frequency of injections be recovered by reinstating more frequent injections? Do patients who require frequent injections for 2 years to control edema gradually become less dependent on injections and, if not, are there other strategies that may help achieve stabilization? What is the final visual outcome in patients who have had resolution of edema? Additional studies and continued long-term follow-up are needed to answer these questions.

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## Footnotes and Financial Disclosures

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