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Individualized Stabilization Criteria–Driven Ranibizumab versus Laser in Branch Retinal Vein Occlusion

Six-Month Results of BRIGHTER

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Purpose: To compare the 6-month efficacy and safety profile of an individualized stabilization criteria–driven pro re nata (PRN) regimen of ranibizumab 0.5 mg with or without laser versus laser alone in patients with visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO).

Design: A 24-month, prospective, open-label, randomized, active-controlled, multicenter, phase IIIb study.

Participants: A total of 455 patients.

Methods: Eligible patients were randomized 2:2:1 to receive ranibizumab (n = 183), ranibizumab with laser (n = 180), or laser only (n = 92). Patients treated with ranibizumab with or without laser received a minimum of 3 initial monthly ranibizumab injections until visual acuity (VA) stabilization, and VA-based PRN dosing thereafter. In the ranibizumab with laser and laser-only groups, laser was given at the investigator's discretion at a minimum interval of 4 months and if VA was <79 letters.

Main Outcome Measures: Mean change from baseline at month 6 in best-corrected visual acuity (BCVA) (primary end point) and central subfield thickness, and safety over 6 months. Exploratory objectives were to evaluate the influence of baseline BCVA, disease duration, and ischemia on BCVA outcomes at month 6.

Results: Baseline mean BCVA was 57.7 letters, and mean BRVO duration was 9.9 months. Ranibizumab with or without laser was superior to laser only in improving mean BCVA from baseline at month 6 (14.8 and 14.8 vs. 6.0 letters; both $P < 0.0001$; primary end point met). Patients with a shorter BRVO duration at baseline had a higher mean BCVA gain than those with a longer BRVO duration. Patients with a poor baseline VA had a better BCVA gain than those with a higher baseline VA, although final BCVA was lower in those with poor baseline VA. In the ranibizumab with or without laser groups, the presence of some macular ischemia at baseline did not influence mean BCVA gains. There were no new ocular or nonocular safety events.

Conclusions: Ranibizumab with an individualized VA-based regimen, with or without laser, showed statistically significant superior improvement in BCVA compared with laser alone in patients with BRVO. Overall, there were no new safety events other than those reported in previous studies. *Ophthalmology 2016;123:1332-1344*

*Supplemental material is available at www.aaojournal.org.

Anti–vascular endothelial growth factor (VEGF) treatment is the current standard of care for macular edema secondary to branch retinal vein occlusion (BRVO).[1] Ranibizumab 0.5 mg was approved by the US Food and Drug Administration in June 2010 and by the European Union in 2011 for the treatment of visual impairment due to macular edema secondary to BRVO, based on the 6-month results of a phase III, randomized, double-masked, controlled study, the BRAnch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) trial, using a fixed monthly injection regimen in the first 6 months.[2]

The BRIGHTER study (group members of this study are cited in Appendix 1, available at www.aaojournal.org) was a phase IIIb, multicenter study assessing the efficacy and safety profile of an individualized stabilization criteria–driven pro re nata (PRN) dosing regimen of ranibizumab 0.5 mg alone or in combination with laser versus laser photocoagulation in patients with visual impairment due to macular edema secondary to BRVO.

This study is being conducted to show that the stabilization criteria–driven PRN dosing regimen of ranibizumab 0.5 mg, as approved in the European Union,[3] with or without

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adjunctive laser has efficacy similar to the monthly dosing regimen that was assessed in the BRAVO study.[2]

The BRAVO study was the first prospective 12-month, randomized, sham-controlled, multicenter study that demonstrated the effectiveness of ranibizumab in managing patients with macular edema secondary to BRVO. The improvements in best-corrected visual acuity (BCVA) and central foveal thickness (CFT) observed with a monthly dosing of ranibizumab 0.5 mg in the first 6 months (baseline to month 5; at month 6, mean change in BCVA: +18.3 letters [primary end point] and mean change in CFT: −345.2 μm)[2] were largely maintained with a PRN dosing regimen and monthly monitoring until month 12 (mean change in BCVA: +18.3 letters and mean change in CFT: −347.4 μm).[4]

The HORIZON study (cohort 2; ClinicalTrials.gov identifier: NCT00379795) was a 1-year, open-label extension of the BRAVO and Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUslon Study: Evaluation of Efficacy and Safety (CRUISE) studies. In this study, it was observed that the gains in BCVA achieved at the end of 12 months in the BRAVO and CRUISE studies were maintained for an additional 12 months with a PRN dosing regimen and with less frequent monitoring. A total of 60.3% of patients gained ≥15 letters in the HORIZON study (similar to 60.3% at month 12 in the BRAVO study).[5,6]

The BRIGHTER study is designed to address the following questions to aid physicians in optimizing treatment for patients with BRVO: (1) provide long-term data on the efficacy and safety of the individualized visual acuity (VA) stabilization criteria−driven PRN dosing regimen of ranibizumab 0.5 mg in a broad patient population with BRVO, including those with macular ischemia; and (2) the impact of adjunct laser treatment on BCVA outcome and the number of ranibizumab injections required. Here, we report the 6-month primary and main secondary outcomes from the 24-month BRIGHTER study (Group members of this study are cited in Appendix 1, available at www.aaojournal.org).

Methods

Study Design

The BRIGHTER study was a 24-month, phase IIIb, randomized, open-label, active-controlled, 3-arm, multicenter study assessing the efficacy and safety profile of an individualized stabilization criteria−driven PRN dosing regimen of ranibizumab 0.5 mg with or without laser versus laser alone in patients with visual impairment due to macular edema secondary to BRVO. The study is being conducted across 17 countries worldwide (Appendix 2, available at www.aaojournal.org). The study started in May 2012 and was completed in 2015. The first 6 months of the BRIGHTER study were conducted from May 2012 and November 2015 and included recruitment and all the other steps.

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was reviewed and approved by an independent ethics committee or institutional review board at each contributing center. Patients provided written informed consent before entering the study. The study is registered with Clinicaltrials.gov as NCT01599650.

Patients

The study population consisted of patients aged ≥18 years with visual impairment due to macular edema secondary to BRVO. The key inclusion criteria included a BCVA letter score at screening and baseline between 73 and 19 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, inclusive (approximate Snellen equivalent of 20/40 and 20/400).

The key exclusion criteria included stroke or myocardial infarction <3 months before screening; uncontrolled blood pressure (>160/>100 mmHg) at screening or baseline; periocular or ocular infection or inflammation at screening or baseline; intravitreal anti-VEGF injections ≤3 months before baseline and systemic anti-VEGF injections ≤6 months before baseline; uncontrolled glaucoma (intraocular pressure ≥30 mmHg on medication or according to the investigator's judgment) at the time of screening or baseline or diagnosed within 6 months before baseline; laser photocoagulation for macular edema ≤4 months before baseline; intraocular or periocular corticosteroid use ≤3 months before baseline; and known hypersensitivity to ranibizumab or any component of the ranibizumab formulation or fluorescein. In addition, pregnant or nursing women were excluded from the study (inclusion and exclusion criteria are listed in Appendix 3, available at www.aaojournal.org).

Randomization and Treatment

At enrollment, eligible patients were randomized in a 2:2:1 ratio to receive ranibizumab 0.5 mg, ranibizumab 0.5 mg with laser, or laser alone. The randomization list was generated using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization was balanced across the sites. Although this was an open-label study, the vision examiner who assessed the BCVA outcomes was masked and not allowed to perform any additional study tasks that would have unmasked him or her to study treatment.

In the ranibizumab with or without laser groups, ranibizumab 0.5 mg was administered as recommended in the European Union Summary of Product Characteristics (2012).[7] Patients received ranibizumab 0.5 mg injections on day 1, followed by initial monthly injections until the study eye's VA was stable (based on the judgment of the investigator) for at least 3 consecutive months; by design, at least 3 initial injections were required[8] (Fig 1, available at www.aaojournal.org). Once VA was stable, ranibizumab treatment was temporarily discontinued at the investigator's discretion. In the ranibizumab with laser and laser-only groups, patients were treated with laser as soon as indicated by the investigator. When ranibizumab and laser were to be administered on the same day to the study eye, the laser treatment was applied ≥30 minutes before the ranibizumab injection.

Maintenance and Re-treatment

All patients were monitored monthly for VA and disease activity. If there was a loss of VA due to disease activity as judged by the investigator, monthly ranibizumab injections were again administered to the patients in the ranibizumab with or without laser groups until stability was achieved for 3 consecutive months; this required at least 2 consecutive injections.[8] In the ranibizumab with laser and laser-only groups, patients were re-treated with laser at the investigator's discretion at minimum intervals of 4 months in the presence of macular edema secondary to BRVO, as long as the BCVA was <79 letters.

In all 3 groups, the last possible treatment was administered at month 5, and the last assessment was performed at month 6 for

this 6-month analysis. If both eyes were eligible at screening and baseline, the study eye was selected on the basis of the investigator's discretion. The other eye (labeled the fellow eye) was allowed to receive ranibizumab treatment within the study according to the local label, according to the investigator's judgment. The use of rescue medication was not permitted in this study.

Study Objectives

The primary objective of this 24-month study was to demonstrate the superior efficacy of ranibizumab with or without laser when compared with laser alone over 6 months. This was assessed by the mean change in BCVA from baseline at month 6 in patients treated with ranibizumab with or without laser versus laser alone (primary end point). The secondary objectives were (1) to compare the efficacy of ranibizumab with or without laser versus laser alone for (a) the mean average change in BCVA from baseline to month 1 through month 6, (b) the proportion of patients with a BCVA improvement of $\geq$10/$\geq$15/$\geq$30 letters at month 6, (c) the proportion of patients attaining a BCVA of $\geq$73 letters at month 6, and (d) the mean change in central reading center (CRC)−assessed central subfield thickness (CSFT) from baseline to month 6; (2) to assess the treatment exposure of ranibizumab and laser; and (3) to evaluate the safety profile of ranibizumab over 6 months. An exploratory objective was to evaluate the efficacy of the 3 treatments in relation to the following baseline characteristics: presence of macular ischemia (present and absent); BCVA ($\leq$39, 40−59, and $\geq$60 letters); and duration of BRVO ($\leq$12 and >12 months), by assessing the mean average change in BCVA from month 1 through month 6. An additional exploratory objective was to assess the change from baseline to month 6 of the CRC-assessed categoric optical coherence tomography (OCT) parameters (CSFT categorized, CFT categorized, visible intraretinal cystoid fluid [IRF], and subretinal fluid [SRF]). Definitions of these quantitative and categoric spectral-domain OCT parameters are listed in Appendix 4 (available at www.aaojournal.org).

Efficacy and Safety Assessments

Study assessments were performed at screening, baseline (day 1), day 8, and monthly visits.

Best-Corrected Visual Acuity. The BCVA was assessed by certified vision examiners at every study visit using ETDRS VA testing charts at an initial testing distance of 4 m. If it was not possible to perform a subjective refraction or VA testing at 4 m because VA was too poor for the patient to read $\geq$4 letters on the ETDRS chart at this distance, the refraction or VA testing were attempted at 1 m.

Optical Coherence Tomography. Optical coherence tomography was performed by certified site personnel at each visit using spectral-domain OCT equipment (e.g., Heidelberg Spectralis [Heidelberg Engineering, Heidelberg, Germany]; Cirrus HD-OCT [Carl Zeiss, Oberkochen, Germany]; 3D-OCT 1000 or 3D-OCT 2000 [Topcon, Tokyo, Japan]; and Nidek RS-3000 [Nidek, Fremont, CA]). The same equipment was used for assessment throughout the study. The investigator or designated study staff evaluated the images according to the standard practice and recorded the required variables in the clinical database. The images also were assessed by a CRC to ensure a standardized evaluation of the CSFT (the average retinal thickness of the circular area with a 1-mm diameter around the foveal center) and to capture the presence or absence of qualitative parameters (i.e., CFT, IRF, and SRF). Raw data of the images were evaluated in validated CRC software. The inner and outer retinal boundaries were segmented at predefined standardized locations to ensure standardization across the used spectral-domain OCT instruments.

Fluorescein Angiography and Color Fundus Photography. Fluorescein angiography (in conjunction with 7-field color fundus photography) images were evaluated by the investigator for the presence or absence of macular edema, capillary leakage, and nonperfusion within the 3-mm perifoveal subfield.

The CRC used a standardized grading system to assess macular ischemia on fluorescein angiography, as reported previously.[9] Macular ischemia was characterized by the extent of retinal capillary loss (presence or absence of nonperfusion) in the ETDRS-like grid center subfield, as well as inner and outer subfields (Appendix 5, available at www.aaojournal.org). We defined macular ischemia as present if capillary loss was scored as mild, moderate, severe, or completely destroyed in $\geq$1 location of the center, inner, or outer subfields of the grid (Appendix 5, available at www.aaojournal.org). In this article we present only the efficacy results based on CRC-assessed macular ischemia. The investigator used all images to decide the need for re-treatment.

Treatment Exposure. Information on the number of ranibizumab injections or laser administration over 6 months was collected.

Safety Assessments. Safety assessments included type, frequency, and severity of adverse events (AEs) and serious AEs (SAEs) over 6 months.

Statistical Analysis

By assuming a standard deviation (SD) of 14 letters for the change (normal distributed) in BCVA from baseline at month 6, based on a randomization ratio of 2:2:1 and estimating a dropout rate of approximately 10%, a sample size of 180 randomized patients each in the ranibizumab and ranibizumab + laser arms and 90 patients in the laser-only arm was considered. This sample size had a power of 90.5% to detect a treatment difference of 7 or more letters at a 1-sided α level of 0.0125 for an unstratified analysis (based on unstratified Mann−Whitney test using PASS 2002 software; NCSS, LLC, Kaysville, UT).

The primary and secondary efficacy outcomes were analyzed within the full analysis set (FAS) using the last observation carried forward approach. The FAS included all randomized patients who had $\geq$1 post-baseline assessment for BCVA in the study eye and who received $\geq$1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment.

The hypothesis of the superiority of ranibizumab with or without laser compared with laser alone was tested in parallel according to the Hochberg procedure, controlling the overall 1-sided α level at 0.025. The primary and secondary efficacy outcomes related to the mean change in BCVA from baseline were assessed on the basis of pairwise analysis of variance models that included factors for treatment and baseline BCVA category (BCVA $\leq$39, 40−59, and $\geq$60 letters). The least squares means and standard error were calculated for each of the treatment groups, along with the 2 pairwise differences of their 95% confidence interval (CI). The number and proportion of patients with BCVA letter gain or loss from baseline were analyzed by a stratified Cochran−Mantel−Haenszel test with stratification based on baseline BCVA ($\leq$39, 40−59, $\geq$60 letters). The CRC-assessed CSFT was summarized descriptively and analyzed via pairwise analysis of variance models including factors for treatment, OCT machine type, and categorized baseline BCVA ($\leq$39, 40−59, and $\geq$60 letters). The CRC-assessed categoric OCT parameters were summarized using FAS observed data for the study eye.

All safety analyses were descriptive and performed on the safety set that included all patients who had $\geq$1 post-baseline safety assessment and received $\geq$1 administration of the study treatment, except for patients randomized to laser monotherapy, who were included even without receiving the study treatment.

Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC).

Results

Patient Disposition

A total of 455 patients were randomized to receive ranibizumab (183 patients), ranibizumab with laser (180 patients), or laser alone (92 patients) (Fig 2). A total of 424 patients (93.2%) completed the first 6 months of the study (174 in the ranibizumab group, 170 in the ranibizumab with laser group, and 80 in the laser-only group) (Fig 2). Overall, withdrawal of consent (n = 12) and AEs (n = 8) were the most common reasons for study discontinuation. The FAS included 180 patients receiving ranibizumab, 178 patients receiving ranibizumab with laser, and 90 patients receiving laser monotherapy. The safety analysis set included 180 patients receiving ranibizumab, 183 patients receiving ranibizumab with laser (there were 3 patients in the laser monotherapy group who received ranibizumab and 1 patient in the ranibizumab monotherapy group who received laser treatment, resulting in percentages >100%), and 88 patients receiving laser monotherapy.

The baseline demographic characteristics were comparable among the 3 treatment groups (Table 1). Overall, the mean (SD) age of the patients was 66.3 (10.30) years, the proportion of male and female patients was similar (49.7% vs. 50.3%), and the majority (94.9%) of patients were white (Table 1). The baseline mean (SD) BCVA was 57.7 (12.88) letters, and the majority of patients (52.5%) had a BCVA letter score ≥60 at baseline (Table 1). The mean (SD) duration of BRVO was 9.9 (21.28) months, and the median duration was 2.9 months (Table 1). The BRVO subtype was BRVO in 89.0% of patients and hemi-retinal vein occlusion in 10.5% of patients (Table 1). Overall, 24.8% of patients in the randomized set had ischemic perfusion type at baseline, according to the investigator's assessment. The proportion of patients with macular ischemia at baseline based on CRC assessment was similar between treatment groups (48.1% of patients in the ranibizumab group, 40.0% of patients in the ranibizumab with laser group, and 44.6% of patients in the laser only group). There were 31.1%, 37.8%, and 31.5% of patients with macular ischemia as "cannot grade" based on CRC assessment in the ranibizumab, ranibizumab with laser, and laser-only groups, respectively.

Efficacy

Best-Corrected Visual Acuity. Ranibizumab with or without laser was superior to laser alone in improving mean (SD) BCVA from baseline at month 6 (14.8 [10.70] and 14.8 [11.13] vs. 6.0 [14.27] letters, respectively; both $P < 0.0001$); thus, the primary end point was met (Fig 3). Likewise, mean (SD) average gain in BCVA from month 1 through month 6 was higher in the ranibizumab (13.2 [9.60] letters) and ranibizumab with laser groups (13.2 [9.89] letters) compared with the laser-only group (4.8 [11.69] letters); estimated least square means (standard error; 95% CI) treatment difference versus laser were 9.4 letters [1.21; 7.0−11.7] ($P < 0.0001$) for ranibizumab and 8.2 letters [1.24; 5.8−10.6] ($P < 0.0001$) for ranibizumab with laser. In the ranibizumab and ranibizumab with laser groups, a rapid and clinically relevant improvement in mean BCVA was observed at month 1, which continued up to month 3 and slightly increased from month 3 until the last assessment time point at month 6 (Fig 3).

At month 6, a larger proportion of patients gained ≥10/≥15/≥30 letters with ranibizumab with or without laser versus laser alone (Fig 4). At month 6, 65.6% and 54.5% of patients attained a BCVA score of ≥73 letters with ranibizumab and ranibizumab with laser,

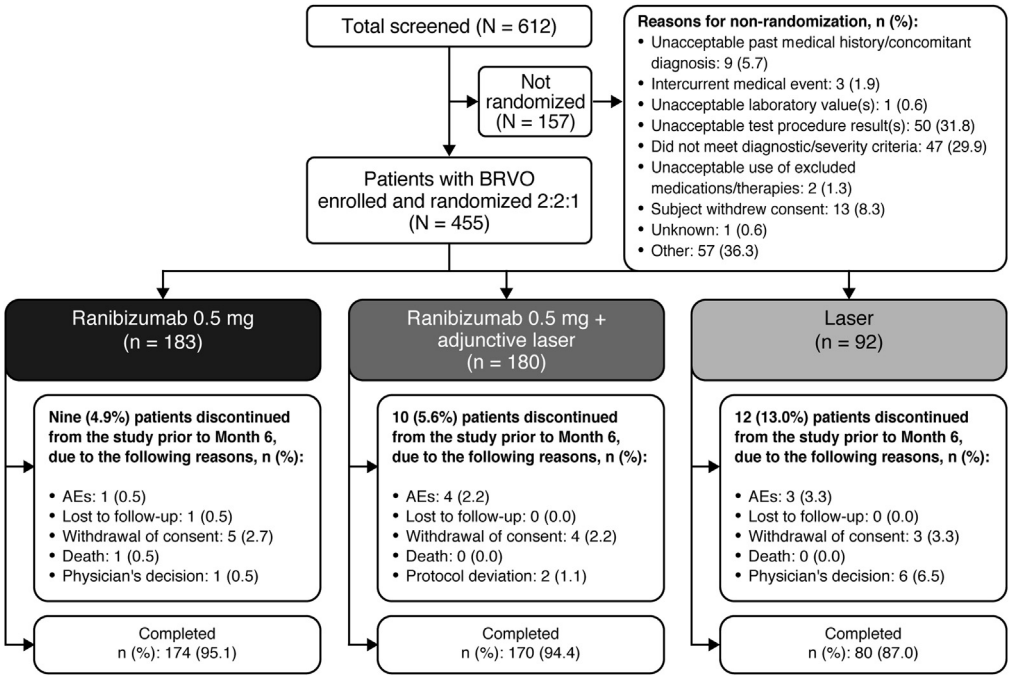


Figure 2. Patient disposition (randomized set). Randomized set consisted of all patients who were randomized. Because patients with multiple reasons are counted once for each reason of nonrandomization, percentages may add up to more than 100%. AE = adverse event; BRVO = branch retinal vein occlusion.

Table 1. Baseline Demographics, Disease, and Ocular Characteristics (Randomized Set*)

Demographic Variable	Ranibizumab 0.5 mg (n = 183)	Ranibizumab 0.5 mg + laser (n = 180)	Laser monotherapy (n = 92)	Total (N = 455)
Age, yrs				
n	183	180	92	455
Mean (SD)	64.7 (10.34)	67.3 (10.41)	67.7 (9.67)	66.3 (10.30)
Sex, n (%)				
Male	93 (50.8)	96 (53.3)	37 (40.2)	226 (49.7)
Female	90 (49.2)	84 (46.7)	55 (59.8)	229 (50.3)
Predominant race, n (%)				
White	171 (93.4)	172 (95.6)	89 (96.7)	432 (94.9)
Black	1 (0.5)	1 (0.6)	0	2 (0.4)
Asian	5 (2.7)	3 (1.7)	3 (3.3)	11 (2.4)
Native American	1 (0.5)	0	0	1 (0.2)
Other	5 (2.7)	4 (2.2)	0	9 (2.0)
VA (letters)				
n	181	179	91	451
Mean (SD)	59.5 (11.77)	56.6 (13.16)	56.5 (14.13)	57.7 (12.88)
VA stratification group, n (%)				
≤39 letters	16 (8.7)	22 (12.2)	11 (12.0)	49 (10.8)
40–59 letters	55 (30.1)	72 (40.0)	36 (39.1)	163 (35.8)
≥60 letters	110 (60.1)	85 (47.2)	44 (47.8)	239 (52.5)
Missing	2 (1.1)	1 (0.6)	1 (1.1)	4 (0.9)
IOP, mmHg				
n	181	179	91	451
Mean (SD)	15.1 (2.49)	15.4 (3.02)	15.2 (2.88)	15.2 (2.79)
Subtype of BRVO, n (%)				
Hemi	19 (10.4)	19 (10.6)	10 (10.9)	48 (10.5)
Branch	164 (89.6)	159 (88.3)	82 (89.1)	405 (89.0)
Missing	0	2 (1.1)	0	2 (0.4)
Perfusion type,† n (%)				
Ischemic	47 (25.7)	42 (23.3)	24 (26.1)	113 (24.8)
Nonischemic	135 (73.8)	134 (74.4)	66 (71.7)	336 (73.8)
Missing	1 (0.5)	4 (2.2)	1 (1.1)	6 (1.3)
Duration of BRVO, months				
n	181	179	90	450
Mean (SD)	10.3 (19.63)	9.2 (19.92)	10.5 (26.66)	9.9 (21.28)
Median	3.1	3.3	2.0	2.9
Duration of BRVO, n (%)				
≤12 mos	145 (79.2)	145 (80.6)	76 (82.6)	366 (80.4)
>12 mos	36 (19.7)	34 (18.9)	14 (15.2)	84 (18.5)
Missing	2 (1.1)	1 (0.6)	2 (2.2)	5 (1.1)

BRVO = branch retinal vein occlusion; IOP = intraocular pressure; SD = standard deviation; VA = visual acuity.
Percentages are based on the total number of patients in the randomized set.
Baseline was defined as the last available nonmissing value collected just before the start of treatment.
*Consisted of all patients who were randomized.
†Perfusion type as indicated by the investigator.

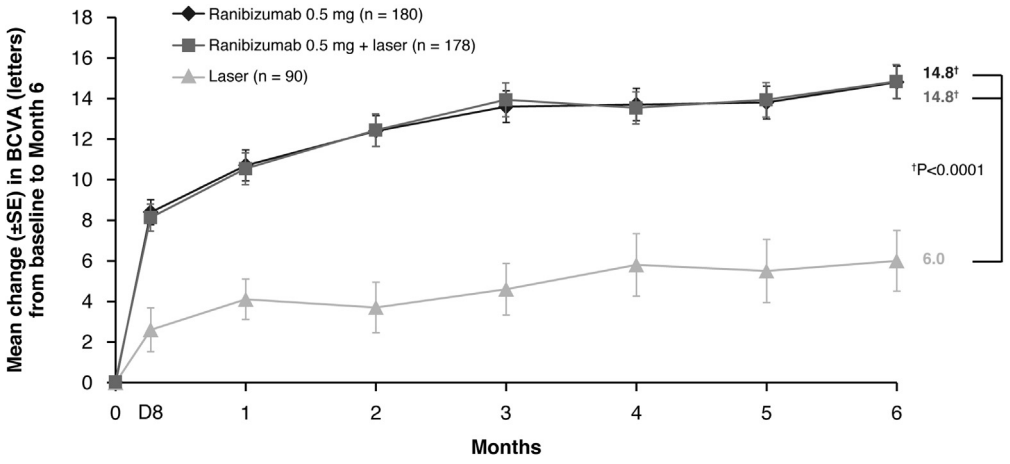
respectively, compared with 31.1% of patients with laser only (estimated treatment difference vs. laser, 34.44% [95% CI, 22.6–46.3] for ranibizumab and 23.38% [95% CI, 11.3–35.4] for ranibizumab with laser; both $P < 0.0001$).

Mean gains in BCVA from baseline to month 6 in the ranibizumab with or without laser groups were similar between patients with or without macular ischemia (CRC assessed) at baseline. Mean (SD) change in BCVA from baseline to month 6 in patients with macular ischemia was 14.3 (10.52) letters in the ranibizumab group, 14.4 (8.72) letters in the ranibizumab with laser group, and 9.2 (11.65) letters in the laser-only group (Fig 5). Mean (SD) change in BCVA from baseline at month 6 in patients without macular ischemia was 11.9 (10.06) letters in the ranibizumab group, 11.8 (8.66) letters in the ranibizumab with laser group, and 2.7 (17.22) letters in the laser-only group (Fig 5).

Mean gain in BCVA at month 6 by baseline VA subgroups (≤39/40–59/≥60 letters) was 20.9/19.5/11.6 letters in the ranibizumab group, 19.5/17.9/11.1 letters in the ranibizumab with laser group, and 18.7/11.4/−1.4 letters in the laser-only group (Fig 6). In both the ranibizumab and ranibizumab with laser groups, patients with a poor baseline VA had a better mean BCVA gain at month 6 than those with a higher baseline VA, although the absolute final BCVA values were lower in those with poor baseline VA (Fig 6).

Mean gain in BCVA by prior duration of BRVO (≤12/>12 months) was 16.4/8.4 letters in the ranibizumab group, 15.0/11.5 letters in the ranibizumab with laser group, and 5.9/7.1 letters in the laser-only group (Fig 7).

Anatomic Outcomes. At month 6, there was a greater reduction in CRC-assessed mean CSFT in patients treated with



Mean (±SD) BCVA letters (absolute value)	Baseline	Day 8	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Ranibizumab 0.5 mg	59.5 (11.80)	68.0 (11.62)	70.2 (12.35)	71.9 (12.26)	73.1 (12.28)	73.2 (12.40)	73.3 (12.25)	74.3 (12.27)
Ranibizumab 0.5 mg + laser	56.5 (13.21)	64.6 (13.57)	67.1 (13.22)	68.9 (13.91)	70.4 (13.77)	70.1 (14.72)	70.5 (14.61)	71.4 (14.43)
Laser	57.3 (13.70)	59.5 (14.88)	61.1 (13.45)	60.5 (12.58)	61.4 (13.47)	61.5 (13.89)	62.8 (13.46)	62.8 (14.08)

Figure 3. Mean change in best-corrected visual acuity (BCVA) from baseline to month 6 (full analysis set [FAS]). The FAS consisted of all randomized patients who had ≥1 postbaseline assessment for BCVA in the study eye and who received ≥1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment. †Both ranibizumab and ranibizumab + laser versus laser alone, pairwise analysis of variance. SE = standard error.

ranibizumab with or without laser compared with patients treated with laser alone (223.3/240.1 vs. 89.8 μm; $P < 0.0001$) (Fig 8). At month 6, the proportion of patients with CSFT and CFT ≤450 μm increased from baseline in all treatment groups; the proportion was higher in the ranibizumab with or without laser groups than in the laser-only group (Table 2A, available at www.aaojournal.org). The proportion of patients with visible IRF and SRF decreased from baseline in all treatment groups; the proportion was higher in the ranibizumab with or without laser groups than in the laser-only group (Table 2B, available at www.aaojournal.org).

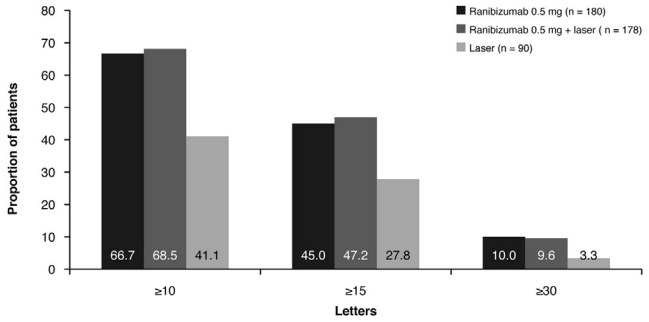


Figure 4. Categorized gain in best-corrected visual acuity (BCVA) at month 6 (full analysis set [FAS]). The FAS consisted of all randomized patients who had ≥1 post-baseline assessment for BCVA in the study eye and who received ≥1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment.

Treatment Exposure

Ranibizumab Injections. The mean number of ranibizumab injections over 6 months was 4.8 and 4.5 in the ranibizumab and ranibizumab with laser groups, respectively (Fig 9).

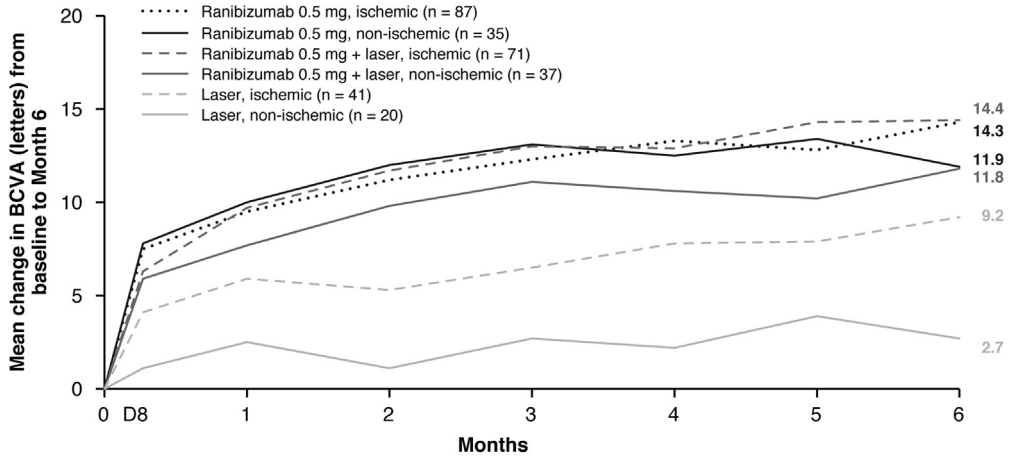
Laser Treatments. The mean number of laser treatments given up to 6 months was 0.0, 0.8, and 1.2 in the ranibizumab, ranibizumab with laser, and laser-only groups, respectively (Fig 10).

Safety

Serious Adverse Events. Ocular SAEs were reported in the study eye in 2 patients in the ranibizumab with laser group during the 6 months of the study: macular hole in 1 patient (not considered by the investigator to be related to the study drug or ocular injection) and ocular ischemic syndrome (considered by the investigator to be related to the study drug) in the other patient (Table 3, available at www.aaojournal.org). Nonocular SAEs were reported in 10, 7, and 2 patients in the ranibizumab, ranibizumab with laser, and laser-only groups, respectively (Table 3, available at www.aaojournal.org). One patient died of acute respiratory failure in the ranibizumab group (Table 3, available at www.aaojournal.org). The death was not considered by the investigator to be related to the study treatment or ocular injection.

Adverse Events. Ocular AEs in the study eye were reported in 28.3%, 37.2%, and 13.6% of patients in the ranibizumab, ranibizumab with laser, and laser-only groups, respectively (Table 4). Conjunctival hemorrhage and eye pain were the most commonly reported ocular AEs in patients receiving ranibizumab or ranibizumab with laser (Table 4).

The incidence of nonocular AEs was similar among the 3 groups (Table 4). Hypertension was the most common nonocular AE reported in all 3 groups. Ocular and nonocular AEs



Mean (±SD) BCVA letters (absolute value)	Baseline	Day 8	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Ranibizumab 0.5 mg								
Ischemic	60.7 (11.13)	68.1 (11.45)	70.1 (12.13)	71.8 (12.36)	72.9 (12.41)	73.9 (11.75)	73.3 (11.76)	74.9 (12.31)
Non-ischemic	60.6 (12.59)	68.3 (12.91)	70.6 (13.27)	72.6 (13.46)	73.7 (13.01)	73.1 (14.32)	74.0 (13.20)	72.5 (14.00)
Ranibizumab 0.5 mg + laser								
Ischemic	58.7 (11.82)	66.5 (12.79)	68.4 (12.66)	70.4 (13.65)	71.6 (13.16)	71.6 (13.10)	73.0 (12.72)	73.1 (12.59)
Non-ischemic	60.3 (11.15)	66.1 (14.76)	68.1 (13.73)	70.1 (13.10)	71.4 (13.54)	71.0 (13.60)	70.5 (12.92)	72.2 (12.61)
Laser								
Ischemic	56.8 (15.53)	60.9 (16.58)	61.9 (14.22)	60.9 (12.92)	62.1 (14.55)	63.4 (14.21)	63.4 (14.60)	64.7 (14.29)
Non-ischemic	60.6 (9.79)	61.7 (10.44)	63.1 (11.54)	61.7 (11.86)	63.3 (11.03)	62.8 (11.38)	64.5 (12.71)	63.3 (14.01)

Figure 5. Mean change in best-corrected visual acuity (BCVA) from baseline to month 6 by baseline macular ischemia (full analysis set [FAS]). The FAS consisted of all randomized patients who had ≥1 postbaseline assessment for BCVA in the study eye and who received ≥1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment. D = day.

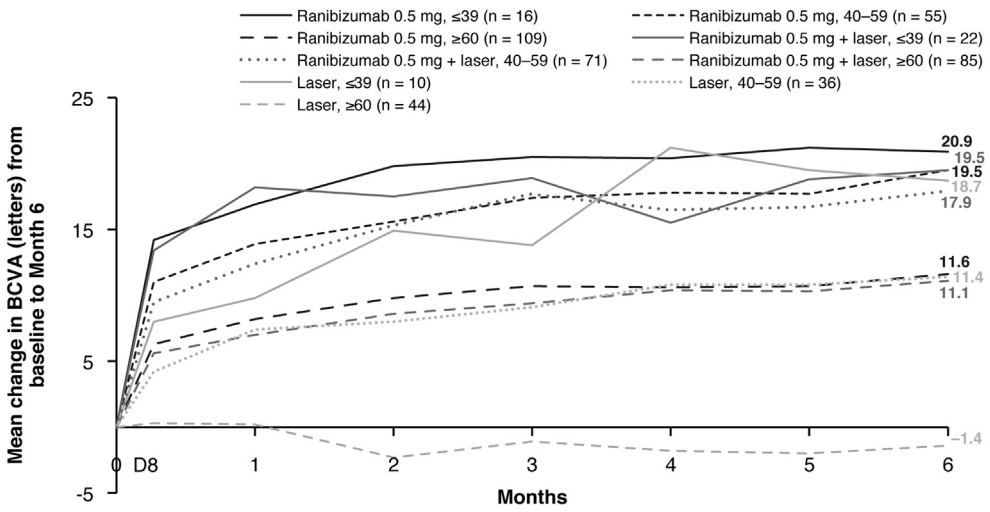
suspected to be related to the study drug treatment during the first 6 months of the study are listed in Table 5 (available at www.aaojournal.org). Treatment- or ocular injection–related ocular AEs were reported in 17.8% of patients in the ranibizumab group and 23.5% of patients in the ranibizumab with laser group. Nonocular AEs occurred in 1.7% of patients in the ranibizumab group, 2.2% of patients in the ranibizumab with laser group, and none in the laser-only group. Ocular and nonocular AEs leading to study drug discontinuation are listed in Table 6 (available at www.aaojournal.org).

There were no reports of retinal neovascularization during the 6-month period of this study. Retinal hemorrhages were reported in <2% of patients treated with ranibizumab (ranibizumab, 0.6%; ranibizumab with laser, 1.1%) and in 3.4% of patients treated with laser alone. Vitreous hemorrhages were reported in 0.6% of patients in the ranibizumab group, 1.1% of patients in the ranibizumab with laser group, and none in the laser-only group. There were no cases of neovascular glaucoma or iris neovascularization during the first 6-month period of the 24-month BRIGHTER study.

Discussion

The BRIGHTER study evaluated the individualized stabilization criteria–driven PRN dosing regimen of ranibizumab 0.5 mg, mainly based on VA stabilization criteria, with or without laser versus laser alone in patients with visual impairment due to macular edema secondary to BRVO and with a longer disease duration. Laser treatment, the active comparator in this study, has previously been shown to stabilize VA in patients with BRVO, but improvements in VA are suggested to be delayed and of lower amplitude.[10,11] In addition, in patients with diabetic retinopathy, the structural damage due to repeated treatment with laser alone has been shown to worsen over time because of an enlargement of coagulation scars.[12] Thus, this study assessed the combination of ranibizumab with laser to evaluate the potential synergistic benefits. The effect of laser treatment used in combination with ranibizumab may, theoretically, result in better maintenance of the VA gains obtained with ranibizumab, which may reduce the need for re-treatment with ranibizumab or the number of follow-up visits.

In this study, the individualized VA stabilization criteria–driven PRN treatment with ranibizumab 0.5 mg with or without laser resulted in a significant improvement in BCVA at month 6 compared with laser alone. This dosing regimen of ranibizumab is as recommended in the European Union,[7] and the study results further validate this



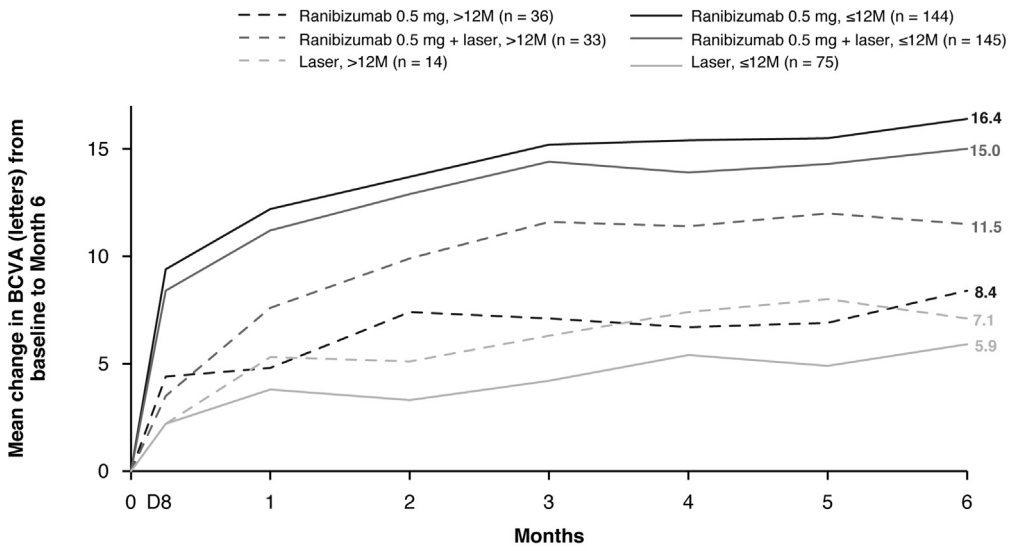
Mean (±SD) BCVA letters (absolute value)	Baseline	Day 8	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Ranibizumab 0.5 mg								
≤39	33.6 (6.05)	47.8 (12.70)	50.6 (14.68)	53.4 (14.00)	54.1 (13.74)	54.1 (14.89)	54.8 (15.57)	54.6 (14.12)
40–59	51.5 (5.78)	62.5 (10.34)	65.4 (11.93)	67.1 (12.35)	68.9 (12.61)	69.3 (12.39)	69.2 (13.06)	71.0 (12.47)
≥60	67.3 (3.84)	73.6 (6.38)	75.6 (7.31)	77.1 (7.45)	78.0 (7.59)	78.0 (7.92)	78.0 (6.93)	78.9 (7.70)
Ranibizumab 0.5 mg + laser								
≤39	31.0 (5.08)	44.5 (11.17)	49.2 (13.85)	48.5 (15.55)	50.0 (17.24)	46.5 (19.76)	49.8 (20.85)	50.5 (20.46)
40–59	51.4 (5.68)	60.9 (10.39)	63.8 (11.65)	66.7 (11.79)	69.1 (11.14)	68.0 (10.46)	68.2 (11.53)	69.3 (10.91)
≥60	67.5 (4.45)	73.1 (8.68)	74.5 (7.66)	76.0 (8.18)	76.9 (8.29)	77.9 (7.52)	77.7 (7.78)	78.6 (8.04)
Laser								
≤39	27.0 (6.85)	35.0 (23.51)	36.9 (13.39)	43.0 (8.07)	41.9 (11.29)	44.2 (9.82)	47.6 (9.43)	46.8 (5.41)
40–59	50.9 (5.82)	54.1 (9.54)	58.7 (9.34)	59.3 (9.27)	60.4 (9.62)	60.6 (11.54)	62.1 (11.61)	62.7 (12.80)
≥60	67.8 (4.28)	68.1 (7.91)	68.1 (9.42)	65.6 (12.04)	66.8 (12.45)	66.0 (13.40)	66.9 (13.25)	66.5 (14.03)

Figure 6. Mean change in best-corrected visual acuity (BCVA) from baseline to month 6 by baseline BCVA (full analysis set [FAS]). FAS consisted of all randomized patients who had ≥1 postbaseline assessment for BCVA in the study eye and who received ≥1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment. D = day.

recommended dosing regimen. The 6-month primary analysis did not show additional benefits with the ranibizumab plus laser combination over ranibizumab monotherapy, either in BCVA outcomes or in the required number of injections, which could be due to the short duration assessment of this 24-month study.

The patients in this study required a mean of 4.8 ranibizumab 0.5 mg injections (of which 3 were mandatory per protocol) over 6 months to achieve mean BCVA gains of +14.8 letters. In real-life studies with ranibizumab in patients with neovascular age-related macular degeneration or central retinal vein occlusion, the mean number of injections over a 1-year period have been reported to range between 4 and 5 in the retrospective analysis part of the LUMINOUS study and 4.4 in the VERO study.[13,14]

At month 6, the proportion of patients with a gain of ≥15 letters in the BRAVO study with monthly ranibizumab treatment was higher than in the BRIGHTER study with stabilization criteria–driven PRN ranibizumab treatment (61.1% vs. 45.0%). The mean change in BCVA from baseline at month 6 was numerically higher in the BRAVO study (+18.3 letters) compared with the BRIGHTER study (+14.8 letters),[4] which could be due to the differences in patient baseline characteristics in the 2 studies. Patients in the BRIGHTER study had a higher mean baseline BCVA score (59.5 letters in BRIGHTER vs. 53.0 letters in BRAVO) and a longer mean duration of BRVO (9.9 months in BRIGHTER vs. 3.3 months in BRAVO). However, the absolute mean BCVA at month 6 was higher in the BRIGHTER study than in the BRAVO study (74.3 vs. 71.3 letters) (Fig 11), with a lower mean number of injections (4.8 vs. 5.7, respectively). The functional outcomes observed at month 6 of the BRIGHTER study were similar to those of the VIBRANT study (assessing aflibercept for the treatment of BRVO[15]), in which 52.7% of patients gained ≥15 letters and mean BCVA change



Mean (±SD) BCVA letters (absolute value)	Baseline	Day 8	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Ranibizumab 0.5 mg								
≤12 M	58.4 (11.88)	67.8 (11.83)	70.6 (12.69)	72.0 (12.29)	73.6 (12.04)	73.8 (12.51)	73.8 (12.61)	74.8 (12.16)
>12 M	64.1 (10.43)	68.5 (10.92)	68.9 (10.91)	71.5 (12.27)	71.1 (13.19)	70.8 (11.82)	71.0 (10.53)	72.5 (12.72)
Ranibizumab 0.5 mg + laser								
≤12 M	56.2 (13.48)	64.6 (14.68)	67.4 (14.00)	69.1 (14.71)	70.6 (14.54)	70.1 (15.66)	70.5 (15.46)	71.2 (15.94)
>12 M	58.1 (12.01)	61.6 (14.33)	65.9 (9.04)	68.2 (9.81)	69.9 (9.86)	69.7 (9.73)	70.3 (10.23)	69.8 (10.65)
Laser								
≤12 M	57.9 (14.06)	60.2 (15.24)	61.4 (13.72)	60.7 (13.04)	61.6 (13.93)	62.8 (13.92)	62.3 (14.83)	63.2 (4.38)
>12 M	54.3 (12.29)	56.5 (13.51)	59.6 (12.82)	59.4 (10.44)	60.6 (11.67)	61.6 (11.59)	62.3 (12.91)	61.4 (12.80)

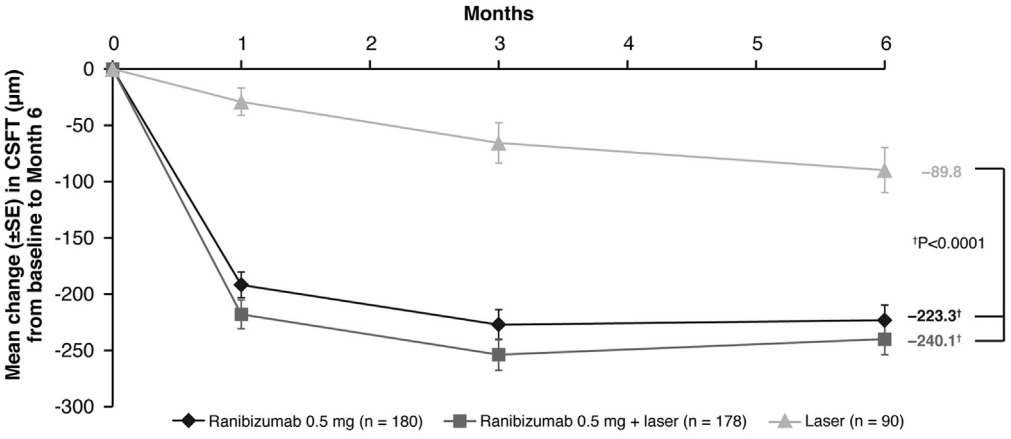
Figure 7. Mean change in best-corrected visual acuity (BCVA) from baseline to month 6 by duration of branch retinal vein occlusion (full analysis set [FAS]). The FAS consisted of all randomized patients who had ≥1 postbaseline assessment for BCVA in the study eye and who received ≥1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment. D = day; M = month.

from baseline was 17.0 letters, and provide further support to the findings of VIBRANT that suppression of VEGF over 6 months provides superior visual outcomes compared with treatment with focal/grid laser alone. However, any comparisons between BRIGHTER and previous studies of patients with BRVO need to be interpreted with caution considering the differences in the patient populations, study designs, and anti-VEGF treatment regimens investigated.

The exploratory subgroup analysis performed in the BRIGHTER study showed that the individualized stabilization criteria–driven PRN dosing regimen of ranibizumab was effective in patients with BRVO irrespective of the baseline VA, disease duration, or presence of macular ischemia. The mean change in BCVA from baseline at month 6 with ranibizumab treatment was similar between patients with ischemia and patients without ischemia. The difference in the percentage of patients at baseline with CRC-assessed macular ischemia and investigator-assessed nonperfusion could be related to the individual assessment method used and needs to be investigated in future studies. In addition, the impact of the severity and location of ischemia on efficacy warrants further investigation.

Several studies of anti-VEGF for other indications have shown baseline VA to be an important predictor of VA outcomes at later time points.[16–19] Likewise, in BRIGHTER, the mean gain in BCVA at month 6 was higher in patients with lower baseline VA scores, whereas the absolute final BCVA values were lower in those with poor baseline VA. In addition, BCVA gain at month 6 was higher in patients with a shorter duration of disease, suggesting that early treatment initiation with ranibizumab irrespective of the BCVA scores may provide better VA gains in patients with BRVO. This is supported by the reduced visual gains observed in the sham arm of the BRAVO study due to delayed treatment initiation (switching into PRN treatment after 6 months). Similar findings have been reported in the sham arms of studies of ranibizumab for other indications,[20] as well as in observational studies of patients with age-related macular degeneration.[21,22]

No new safety concerns were identified with ranibizumab with or without laser treatment. The single death reported in

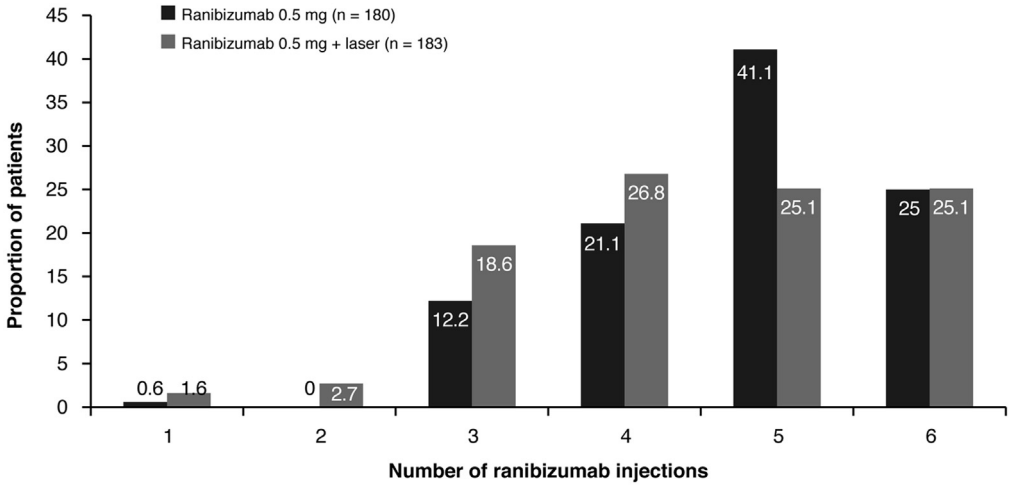


Mean (±SD) CSFT (µm) (absolute value)	Baseline	Month 1	Month 3	Month 6
Ranibizumab 0.5 mg	529.5 (144.97)	340.4 (111.98)	308.6 (95.55)	312.6 (104.61)
Ranibizumab 0.5 mg + laser	553.8 (170.06)	335.8 (107.88)	299.6 (88.13)	313.2 (86.38)
Laser	543.6 (179.21)	514.5 (181.09)	475.7 (165.74)	451.6 (169.73)

Figure 8. Mean change in central subfield foveal thickness (CSFT) from baseline to month 6 (full analysis set [FAS]). The FAS consisted of all randomized patients who had ≥1 postbaseline assessment for BCVA in the study eye and who received ≥1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment. †Both ranibizumab and ranibizumab + laser versus laser alone, pairwise analysis of variance. SE = standard error.

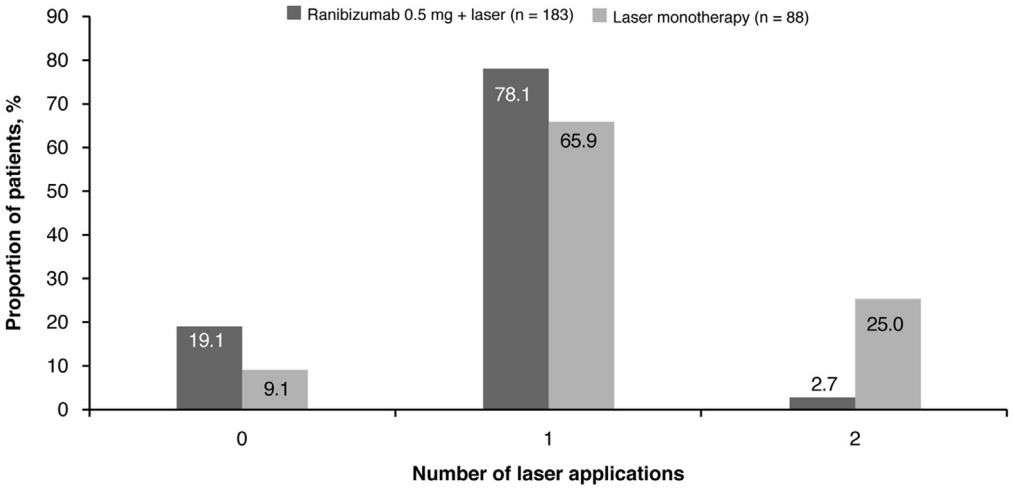
the ranibizumab group was not related to the study drug. There were no reports of endophthalmitis, neovascular glaucoma, or iris neovascularization.

This is a 6-month primary analysis of a study. This short period was insufficient to provide conclusive evidence of the benefits of combining laser with ranibizumab, especially because laser administration occurred at a minimum interval of 4 months. The exploratory analysis of the effect of ranibizumab treatment focused on macular ischemia. This study explicitly



Number of injections	Ranibizumab 0.5 mg (n=180)	Ranibizumab 0.5 mg + laser (n=183)
Mean (SD)	4.8 (1.00)	4.5 (1.22)
Median	5.0	5.0

Figure 9. Ranibizumab treatment exposure up to month 6 (safety set). Safety set consisted of all patients who had ≥1 postbaseline safety assessment and received ≥1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment. The total number of injections per patient is calculated, and these per-patient values are summarized. SD = standard deviation.



Number of laser applications	Ranibizumab 0.5 mg + laser (n=183)	Laser monotherapy (n=88)
Mean (SD)	0.8 (0.44)	1.2 (0.57)
Median	1.0	1.0

Figure 10. Laser treatment exposure up to month 3 (safety set). Safety set consisted of all patients who had ≥1 postbaseline safety assessment and received ≥1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment. Multiple sessions for the initial laser treatment are counted as 1 application. The total number of laser applications per patient is calculated, and these per-patient values are summarized. SD = standard deviation.

excluded patients with previous treatments within 3 months like other randomized studies to facilitate comparison.

Table 4. Ocular (Study Eye) and Nonocular Adverse Events Regardless of Study Drug Relationship (Safety Set*)

Preferred Term n (%)	Ranibizumab 0.5 mg (n = 180)	Ranibizumab 0.5 mg + Laser (n = 183)	Laser Monotherapy (n = 88)
Ocular AEs, total	51 (28.3)	68 (37.2)	12 (13.6)
Conjunctival hemorrhage	11 (6.1)	12 (6.6)	0 (0)
Eye pain	8 (4.4)	10 (5.5)	0 (0)
Vitreous detachment	6 (3.3)	4 (2.2)	0 (0)
IOP increased	5 (2.8)	8 (4.4)	0 (0)
Vitreous floaters	3 (1.7)	5 (2.7)	2 (2.3)
Nonocular AEs, total	60 (33.3)	52 (28.4)	27 (30.7)
Hypertension	11 (6.1)	10 (5.5)	5 (5.7)
Nasopharyngitis	6 (3.3)	5 (2.7)	3 (3.4)
Headache	4 (2.2)	6 (3.3)	3 (3.4)

AE = adverse event; IOP = intraocular pressure.
Preferred terms that occurred in ≥2% of the safety set are included in this summary. Preferred terms are sorted in descending frequency, as reported in the ranibizumab 0.5 mg column. A patient with multiple occurrences of an AE under 1 treatment is counted only once in the AE category for that treatment.
*Consisted of all patients who had ≥1 postbaseline safety assessment and received ≥1 administration of study treatment, except patients randomized to laser monotherapy, who were included even without receiving study treatment.

The 24-month results of the BRIGHTER study are expected to provide additional information on the long-term efficacy and safety of the individualized stabilization criteria–driven dosing of ranibizumab 0.5 mg, as well as the long-term benefits of combining ranibizumab with laser. The individualized stabilization criteria–driven dosing regimen used in this study led to an average reduction of 1 injection over the course of 6 months in comparison with monthly dosing. The second-year data from this study will provide further information on the benefits of fewer visits combined with the individualized dosing regimen.

In conclusion, the 6-month data from the BRIGHTER study demonstrate that an individualized ranibizumab treatment with or without laser is superior to laser monotherapy in significantly improving BCVA in patients with BRVO. The exploratory analysis showed similar BCVA

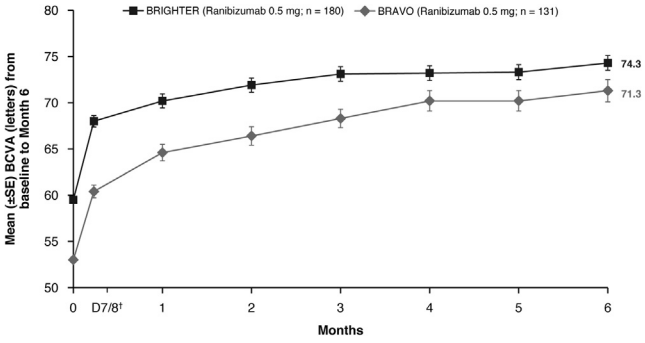


Figure 11. Mean best-corrected visual acuity (BCVA) from baseline to month 6 in BRIGHTER and BRAVO. †BCVA was assessed on day 7 in BRAVO and day 8 in BRIGHTER. D = day.

gains between patients with macular ischemia and patients without macular ischemia, and suggests that better VA gains may be obtained at 6 months with early treatment initiation irrespective of the baseline BCVA scores. Overall, there were no safety concerns other than those reported in the previous studies.

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Footnotes and Financial Disclosures

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*Group members are listed in Appendix 1 (available at www.aaojournal.org).

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Abbreviations and Acronyms:

AE = adverse event; **BCVA** = best-corrected visual acuity; **BRAVO** = BRAnch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; **BRVO** = branch retinal vein occlusion; **CFT** = central foveal thickness; **CI** = confidence interval; **CRC** = central reading center; **CRUISE** = Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUslon Study: Evaluation of Efficacy and Safety; **CSFT** = central subfield thickness; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FAS** = full analysis set; **IRF** = intraretinal cystoid fluid; **OCT** = optical coherence tomography; **PRN** = pro re nata; **SAE** = serious adverse event; **SD** = standard deviation; **SRF** = subretinal fluid; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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