Sustained Benefits from Ranibizumab for Macular Edema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study

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Purpose: Assess 12-month efficacy and safety of intraocular injections of 0.3 mg or 0.5 mg ranibizumab in patients with macular edema after branch retinal vein occlusion (BRVO).

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

Participants: A total of 397 patients with macular edema after BRVO.

Methods: Eligible patients were randomized 1:1:1 to 6 monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections. After 6 months, all patients with study eye best-corrected visual acuity (BCVA) ≤20/40 or central subfield thickness ≥250 μm were to receive ranibizumab. Patients could receive rescue laser treatment once during the treatment period and once during the observation period if criteria were met.

Main Outcome Measures: The main efficacy outcome reported is mean change from baseline BCVA letter score at month 12. Additional visual and anatomic parameters were assessed.

Results: Mean (95% confidence interval) change from baseline BCVA letter score at month 12 was 16.4 (14.5–18.4) and 18.3 (15.8–20.9) in the 0.3 mg and 0.5 mg groups, respectively, and 12.1 (9.6–14.6) in the sham/0.5 mg group ($P < 0.01$, each ranibizumab group vs. sham/0.5 mg). The percentage of patients who gained ≥15 letters from baseline BCVA at month 12 was 56.0% and 60.3% in the 0.3 mg and 0.5 mg groups, respectively, and 43.9% in the sham/0.5 mg group. On average, there was a marked reduction in central foveal thickness (CFT) after the first as-needed injection of 0.5 mg ranibizumab in the sham/0.5 mg group, which was sustained through month 12. No new ocular or nonocular safety events were identified.

Conclusions: At month 12, treatment with ranibizumab as needed during months 6–11 maintained, on average, the benefits achieved by 6 monthly ranibizumab injections in patients with macular edema after BRVO, with low rates of ocular and nonocular safety events. In the sham/0.5 mg group, treatment with ranibizumab as needed for 6 months resulted in rapid reduction in CFT to a similar level as that in the 0.3 mg ranibizumab treatment group and an improvement in BCVA, but not to the extent of that in the 2 ranibizumab groups. Intraocular injections of ranibizumab provide an effective treatment for macular edema after BRVO.

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In 1984, the National Eye Institute (NEI)-sponsored Branch Vein Occlusion Study (BVOS) group demonstrated that 65% of eyes (28/43) with a branch retinal vein occlusion (BRVO) treated with laser grid photocoagulation gained ≥2 lines of visual acuity (VA) compared with only 37% of eyes (13/35) with untreated BRVO at the 3-year primary end point.[1] That small seminal study established grid laser as the standard of care for the treatment of edema from BRVO for 25 years. In 2009, the NEI-sponsored Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study group published a larger study[2] (411 patients) and concluded that grid laser photocoagulation should be the recommended therapy for macular edema secondary to BRVO over intravitreal injections of triamcinolone. The SCORE BRVO trial demonstrated that 29% of eyes treated with laser photocoagulation gained ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS)[3] letters of VA at the 1-year primary end point compared with 26% of eyes treated with 1 mg intravitreal triamcinolone and 27% of eyes treated with 4 mg intravitreal triamcinolone. Although VA at the primary end point was not different between groups, the eyes treated with intravitreal triamcinolone had higher rates of cataract progression and intraocular pressure elevation. The SCORE authors noted that ". . . there is a need for improved treatments in the future, because at 12 months, less than one third of study eyes in the standard care

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group (grid laser photocoagulation) had a gain in VA letter score of ≥15, and approximately half of study eyes in the standard care group still had central retinal thickening" (defined as central foveal thickness [CFT] ≥250 μm).

The Ranibizuma*B* for the Treatment of Macular Edema following B*RA*nch Retinal *V*ein *O*cclusion: Evaluation of Efficacy and Safety (BRAVO)[4] study began recruitment in July 2007 and had recruited 397 patients by November 2008. The BRAVO study was designed to test the efficacy and safety of monthly intraocular injections of ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA), a humanized, affinity-matured, anti-vascular endothelial growth factor (VEGF) antibody fragment that binds to and neutralizes all isoforms of VEGF-A and their biologically active degradation products, for the treatment of macular edema following BRVO. Patients were randomly assigned to receive 6 monthly intraocular injections of ranibizumab or sham injections, followed by 6 months of observation, during which patients were eligible to receive monthly "as-needed" ranibizumab treatment if they met prespecified criteria. In addition, all patients were eligible for grid laser photocoagulation once during the treatment period and once during the observation period (beginning at months 3 and 9, respectively) if they met protocol-specified criteria.

Rapid and sustained visual improvements were observed in patients who received monthly injections of 0.3 mg or 0.5 mg ranibizumab compared with sham injections. At the 6-month primary end point of BRAVO, the mean gain from baseline best-corrected visual acuity (BCVA) letter score was 16.6 and 18.3 ETDRS letters in the 0.3 mg and 0.5 mg cohorts, respectively, compared with 7.3 letters in the sham cohort. The percentage of patients who gained ≥15 letters from baseline BCVA at month 6 was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups and 28.8% in the sham group.[5] The safety profile at month 6 in the BRAVO study was consistent with previous phase III ranibizumab trials, with no new safety events identified in patients with BRVO.

Although the BRAVO trial demonstrated significant VA gains at the month 6 end point in patients who received monthly intraocular ranibizumab (and led to Food and Drug Administration approval of ranibizumab in macular edema following retinal vein occlusion), questions remain about long-term outcomes with ranibizumab treatment beyond month 6. The 6-month observation period (i.e., months 6–12) was designed to provide continued assessment of ranibizumab treatment groups, to evaluate whether VA gains could be maintained after switching to as-needed ranibizumab therapy, and to determine whether patients in the sham group would benefit from as-needed treatment after a 6-month delay. We report the month 12 BRAVO safety and efficacy outcomes in an effort to answer these important questions.

Materials and Methods

Study Design

The BRAVO study was a 12-month, phase III, multicenter, randomized trial that included a 6-month, injection-controlled treatment period followed by a 6-month observation period, designed to evaluate the efficacy and safety of intraocular injections of ranibizumab in patients with macular edema following BRVO. The details of BRAVO methodology have been reported[5] and are briefly summarized in this article. During the treatment period (day 0 to month 5), patients received monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab or sham injections. During the observation period (months 6–11), all patients were to receive monthly intraocular ranibizumab if investigator-assessed study eye Snellen equivalent BCVA was ≤20/40 or mean central subfield thickness (CST) was ≥250 μm as measured by Zeiss Stratus 3 (Carl Zeiss Meditec, Inc. Dublin, CA) optical coherence tomography (OCT). The BRAVO study is registered at www.clinicaltrials.gov (NCT00486018; accessed October 21, 2010). 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.

Patients

Eligible patients were aged ≥18 years with foveal center-involved macular edema following BRVO diagnosed within 12 months of screening, study eye Snellen equivalent BCVA 20/40 to 20/400, and mean CST ≥250 μm (assessments at both screening and day 0). Patients were randomized 1:1:1 to receive monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections for 6 months.[5] Randomization was stratified by study center and baseline BCVA letter score ≤34 (approximate Snellen equivalent <20/200), 35 to 54 (approximate Snellen equivalent 20/200 to <20/80), and ≥55 letters, (approximate Snellen equivalent ≥20/80).

During months 6 to 12, patients continued to be evaluated monthly with a complete eye examination, OCT, measurement of vital signs, review of medical history (including concomitant medications and concurrent ocular procedures), and safety assessments. Fluorescein angiography (FA) was performed at months 6, 9, and 12. At months 6 and 12, the NEI Visual Functioning Questionnaire-25 (NEI VFQ-25) was administered. At each visit from months 6 to 11, all patients with study eye BCVA ≤20/40 or mean CST ≥250 μm were to receive intraocular ranibizumab. Patients in the 0.3 mg and 0.5 mg groups received their assigned dose, and patients in the sham group, hereafter referred to as the sham/0.5 mg group, received 0.5 mg ranibizumab.

Patients were eligible for laser treatment once during the 6-month treatment period and once during the 6-month observation period, beginning at months 3 and 9, respectively, if hemorrhages had cleared sufficiently to allow safe application of laser and the following criteria were met: Snellen equivalent BCVA ≤20/40 or mean CST ≥250 μm, and compared with the visit 3 months before the current visit, patient had a gain of <5 letters in BCVA or a decrease of <50 μm in mean CST. Fluorescein angiography obtained within the previous 30 days was used to guide treatment.

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 adverse events (AEs) and serious AEs (SAEs) that had occurred since the patient's last visit and to complete other study assessments.

Outcome Measures

The primary end point of BRAVO was mean change from baseline BCVA letter score at month 6. Secondary outcome measures included mean change from baseline BCVA letter score over time to month 12, proportion of patients who gained ≥15 letters from

baseline BCVA letter score at month 12, proportion of patients who lost ≥15 letters from baseline BCVA letter score at month 12, mean change from baseline CFT over time to month 12, and proportion of patients with CFT ≤250 μm at month 12. Exploratory and post hoc outcomes included mean change from baseline NEI VFQ-25 composite score over time to month 12, proportion of patients with study eye Snellen equivalent ≥20/40 at month 12, proportion of patients with study eye Snellen equivalent ≤20/200 at month 12, proportion of patients with >10 retinal hemorrhages over time to month 12, and proportion of patients with zero retinal hemorrhages over time to month 12. Safety outcomes included the incidence and severity of ocular and nonocular AEs and SAEs.

Optical coherence tomography scans, fundus photographs, and FAs were evaluated by masked graders at the University of Wisconsin Fundus Photograph Reading Center (Madison, WI); CFT was recorded as the center point thickness provided by Stratus 3 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

Analyses of efficacy end points for the observation period were based on the intent-to-treat population, with subjects grouped according to their assigned treatment, and missing values were imputed using the last observation carried forward method, unless otherwise noted. The study was not powered to compare efficacy outcomes between the treatment groups during the 6-month observation period (i.e., at months 7–12). Thus, efficacy analyses during that time were based on descriptive statistics, and presented statistical comparisons of efficacy outcomes between the sham/0.5 mg and ranibizumab treatment groups were performed post hoc. For VA and CFT outcomes, post hoc subgroup analyses based on month 6 treatment status were performed using observed data (i.e., without imputation for missing values). The incidence of key study eye ocular AEs, SAEs potentially related to VEGF inhibition, and Antiplatelet Trialists' Collaboration[4] arterial thromboembolic events were summarized by treatment group. Safety outcomes for the 0.3 mg and 0.5 mg groups were summarized for the cumulative 12-month study period. Safety outcomes for the sham/0.5 mg group were summarized separately for the treatment and observation periods.

Results

Patient Characteristics and Disposition

A total of 397 patients were randomized to receive intraocular injections of 0.3 mg (n = 134) or 0.5 mg (n = 131) ranibizumab or sham injections (n = 132) at 93 centers in the United States. Patient demographics and baseline ocular characteristics were similar across treatment groups. The mean time from diagnosis of BRVO to screening was 3.5 months (median, 2 months for each treatment group), with a duration of ≤3 months in 65% of patients. Mean baseline BCVA letter score was 54.6 letters (approximate Snellen equivalent 20/80), and mean baseline CFT was 520.5 μm. Approximately 95% of enrolled patients completed the study through month 6, and 90% completed through month 12 (Table 1). The most common reason for study discontinuation was the patient's decision to do so. During the 6-month observation period, the percentage of patients treated with ranibizumab when the protocol-specified treatment criteria were met ranged from 78% to 98% across treatment groups and time points. Between months 6 and 12, the mean number of as-needed ranibizumab injections among all randomized patients was 2.8, 2.7, and 3.6 in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups, respectively, and the percentage of patients who did not receive any injections during the observation period was 20.9%, 23.7%, and 12.9%, respectively. Twenty-one of the 397 patients were discontinued from the study before month 6. By excluding those patients, the mean number of as-needed ranibizumab injections received during the observation period was 2.9, 2.8, and 3.8 in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups, respectively, and the percentage of patients who did not receive any injections during the observation period was 17.2%, 20.0%, and 6.5%, respectively. The percentage of patients who received rescue laser treatment during the 6-month observation period was 30.6% (0.3 mg), 23.7% (0.5 mg), and 23.5% (sham/0.5 mg).

Table 1. Patient Disposition and Treatment

	Sham/0.5 mg (n = 132)	Ranibizumab 0.3 mg (n = 134)	Ranibizumab 0.5 mg (n = 131)
Completed study, n (%)			
Through month 6	123 (93.2)	128 (95.5)	125 (95.4)
Through month 12	114 (86.4)	119 (88.8)	123 (93.9)
Mean no. of injections/patient*			
Treatment period	5.5	5.7	5.7
Observation period	3.6	2.8	2.7
Patients receiving first as-needed injection at month 6, n (%)	104 (78.8)	55 (41.0)	50 (38.2)
Rescue laser treatment,† n (%)			
Treatment period‡	76 (57.6)	27 (20.1)	28 (21.4)
Observation period	31 (23.5)	41 (30.6)	31 (23.7)

*During the 6-month treatment period (day 0 to month 5), sham patients received sham injections; during the 6-month observation period (month 6–11), sham patients received 0.5 mg ranibizumab if they met prespecified criteria.
†Patients could receive rescue laser treatment once during the 6-month treatment period and once during the 6-month observation period if they met prespecified criteria.
‡Based on the final database.

Functional Outcomes at Month 12

Change from Baseline BCVA. At month 6, the primary end point, the mean change from baseline BCVA letter score, was 16.6 and 18.3 in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, compared with 7.3 in the sham group.[5] In the 0.3 mg and 0.5 mg treatment groups, these improvements were maintained with as-needed ranibizumab during the observation period, with a mean (95% CI) change from baseline BCVA letter score of 16.4 (14.5–18.4) and 18.3 (15.8–20.9), respectively, at month 12. The sham/0.5 mg group experienced an overall improvement in BCVA letter score during the observation period, with a mean (95% CI) change from baseline of 12.1 (9.6–14.6) at month 12. The mean improvement from baseline BCVA at month 12 in the sham/0.5 mg group was significantly less than that of the 0.3 mg and 0.5 mg treatment groups ($P < 0.01$ for each ranibizumab group vs. sham/0.5 mg) (Fig 1).

From month 6 to 7, mean BCVA letter score decreased in the 0.3 mg and 0.5 mg groups and increased in the sham/0.5 mg group. Across treatment groups, 59.0% (0.3 mg), 61.8% (0.5 mg), and 21.2% (sham/0.5 mg) of patients did not receive ranibizumab treatment at month 6. Most patients who did not receive an injection showed worsening of BCVA from month 6 to 7, with

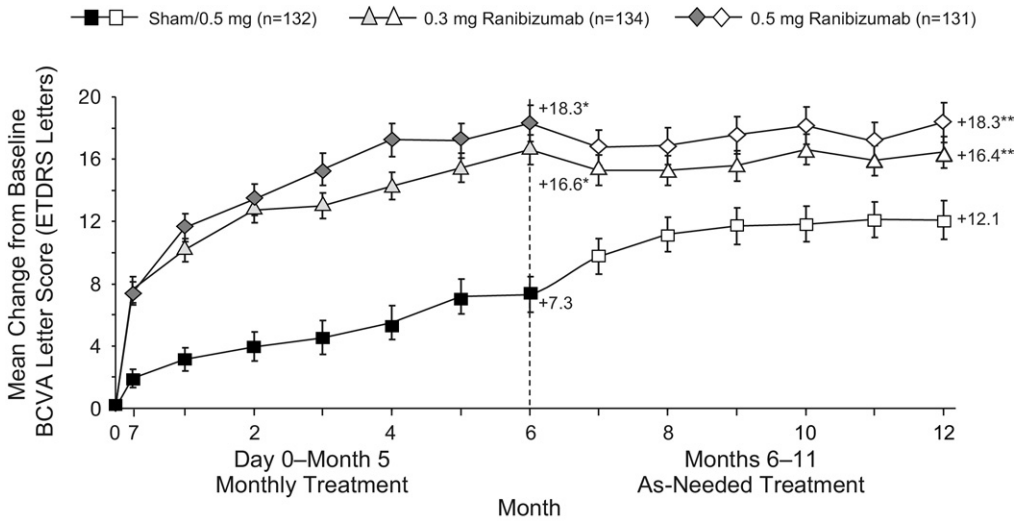

Figure 1. Mean change from study eye baseline BCVA letter score over time to month 12. *$P < 0.0001$ vs. sham, **$P < 0.01$ vs. sham/0.5 mg. Earliest statistically significant group difference was at day 7. The last observation carried forward method was used to impute missing values. Vertical bars are ±1 standard error of the mean. On average, visual gains during the treatment period were maintained in the ranibizumab treatment groups during the observation period. There was substantial improvement in VA in the sham/0.5 mg group during the observation period; however, the mean change from baseline BCVA score of sham/0.5 mg group remained significantly different from that of the 0.3 mg and 0.5 mg groups at month 12. BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; VA = visual acuity.

mean decreases in BCVA letter score of 3.1 (0.3 mg), 2.8 (0.5 mg), and 3.3 (sham/0.5 mg), whereas most of those who received an injection showed improvement in BCVA, with mean increases of 0.7 (0.3 mg), 0.4 (0.5 mg), and 3.7 (sham/0.5 mg) (Fig 2, available at http://aaojournal.org).

Percentage of Patients with a BCVA Letter Score Gain or Loss ≥15. The percentage of patients who had an improvement from baseline BCVA letter score of ≥15 at the month 6 time point was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups and 28.8% in the sham group.[5] This was maintained in the ranibizumab groups during the observation period when ranibizumab was given as needed, and at month 12 the percentage of patients who had an improvement from baseline BCVA letter score of ≥15 was 56.0% (0.3 mg) and 60.3% (0.5 mg) (Table 2). The sham/0.5 mg group showed improvement from ranibizumab injections given as needed throughout the observation period; however, the 43.9% of patients who gained ≥15 in BCVA letter score at month 12 was less than that observed in the ranibizumab groups ($P < 0.05$ for each ranibizumab group vs. sham/0.5 mg). The percentage of patients who lost ≥15 from baseline BCVA letter score was 0% (0.3 mg), 1.5% (0.5 mg), and 4.5% (sham) at month 6 compared with 0.7% (0.3 mg), 2.3% (0.5 mg), and 6.1% (sham/0.5 mg) at month 12.

Percentage of Patients with Snellen Equivalent BCVA >20/40. A Snellen BCVA of ≥20/40 is generally sufficient to support reading and driving and is considered an excellent outcome. The percentage of patients with Snellen equivalent BCVA ≥20/40 was 67.9% (0.3 mg), 64.9% (0.5 mg), and 41.7% (sham) at month 6,[5] compared with 67.9% (0.3 mg), 66.4% (0.5 mg), and 56.8% (sham/0.5 mg) at month 12. Snellen equivalent BCVA outcomes are broken down into several categories in Table 3.

Percentage of Patients with Snellen Equivalent BCVA <20/200. Snellen equivalent BCVA ≤20/200 is a poor visual outcome and is defined as legal blindness. This outcome occurred in the study eye in 1.5% (0.3 mg), 0.8% (0.5 mg), and 9.1% (sham) of patients at month 6,[5] compared with 2.2% (0.3 mg), 3.8% (0.5 mg), and 6.8% (sham/0.5 mg) of patients at month 12.

Impact of Visual Outcome on Daily Life Activities. At month 6, the mean increase from baseline NEI VFQ-25 composite score was 9.3 points (0.3 mg) and 10.4 points (0.5 mg) in the ranibizumab treatment groups compared with 5.4 points in the sham group.[5] Treatment with ranibizumab as needed from months 6 to 11 maintained, on average, the increases in the 2 ranibizumab groups (9.0 points in the 0.3 mg group, 10.2 points in the 0.5 mg group) and resulted in a mean increase (from baseline) of 7.4 points in the sham/0.5 mg group (Fig 3).

Anatomic Outcomes at Month 12

Change From Baseline CFT. At the month 6 time point, the mean change from baseline CFT was a reduction of 337.3 μm and 345.2 μm in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, compared with a reduction of 157.7 μm in the sham group.[5] In the 0.3 mg and 0.5 mg treatment groups, these reductions were maintained with as-needed ranibizumab during the observation period, with a mean reduction from baseline CFT of 313.6 μm and 347.4 μm, respectively, at month 12 (Fig 4). The sham/0.5 mg group experienced an overall improvement in CFT during the observation period, with a mean reduction from baseline of 273.7 μm at month 12. The mean improvement from baseline CFT at month 12 in the sham/0.5 mg group was significantly less than that of the 0.5 mg treatment group ($P < 0.05$ sham/0.5 mg vs. 0.5 mg).

Most patients in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups who did not receive an injection of as-needed ranibizumab at month 6 showed worsening of CFT from month 6 to 7, with mean increases of 99 μm, 64 μm, and 60 μm, respectively, from month 6 to 7, whereas most who received an injection showed improvement or no change in CFT from month 6 to 7, with mean reductions of 4 μm, 14 μm, and 137 μm, respectively, from month 6 to 7 (Fig 5, available at http://aaojournal.org).

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 this is to determine the percentage of patients with CFT ≤250 μm. At the month 6 time point, 91.0% (0.3 mg) and 84.7% (0.5 mg) of ranibizumab-treated patients had a CFT ≤250 μm compared with 45.5% of patients in the sham group.[5] At month 12, the percentages in the ranibizumab

Table 2. Change from Baseline Study Eye Best-Corrected Visual Acuity at Month 12

Change from Baseline BCVA (ETDRS Letters) at Month 12	Sham/0.5 mg (n = 132)	Ranibizumab 0.3 mg (n = 134)	Ranibizumab 0.5 mg (n = 131)
Mean (SD)	12.1 (14.4)	16.4 (11.6)	18.3 (14.6)
95% CI for mean	9.6–14.6	14.5–18.4	15.8–20.9
Difference in means (vs. sham/0.5 mg)		4.3	6.2
95% CI for difference		1.2–7.5	2.7–9.8
P value (ranibizumab vs. sham/0.5 mg)		0.0035	0.0007
Distribution of change at month 12, n (%)			
Gain			
≥15 letters	58 (43.9)	75 (56.0)	79 (60.3)
10–14 letters	22 (16.7)	23 (17.2)	17 (13.0)
5–9 letters	21 (15.9)	15 (11.2)	15 (11.5)
No change, ±4.0 letters	21 (15.9)	18 (13.4)	14 (10.7)
Loss			
5–9 letters	1 (0.8)	2 (1.5)	3 (2.3)
10–14 letters	1 (0.8)	0	0
≥15 letters	8 (6.1)	1 (0.7)	3 (2.3)
≥15-letter gain, %			
Month 7	34.1	50.0	59.5
Month 8	39.4	50.7	53.4
Month 9	40.2	50.7	58.0
Month 10	41.7	54.5	58.8
Month 11	38.6	47.8	60.3

BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation. Last observation carried forward method was used to impute missing data.

groups were similar to or slightly lower than those at month 6 (83.6% [0.3 mg] and 86.3% [0.5 mg]) and had increased markedly to 78.8% in the sham/0.5 mg group (Table 4).

Retinal Hemorrhages. Indirect ophthalmoscopy or biomicroscopy by investigators indicated that 3.7% (0.3 mg), 1.5% (0.5 mg), and 4.5% (sham) of patients had no intraretinal hemorrhages at baseline, whereas 76.1%, 75.6%, and 78.0%, respectively, had >10 intraretinal hemorrhages (Fig 6, available at http://aaojournal.org). A greater increase was observed in the percentage of patients with no intraretinal hemorrhage in the 0.3 mg and 0.5 mg groups compared with the sham group at month 6 and the sham/0.5 mg group at month 12, and the percentage of patients who had >10 intraretinal hemorrhages decreased more rapidly in the ranibizumab treatment groups compared with the sham/0.5 mg group.

Safety Outcomes at Month 12

The most frequently reported key study eye AEs were cataract (4.5% [0.3 mg, 12-month rate], 6.2% [0.5 mg, 12-month rate], 3.1% [sham, 6-month treatment period rate], and 2.6% [sham/0.5 mg, 6-month observation period rate]) and vitreous hemorrhage (5.2% [0.3 mg, 12-month rate], 1.5% [0.5 mg, 12-month rate], 4.6% [sham, 6-month treatment period rate], and 0.9% [sham/0.5 mg, 6-month observation period rate]) (Table 5).

The incidence of nonocular SAEs potentially related to VEGF inhibition throughout the 12-month study was 6 each in the 0.3 mg (4.5%) and 0.5 mg (4.6%) groups. One nonocular SAE potentially related to VEGF inhibition (0.8%) was reported in the sham group during the 6-month treatment period, and 2 SAEs (1.7%) were reported in the sham/0.5 mg group during the 6-month observation period (Table 6). One patient in the 0.3 mg group experienced an ischemic stroke, 1 patient each in the 0.5 mg and sham groups had a hemorrhagic stroke, and 1 patient each in the 0.5 mg and sham/0.5 mg groups had an acute myocardial infarction, all of which qualified as Antiplatelet Trialists' Collaboration arterial thromboembolic events (Table 6).

Discussion

During the initial treatment period, monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab provided rapid visual and anatomic improvements in patients with BRVO. The mean gain in BCVA ETDRS letter score was 7.5 by day 7 and 16.6 (0.3 mg) and 18.3 letters (0.5 mg) at month 6. Beginning at month 6 and throughout the observation period, patients continued to be examined monthly and could receive intraocular injections of ranibizumab if ETDRS refracted BCVA was ≤20/40 or mean CST was ≥250 μm according to Stratus 3 OCT. This as-needed treatment paradigm led to a mean of 2.8 (0.3 mg) and 2.7 (0.5 mg) additional injections during the 6-month observation period, and at month 12, the mean

Table 3. Snellen Equivalent Study Eye Best-Corrected Visual Acuity

	Baseline			Month 6*			Month 12*		
		Ranibizumab			Ranibizumab			Ranibizumab	
Study Eye BCVA (Approximate Snellen Equivalent), n (%)	Sham (n=132)	0.3 mg (n = 134)	0.5 mg (n = 131)	Sham† (n = 132)	0.3 mg (n = 134)	0.5 mg (n = 131)	Sham/0.5 mg† (n = 132)	0.3 mg (n = 134)	0.5 mg (n = 131)
≥20/20	0	0	0	9 (6.8)	27 (20.1)	26 (19.8)	17 (12.9)	27 (20.1)	26 (19.8)
20/25–20/40	19 (14.4)	21 (15.7)	15 (11.5)	46 (34.8)	64 (47.8)	59 (45.0)	58 (43.9)	64 (47.8)	61 (46.6)
20/50–20/63	44 (33.3)	46 (34.3)	36 (27.5)	27 (20.5)	25 (18.7)	25 (19.1)	23 (17.4)	28 (20.9)	22 (16.8)
20/80–20/160	55 (41.7)	53 (39.6)	59 (45.0)	38 (28.8)	16 (11.9)	20 (15.3)	25 (18.9)	12 (9.0)	17 (13.0)
20/200–20/500	14 (10.6)	14 (10.4)	21 (16.0)	12 (9.1)	2 (1.5)	1 (0.8)	9 (6.8)	3 (2.2)	5 (3.8)
<20/500	0	0	0	0	0	0	0	0	0

BCVA = best-corrected visual acuity.
Baseline and month 6 data are based on month 6 database.
*Last observation carried forward method was used to impute missing data.
†During the 6-month treatment period (day 0 to month 5), sham patients received sham injections; during the 6-month observation period (month 6–11), sham patients received 0.5 mg ranibizumab if they met prespecified criteria.

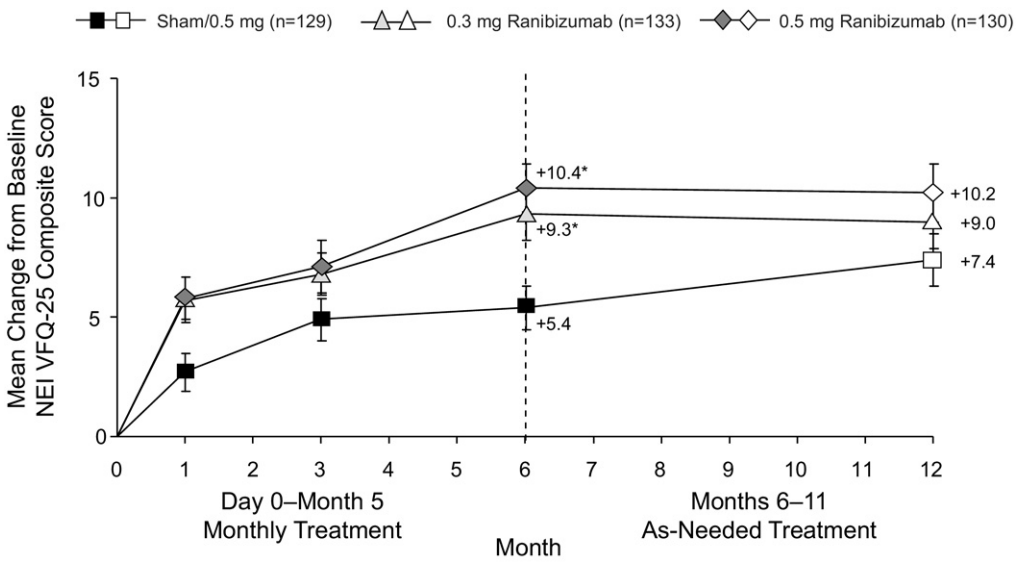

Figure 3. Mean change from baseline NEI VFQ-25 composite score over time to month 12. *$P < 0.005$ vs. sham. The last observation carried forward method was used to impute missing data. Vertical bars are ±1 standard error of the mean. The composite score increased rapidly and was significantly greater in the ranibizumab treatment groups compared with the sham group at month 6. During the observation period, on average, the composite score remained stable in the ranibizumab groups and increased substantially in the sham/0.5 mg group, which was no longer significantly different than the ranibizumab groups at month 12. NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25.

letter score gain experienced after the initial 6 monthly ranibizumab injections was maintained (16.4 in 0.3 mg group and 18.3 in 0.5 mg group). Patient-reported improvements in visual function mirrored improvements in BCVA, with increases in NEI VFQ-25 composite scores observed at month 6 maintained at month 12.

Retinal diseases that are responsive to anti-VEGF therapy can be roughly divided into choroidal neovascular processes that predominantly affect the outer retina (e.g., photoreceptors and retinal pigment epithelium complex) and retinal vascular diseases that predominantly affect the inner retina. Outer retinal diseases with edema, such as neovas-

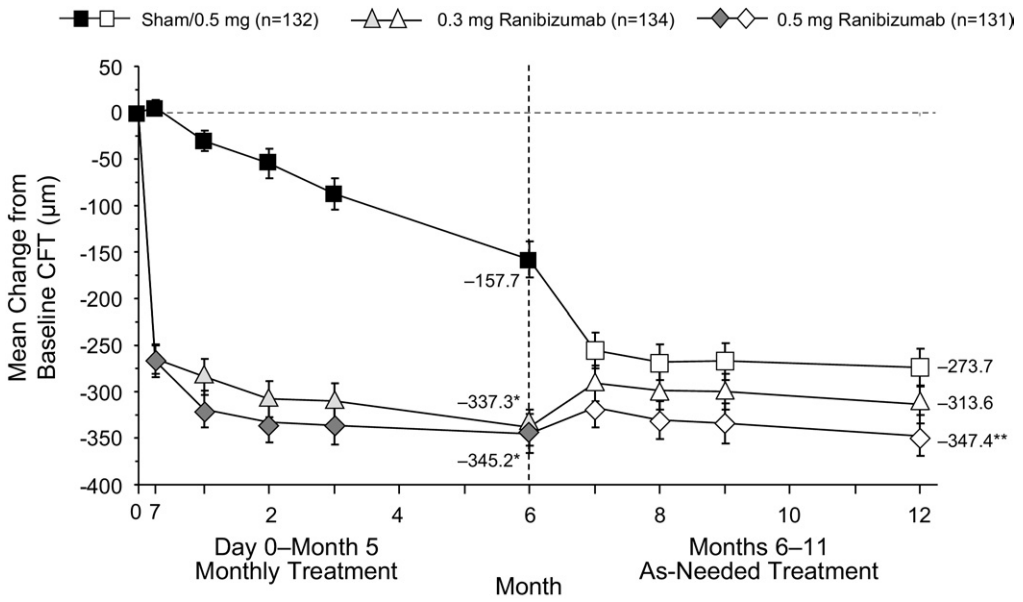

Figure 4. Mean change from baseline CFT over time to month 12. Month 6 values are based on month 6 database. *$P < 0.0001$ vs. sham. **$P < 0.05$ vs. sham/0.5 mg (post hoc analysis). The last observation carried forward method was used to impute missing values. Earliest statistically significant group difference was at day 7. Vertical bars are ±1 standard error of the mean. On average, improvements in CFT during the treatment period were maintained in the ranibizumab groups during the observation period. There was substantial improvement in the sham/0.5 mg group during the observation period; however, the mean change from baseline CFT in the sham/0.5 mg group remained significantly different from that of the 0.5 mg group at month 12. Note that at baseline, mean sham-group CFT was 488.0 μm, compared with 522.1 μm (0.3 mg) and 551.7 μm (0.5 mg) in the ranibizumab treatment groups. CFT = central foveal thickness.

Table 4. Study Eye Central Foveal Thickness

	Sham/0.5 mg (n = 132)	Ranibizumab 0.3 mg (n = 134)	Ranibizumab 0.5 mg (n = 131)
Baseline, n (%)			
≤250 μm	19 (14.4)	8 (6.0)	6 (4.6)
>250–400 μm	28 (21.2)	35 (26.1)	28 (21.4)
>400 μm	85 (64.4)	91 (67.9)	97 (74.0)
Month 6,* n (%)			
≤250 μm	60 (45.5)	122 (91.0)	111 (84.7)
>250–400 μm	24 (18.2)	7 (5.2)	8 (6.1)
>400 μm	48 (36.4)	5 (3.7)	12 (9.2)
Month 12,* n (%)			
≤250 μm	104 (78.8)	112 (83.6)	113 (86.3)
>250–400 μm	14 (10.6)	13 (9.7)	7 (5.3)
>400 μm	14 (10.6)	9 (6.7)	11 (8.4)

Baseline and month 6 data are based on month 6 database.
*Last observation carried forward method was used to impute missing data at post-baseline time points.

cular age-related macular degeneration (AMD), cause rapid and often irreversible vision loss secondary to damage to the critical photoreceptors in a relatively short period of time. Chronic continuous monthly suppression of VEGF with ranibizumab in wet AMD significantly improves VA,[6,7] but less frequent therapy almost uniformly leads to loss of these gains (Singer M, Wong P, Wang P-W, Scott L. HORIZON extension trial of ranibizumab (Lucentis, Genentech, South San Francisco, CA) for neovascular age-related macular degeneration (AMD): cumulative 2-year safety/efficacy results. Paper presented at ARVO, May 3–7, 2009; Ft. Lauderdale, FL) (also see Regillo et al[8] and Abraham et al[9]).

Most inner retinal diseases (e.g., retinal venous occlusive disease and diabetic macular edema) either follow acute vascular events (arterial or venous occlusion) or result from chronic retinal vascular damage secondary to diabetes mellitus or hypertension. The retinal pigment epithelium pump attempts to keep the engine of phototransduction (i.e., the rods and cones) deturgesced during the disease process, allowing eyes in a subset of patients with retinal vascular disease to maintain the capacity for significant visual recovery despite chronic or recurrent edema. On average, maintenance of VA gains with as-needed ranibizumab dosing after 6 months of monthly therapy in BRAVO and its companion Ranibizumab for the Treatment of Macular Edema after *C*entral *R*etinal Vein Occl*U*s*I*on *S*tudy: *E*valuation of Efficacy and Safety (CRUISE) study (Campochiaro PA, personal communication, February 2011) illustrates this phenomenon. In addition, sham patients in both trials demonstrated significant visual gains once as-needed ranibizumab therapy was instituted after 6 months of standard of care. However, in neither trial did patients in the sham/0.5 mg group achieve VA gains from baseline as great as those of patients who received ranibizumab treatment beginning at day 0. This suggests that prolonged edema resulting from undertreatment, because of a PRN dosing schedule or delay in the initiation of treatment, may result in irreversible retinal damage. Further information regarding whether longer periods of edema have a negative consequence on vision will be available from results of the HORIZON retinal vein occlusion extension study, in which patients who completed BRAVO and CRUISE were followed with mandated quarterly visits.

Because BRAVO excluded patients with a diagnosis of BRVO >12 months, our results do not address whether anti-VEGF therapy would benefit patients with chronic disease. The original BVOS report did not exclude chronic cases, and in patients with a diagnosis of BRVO >12 months (approxi-

Table 5. Key Study Eye Adverse Events Through Month 12

	Sham* Day 0 to Month 6 (n = 131)	Sham/0.5 mg† Months 6 to 12 (n = 115)	Ranibizumab 0.3 mg Day 0 to Month 12 (n = 134)	Ranibizumab 0.5 mg Day 0 to Month 12 (n = 130)
AEs, n (%)				
Any intraocular inflammation event (iridocyclitis, iritis, vitritis)	4 (3.1)	1 (0.9)	3 (2.2)	0
Endophthalmitis	0	0	0	1 (0.8)‡
Lens damage	0	0	0	0
Cataract	4 (3.1)	3 (2.6)	6 (4.5)	8 (6.2)
Iris neovascularization	3 (2.3)	0	1 (0.7)	1 (0.8)
Neovascular glaucoma	0	0	0	0
Rhegmatogenous retinal detachment	0	0	1 (0.7) ‡,§	0
Retinal tear	0	0	1 (0.7) ‡,§	0
Vitreous hemorrhage	6 (4.6)	1 (0.9)	7 (5.2)	2 (1.5)

AE = adverse event.
*Outcomes during 6-month treatment period for safety-evaluable sham group (i.e., received at least 1 sham injection).
†Outcomes during 6-month observation period for safety-evaluable sham/0.5 mg group (i.e., received at least 1 injection of 0.5 mg ranibizumab).
‡Reported as serious.
§Same patient had rhegmatogenous retinal detachment and retinal tear.

Table 6. Key Nonocular Serious Adverse Events Through Month 12

	Sham Day 0 to Month 6* (n = 131)	Sham/0.5 mg Months 6–12† (n = 115)	Ranibizumab 0.3 mg Day 0 to Month 12 (n = 134)	Ranibizumab 0.5 mg Day 0 to Month 12 (n = 130)
SAEs potentially related to VEGF inhibition, n (%)	1 (0.8)	2 (1.7)	6 (4.5)	6 (4.6)
Hemorrhagic stroke	1 (0.8)	0	0	1 (0.8)
Ischemic stroke	0	0	1 (0.7)	0
Acute myocardial infarction	0	1 (0.9)	0	1 (0.8)
Unstable angina	0	0	0	1 (0.8)
Hypertension	0	1 (0.9)	3 (2.2)	1 (0.8)
Nonocular hemorrhage, other	0	0	2 (1.5)	1 (0.8)
Intestinal perforation	0	0	0	1 (0.8)
Proteinuria	0	0	0	0
APTC ATEs, n (%)	1 (0.8)	1 (0.9)	1 (0.7)	2 (1.5)
Vascular death	0	0	0	0
Death from unknown cause	0	0	0	0
Nonfatal myocardial infarction	0	1 (0.9)	0	1 (0.8)
Nonfatal hemorrhagic stroke	1 (0.8)	0	0	1 (0.8)
Nonfatal ischemic stroke	0	0	1 (0.7)	0

APTC ATEs = Antiplatelet Trialists' Collaboration arterial thromboembolic events; SAE = serious adverse event; VEGF = vascular endothelial growth factor.
*Outcomes during 6-month treatment period for safety-evaluable sham group (i.e., received at least 1 sham injection).
†Outcomes during 6-month observation period for safety-evaluable sham/0.5 mg group (i.e., received at least 1 injection of 0.5 mg ranibizumab).

mately one third of study patients), the treatment effect of grid laser photocoagulation was not different than in those with a diagnosis of BRVO <12 months. The BVOS included only patients with a diagnosis of BRVO ≥3 months. In the BRAVO study, approximately 65% of patients had a diagnosis ≤3 months, and some of the VA gains in the initial 6 months of the study may be attributable to spontaneous improvement. The VA gains in the sham/0.5 mg group during months 6–11 are not likely to represent spontaneous improvement and more likely attributable to the institution of as-needed ranibizumab therapy. This implies that ranibizumab therapy has a beneficial effect even in more chronic cases.

Greater VA gains might have occurred in the ranibizumab treatment groups and the sham group if patients received monthly ranibizumab injections rather than as-needed therapy during months 6–11. For instance, across all groups, patients who received intraocular ranibizumab at month 6 had mean increases in VA at month 7 compared with mean decreases in those who were not treated at month 6; however, it is likely that some of the observed effect at month 7 may be secondary to a ceiling phenomenon, because it is not possible to have VA gains if the maximum potential VA has been achieved.

After 6 monthly injections, 91.0% of patients receiving 0.3 mg ranibizumab and 84.7% of patients receiving 0.5 mg ranibizumab had CFT ≤250 μm, which implies that the monthly anti-VEGF regimen was able to eliminate macular edema in most patients. On average, as-needed ranibizumab therapy maintained this anatomic effect through month 12; however, some patients in each of the groups had CFT >250 μm at month 12 (16.4% in the 0.3 mg group, 13.7% in the 0.5 mg group, and 21.2% in the sham/0.5 mg group), indicating that resolution of edema was not universal. It is not known if a more frequent treatment regimen (>3.6 average as-needed injections) would eliminate macular edema in the sham/0.5 mg group or whether a higher dose of ranibizumab, such as the 2.0 mg ranibizumab dose currently under investigation for neovascular AMD (Clinicaltrials.gov NCT00891735, accessed October 14, 2010), would lead to a higher percentage of edema-free patients with either monthly or as-needed ranibizumab.

In the BRAVO trial, rescue grid laser photocoagulation was offered once during the 6-month treatment period (at months 3, 4, or 5) and once during the 6-month observation period (at months 9, 10, or 11) for patients who met the protocol-specified treatment criteria. During the observation period, the percentage of patients who received laser treatment decreased in the sham/0.5 mg group, whereas a slightly higher percentage of patients in the ranibizumab groups received rescue laser during the observation period compared with the treatment period. Twenty-nine percent of patients in the grid laser arm of the SCORE-BRVO study gained 15 letters of VA at month 12 without concomitant anti-VEGF therapy. At month 12 in BRAVO, 56.0% (0.3 mg), 60.3% (0.5 mg), and 43.9% (sham/0.5 mg) of patients gained ≥15 ETDRS letters of VA. Although it is possible that some degree of the month 12 improvements in BRAVO patients was secondary to a concomitant laser effect, the immediate VA improvement demonstrated in patients with anti-VEGF therapy had a particular advantage over laser therapy alone.

It is interesting that in both the BRAVO and CRUISE studies, intraretinal hemorrhages cleared more rapidly in the ranibizumab group than in the sham group. The mechanism for this is unknown, but it suggests that in addition to reducing leakage and edema, ranibizumab affects other features of the

disease process in patients with retinal vein occlusion. Hemorrhage is an impediment to grid laser therapy, and more rapid hemorrhage clearance could make it feasible to consider grid laser earlier in patients who have dense macular hemorrhages at initial evaluation. It remains to be seen whether a combination approach, using anti-VEGF therapy to decrease macular hemorrhage (allowing earlier laser) and macular edema (allowing less laser power and more precise photocoagulation burns), would provide greater benefit than using either treatment alone.

In conclusion, although the 6- and 12-month VA gains and anatomic improvements demonstrated in the BRAVO trial are impressive and unprecedented, the necessity for ongoing treatment after 6 months of monthly ranibizumab therapy implies that anti-VEGF therapy does not alter the underlying pathophysiology of an anatomic blockage in the retinal vein. This blockage undoubtedly continues to compromise arterial perfusion and leads to persistent hypoxia and VEGF production in the affected retina, which in turn leads to recurrent edema and decreased vision in many patients once VEGF blockade diminishes. Future therapies that address the vein blockage primarily or reduce VEGF production in the affected retina may be necessary to reduce the need for ongoing injection therapy in many patients. Until that time, the mainstay of treatment for macular edema following BRVO is likely to involve frequent intraocular anti-VEGF injections with or without grid laser photocoagulation.

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Footnotes and Financial Disclosures

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