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Sustained Benefits of Ranibizumab with or without Laser in Branch Retinal Vein Occlusion

24-Month Results of the BRIGHTER Study

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Purpose: To evaluate the long-term (24-month) efficacy and safety of ranibizumab 0.5 mg administered pro re nata (PRN) with or without laser using an individualized visual acuity (VA) stabilization criteria in patients with visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO).

Design: Phase IIIb, open-label, randomized, active-controlled, 3-arm, multicenter study.

Participants: A total of 455 patients.

Methods: Patients were randomized (2:2:1) to ranibizumab 0.5 mg (n = 183), ranibizumab 0.5 mg with laser (n = 180), or laser (with optional ranibizumab 0.5 mg after month 6; n = 92). After initial 3 monthly injections, patients in the ranibizumab with or without laser arms received VA stabilization criteria-driven PRN treatment. Patients assigned to the laser arm received laser at the investigator's discretion.

Main Outcome Measures: Mean (and mean average) change in best-corrected visual acuity (BCVA) and central subfield thickness (CSFT) from baseline to month 24, and safety over 24 months.

Results: A total of 380 patients (83.5%) completed the study. Ranibizumab with or without laser led to superior BCVA outcomes versus laser (monotherapy and combined with ranibizumab from month 6; 17.3/15.5 vs. 11.6 letters; $P < 0.0001$). Ranibizumab with laser was noninferior to ranibizumab monotherapy (mean average BCVA change: 15.4 vs. 15.0 letters; $P < 0.0001$). However, addition of laser did not reduce the number of ranibizumab injections (mean injections: 11.4 vs. 11.3; $P = 0.4259$). A greater reduction in CSFT was seen with ranibizumab with or without laser versus laser monotherapy over 24 months from baseline (ranibizumab monotherapy −224.7 μm, ranibizumab with laser −248.9 μm, laser [monotherapy and combined with ranibizumab from month 6] −197.5 μm). Presence of macular ischemia did not affect BCVA outcome or treatment frequency. There were no reports of neovascular glaucoma or iris neovascularization. No new safety signals were identified.

Conclusions: The BRIGHTER study results confirmed the long-term efficacy and safety profile of PRN dosing driven by individualized VA stabilization criteria using ranibizumab 0.5 mg in patients with BRVO. Addition of laser did not lead to better functional outcomes or lower treatment need. The safety results were consistent with the well-established safety profile of ranibizumab. *Ophthalmology 2017;■:1−10 © 2017 American Academy of Ophthalmology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Branch retinal vein occlusion (BRVO) is one of the most common retinal vascular diseases and affects approximately 0.4% of the population worldwide.[1] Primary treatment options for BRVO include anti-vascular endothelial growth factor agents as monotherapy or in combination with laser.[2] Ranibizumab, an anti-vascular endothelial growth factor antibody fragment, has a well-established efficacy and safety profile, and is approved for several retinal conditions, including the treatment of visual impairment due to macular edema secondary to BRVO and central retinal vein occlusion.[3–5]

The BRIGHTER study (NCT01599650) evaluated the long-term efficacy and safety profile of ranibizumab 0.5 mg in a broad population of patients with BRVO, including those with retinal ischemia. The study was conducted (1) to provide data on long-term efficacy and safety of an individualized visual acuity (VA) stabilization criteria-driven pro re nata (PRN) dosing regimen of ranibizumab 0.5 mg with or without laser versus laser and (2) to evaluate the impact of adjunct laser treatment on VA outcome and the number of ranibizumab injections required.[6,7] Six-month results of the BRIGHTER study demonstrated superiority

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of ranibizumab 0.5 mg with or without laser compared with laser in improving best-corrected VA (BCVA), irrespective of the baseline macular ischemia status or disease duration.[7] We report the 24-month results of the BRIGHTER study.

Methods

Detailed materials and methods have been described by Tadayoni et al.[7] We report a brief summary.

Study Design

BRIGHTER was a 24-month, phase IIIb, randomized, open-label, active-controlled, 3-arm, multicenter study. It enrolled patients with BRVO from 17 countries worldwide. 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.

Patients

The detailed inclusion and exclusion criteria have been described by Tadayoni et al.[7] Briefly, the study included treatment-naïve patients aged ≥18 years with visual impairment due to macular edema secondary to BRVO and a BCVA letter score at screening and baseline between 73 and 19 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (approximate Snellen chart equivalent of 20/40 and 20/400).

Randomization and Treatment

All eligible patients were randomly assigned (2:2:1) to receive ranibizumab 0.5 mg (ranibizumab monotherapy), ranibizumab 0.5 mg with laser (ranibizumab + laser), or laser (laser monotherapy).

Visual acuity was the primary trigger of re-treatment; and a decrease of VA associated with disease activity (detected on optical coherence tomography [OCT] or by any other means) warranted re-treatment.

According to the treatment protocol, patients were to receive monthly ranibizumab treatment until the study eye's VA was stable for 3 consecutive monthly assessments (this implies a minimum of 3 injections given at monthly intervals from baseline). Once VA did not change after the last monthly treatment during the initial monthly treatment period or during any period of re-treatments (i.e., was stable), the next re-treatment was warranted only when VA decrease and the decrease was due to disease activity in the opinion of the investigator.

There were 2 treatment periods in the study: treatment period 1 (day 1 to month 6) and treatment period 2 (months 6–23).

In treatment period 1, patients from the ranibizumab monotherapy and ranibizumab + laser arms received individualized, stabilization criteria-driven, PRN ranibizumab 0.5 mg (as recommended in the European Summary of Product Characteristics 2012).[5] After injection on day 1, monthly treatment was continued until BCVA was stable (i.e., no change in BCVA for at least 3 consecutive months). If BCVA stability was achieved, ranibizumab treatment was temporarily discontinued and monthly monitoring was continued until BCVA loss due to disease activity warranted re-treatment with ranibizumab (PRN treatment). Patients in the ranibizumab + laser and laser monotherapy arms were treated with laser (at investigators' discretion) as soon as macular edema was observed. The minimum interval between laser applications was 4 months, and patients were not treated with laser if BCVA was ≥79 letters or dense macular hemorrhage was present.

In treatment period 2, PRN treatment was continued with a possibility to reduce the frequency of monitoring from month 12. Patients in the ranibizumab monotherapy and ranibizumab + laser arms continued to receive individualized, stabilization criteria-driven PRN ranibizumab 0.5 mg. Patients in the laser monotherapy arm continued to receive laser therapy PRN; however, from month 6, these patients were eligible to receive ranibizumab PRN in addition if visual impairment due to macular edema was present (laser + ranibizumab from month 6 arm).

Study Objectives

The study objectives included evaluating efficacy of the individualized, stabilization criteria-driven PRN ranibizumab 0.5 mg with or without laser assessed by the (a) mean change in BCVA from baseline to months 12 and 24; (b) proportion of patients with BCVA gain of ≥5, ≥10, ≥15, and ≥30 letters up to month 24; and proportion of patients with a BCVA value ≥73 letters (20/40 Snellen equivalent) from baseline to month 24; (c) mean change in Central Reading Center (CRC)–assessed central subfield thickness (CSFT) from baseline to month 24; and (d) evaluation of safety. The details of other secondary and exploratory study objectives reported in this article can be found on clinicaltrials.gov and are listed in Appendix 2 (available at www.aaojournal.org).[6] One of the key exploratory objectives was to evaluate the potential to skip visits from months 12 to 24 in patients with persistent VA stabilization in the absence of disease activity by assessing the proportion of patients who successfully skipped at least 1 visit and the number of successfully and unsuccessfully skipped visits.

Efficacy and Safety Assessments

Efficacy Assessments. Certified vision examiners assessed BCVA at every study visit by using ETDRS VA testing charts at an initial testing distance of 4 m. The vision examiner, who assessed parameters constituting the primary end point (BCVA), was masked to study treatment to avoid assessment bias. The OCT was performed by certified site personnel at the study sites at each visit using only spectral-domain OCT equipment, and images were forwarded to the CRC for independent analysis and storage. Throughout the study, patients were assessed using the same equipment. Retinal ischemia was assessed at baseline and months 3, 12, and 24 using fluorescein angiography in conjunction with 7-field color fundus photography, performed by certified operators at the site. We present the results of CRC-assessed macular ischemia, defined as present if the CRC scored retinal capillary loss or nonperfusion as mild, moderate, severe, or completely destroyed in ≥1 location of the center, inner, or outer subfields of the ETDRS grid as described in detail previously.[8]

Treatment Exposure. Data were collected for the number of ranibizumab 0.5 mg injections or laser administered in study eye over 24 months. After month 12, investigators were allowed to extend the interval between monitoring visits to 2 months (skipped visit). The number and outcomes of skipped visits was assessed.

Safety Assessments. At each visit over 24 months, data were collected for adverse events (AEs), serious AEs (SAEs), and their frequency, severity, and relationship to the study drug or ocular injection procedure.

Statistical Analysis

A sample size of 180 patients per arm,[7] while accounting for an approximately 10% dropout rate, had >92.1% power to establish (with a 1-sided α-level of 0.025) noninferiority of ranibizumab + laser compared with ranibizumab monotherapy for mean average

BCVA change from baseline to month 1 through month 24 (secondary end point) by applying a noninferiority margin of 5 letters and assuming an identical efficacy with a common standard deviation (SD) of 13 letters (based on results of the phase III BRAVO study[3]). This sample size also had an approximate 92.4% power to demonstrate a difference (regarding the number of treatments) of at least 1.4 ranibizumab injections in favor of the combination therapy at a 1-sided α-level of 0.025. Statistical analysis was performed using the SAS software version 9.2 (SAS Institute Inc., Cary, NC). Unless specified, all confidence intervals (CIs) and *P* values were 2-sided with a significance level (α) of 0.05.

For key secondary analyses that assessed noninferiority and superiority in 2 steps ranibizumab + laser was compared against ranibizumab monotherapy at a 1-sided α-level of 0.025. The hypothesis testing of the mean average BCVA change from baseline was based on pairwise analysis of variance models that included treatment factors and categorized baseline BCVA scores ($\leq$39, 40−59, and $\geq$60 letters). The least squares (LS) means and standard errors for each treatment arm and the pairwise treatment difference along with their 95% CIs were presented. Noninferiority was determined if the lower bound of the LS 95% CI for treatment difference was above the predefined noninferiority margin of 5 letters. The predefined noninferiority margin of 5 letters was selected based on the consideration that a BCVA change of >5 letters is generally clinically significant. The statistical hypothesis testing of the number of ranibizumab treatments was based on a stratified Cochran−Mantel−Haenszel test with observed values as scores and row mean scores statistic. Stratification was performed based on categories of baseline BCVA scores ($\leq$39, 40−59, and $\geq$60 letters). If the direction of the observed difference supported the superiority outcome (e.g., mean difference > 0), the 2-sided *P* value was converted to a 1-sided *P* value by dividing by 2. Otherwise, the 1-sided *P* value was calculated as 1 − (the 2-sided *P* value divided by 2).

All efficacy analyses were performed using the full analysis set (patients who received $\geq$1 administration of study treatment and underwent $\geq$1 postbaseline assessment for BCVA in the study eye) and last observation carried forward or observed data. Safety analyses were descriptive and performed on the safety set (patients who received $\geq$1 administration of study treatment and underwent $\geq$1 postbaseline safety assessment).

Results

Patient Disposition

Of the 455 patients enrolled in the study, 424 (93.2%) and 380 (83.5%) completed the 6-month and 24-month study duration, respectively (Fig 1). Key reasons for study discontinuation over 24 months were withdrawal of consent (7.0%), AEs (3.3%), lost to follow-up (2.0%), and physician's decision (2.0%). The baseline demographic, ocular, and disease characteristics have been reported[7] and are briefly summarized in Table 1. Overall, the mean (SD) age of the patients was 66.3 (10.30) years with a similar proportion of male and female patients (49.7% vs. 50.3%), and the majority of patients (94.9%) were white (Table 1). Of the 92 patients in the laser arm, 26 (28.3%) received laser monotherapy over the entire study duration, and 66 patients (71.7%) received laser + ranibizumab from month 6.

Efficacy

Best-Corrected Visual Acuity. The BCVA improvements at month 6 in ranibizumab monotherapy and ranibizumab + laser arms were sustained over the 24-month study duration (mean change [SD] in BCVA from baseline: 15.5 [13.91] and 17.3 [12.61] letters, respectively) (Fig 2). At month 24, the proportion of patients gaining $\geq$10/$\geq$15/$\geq$30 letters was higher with ranibizumab monotherapy and ranibizumab + laser arms compared with laser monotherapy (Fig 3, available at www.aaojournal.org). The proportion of patients with a BCVA score of $\geq$73 letters at month 24 was 66.1% and 64.0% in ranibizumab monotherapy and ranibizumab + laser arms, respectively versus 41.7% and 47.0% of patients receiving laser monotherapy and laser + ranibizumab from month 6. Patients receiving laser + ranibizumab from month 6 showed higher BCVA gain compared with those receiving laser monotherapy during the entire study duration (12.1 [15.33] vs. 10.0 [18.30] letters, respectively) (Fig 2).

The mean (SD) average BCVA change from baseline to month 1 through month 24 was 15.4 (10.76) letters in the ranibizumab + laser arm compared with 15.0 (10.86) letters in the ranibizumab monotherapy arm. The LS means difference between the 2

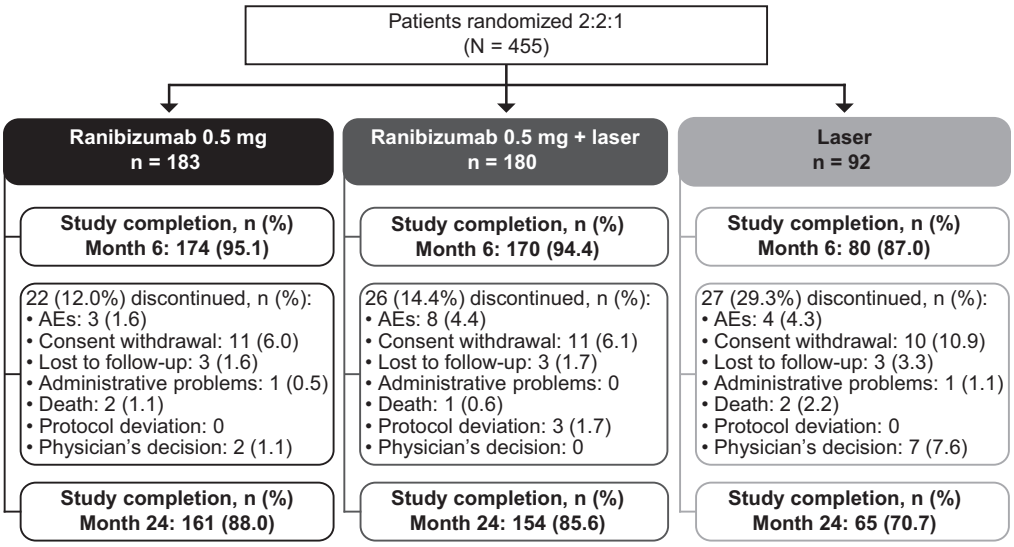


Figure 1. Patient disposition (randomized set). The randomized set consisted of all patients randomized. Because patients with multiple reasons were counted once for each reason of nonrandomization, the percentages may add up to $\geq$100%. AE = adverse event.

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

Characteristics	Ranibizumab 0.5 mg (n = 183)	Ranibizumab 0.5 mg + Laser (n = 180)	Laser Monotherapy (n = 26)	Laser + Ranibizumab 0.5 mg from Month 6 (n = 66)
Mean (SD) age, yrs	64.7 (10.3)	67.3 (10.4)	67.1 (11.0)	67.9 (9.2)
Gender (male), n (%)	93 (50.8)	96 (53.3)	7 (26.9)	30 (45.5)
Race (white), n (%)	171 (93.4)	172 (95.6)	26 (100)	63 (95.5)
Mean (SD) BCVA, letters	59.5 (11.8)	56.6 (13.2)	55.6 (15.1)	56.8 (13.9)
Baseline BCVA (letters), n (%)				
≤39	16 (8.7)	22 (12.2)	3 (11.5)	8 (12.1)
40–59	55 (30.1)	72 (40.0)	11 (42.3)	25 (37.9)
≥60	110 (60.1)	85 (47.2)	11 (42.3)	33 (50.0)
Mean (SD) duration of BRVO, mos	10.3 (19.6)	9.2 (19.9)	2.2 (2.2)	13.8 (30.8)
Baseline BRVO duration n (%)				
<3 mos	89 (48.6)	87 (48.3)	18 (69.2)	34 (51.5)
≥3–<6 mos	24 (13.1)	29 (16.1)	4 (15.4)	6 (9.1)
≥6–<9 mos	20 (10.9)	21 (11.7)	3 (11.5)	6 (9.1)
≥9–<12 mos	12 (6.6)	9 (5.0)	0	5 (7.6)
≥12 mos	36 (19.7)	33 (18.3)	0	14 (21.2)
Missing	2 (1.1)	1 (0.6)	1 (3.5)	1 (1.5)
Perfusion type, n (%)†				
Ischemic	87 (48.3)	71 (39.9)	6 (25.0)	35 (53.0)
Nonischemic	35 (19.4)	37 (20.8)	7 (29.2)	13 (19.7)
Cannot grade	57 (31.7)	68 (38.2)	10 (41.7)	18 (27.3)
Missing	1 (0.6)	2 (1.1)	1 (4.2)	0

BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; SD = standard deviation.
Baseline was defined as the last available nonmissing value collected just before the treatment initiation.
*The randomized set consisted of all randomized patients.
†Data for FAS (ranibizumab 0.5 mg [n = 180], ranibizumab 0.5 mg with laser [n = 178], laser with ranibizumab 0.5 mg after month 6 [n = 66], laser [n = 24]); retinal/macular ischemia defined as present if capillary loss detected by the CRC in any location of center, inner or outer subfields as assessed by the CRC.

treatment arms was −0.7 letters (95% CI, −2.8 letters, 1.4 letters; $P < 0.0001$); the lower bound of the 95% CI was within the protocol-defined noninferiority margin of 5 letters. Over the 24 months, there was no difference in the number of ranibizumab injections in the ranibizumab + laser arm versus the ranibizumab monotherapy arm (11.3 vs. 11.4 injections). The difference in treatment means (standard error) between the ranibizumab + laser and ranibizumab monotherapy arms was −0.1 (0.62), which was not statistically significant ($P = 0.4259$).

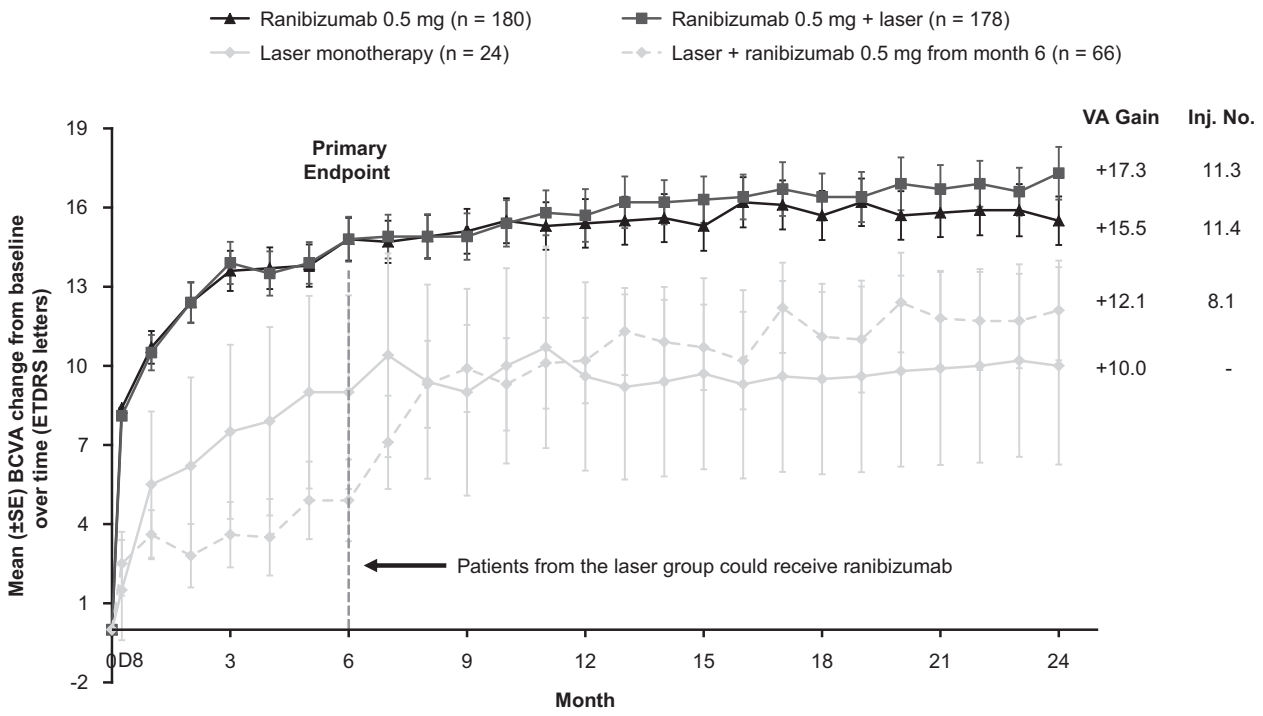
In patients from the ranibizumab monotherapy and ranibizumab + laser arms, mean change in BCVA from baseline to month 24 was similar, irrespective of the macular ischemia status. However, in patients from the laser arm, BCVA gains were numerically higher in patients with macular ischemia compared with those without ischemia (Fig 4). The BCVA gains did not differ based on the severity of macular ischemia, and results were similar in patients with mild-moderate or severe ischemia (Fig 5, available at www.aaojournal.org).

At month 24, patients with a lower baseline BCVA (≤39 letters) showed a numerically higher BCVA gain compared with those having a higher baseline BCVA (40–59 letters and ≥60 letters) (Fig 6, available at www.aaojournal.org). However, absolute BCVA values at month 24 were higher in patients with higher baseline BCVA compared with those having a lower baseline BCVA. Mean BCVA gain by the BRVO duration at baseline (<12/≥12 months) was 17.3/8.4 letters and 18.1/13.8 letters in the ranibizumab monotherapy and ranibizumab + laser arms and 12.4/11.4 letters in the laser monotherapy arm (Fig 7, available at www.aaojournal.org). Patients with a BRVO duration of <3 months had the highest BCVA gain in the ranibizumab monotherapy and ranibizumab + laser arms (+17.7 and +21.3, respectively) followed by those with a BRVO duration of 3 to <6 months (+17.0 and +14.9, respectively) (Fig 8, available at www.aaojournal.org).

Anatomic Outcomes. The reduction in CRC-assessed mean CSFT at month 6 was sustained up to month 24. The mean (SD) change in CSFT from baseline to month 24 was −224.7 (171.14) μm and −248.9 (181.94) μm in the ranibizumab monotherapy and ranibizumab + laser arms, whereas in patients receiving laser monotherapy and laser + ranibizumab from month 6, it was −107.5 (186.94) and, −229.9 (193.87) μm, respectively (Fig 9). Mean change from baseline in CRC-assessed overall central foveal thickness (observed data) at month 24 was −284.4 (190.01) μm, −314.7 (217.70) μm, −211.6 (179.61) μm, and −297.4 (243.61) μm in patients receiving ranibizumab monotherapy, ranibizumab + laser, laser monotherapy, and laser + ranibizumab from month 6, respectively. Compared with baseline, the proportion of patients with CSFT and central foveal thickness ≤450 μm increased (Table 2A, available at www.aaojournal.org) and that of patients with visible intraretinal fluid and subretinal fluid decreased (Table 2B, available at www.aaojournal.org) across the treatment arms at month 24.

Treatment Exposure

Ranibizumab Injections. The mean number of ranibizumab injections was not different in the ranibizumab monotherapy and ranibizumab + laser arms. The mean (SD) number of injections up to month 23 in patients receiving the ranibizumab monotherapy, ranibizumab + laser, and laser + ranibizumab from month 6 was 11.4 (5.81), 11.3 (6.02), and 8.1 (4.86), respectively (Fig 10). The mean number of ranibizumab injections did not differ on the basis of the presence or absence of macular ischemia at baseline. The mean (SD) number of ranibizumab injections (study eye) up to



Mean (±SD) BCVA, letters (absolute value)	Baseline	Day 8	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Ranibizumab 0.5 mg	59.5 (11.80)	68.0 (11.62)	73.1 (12.28)	74.3 (12.27)	74.6 (12.12)	74.9 (12.87)	74.8 (13.98)	75.2 (13.23)	75.3 (13.73)	75.0 (14.65)
Ranibizumab 0.5 mg + laser	56.5 (13.21)	64.6 (13.57)	70.4 (13.77)	71.4 (14.43)	71.5 (14.31)	72.3 (15.31)	72.9 (14.11)	73.0 (14.73)	73.2 (14.02)	73.9 (14.59)
Laser monotherapy	56.9 (14.77)	58.3 (17.41)	64.2 (14.22)	65.8 (17.38)	65.8 (16.65)	66.3 (16.52)	66.5 (17.73)	66.3 (18.07)	66.6 (18.51)	66.8 (18.63)
Laser + ranibizumab 0.5 mg from month 6	57.4 (13.43)	59.9 (14.01)	60.4 (13.15)	61.7 (12.64)	66.7 (13.30)	67.0 (12.92)	67.5 (12.84)	68.0 (13.62)	68.7 (13.45)	69.0 (13.96)

Figure 2. Mean change in best-corrected visual acuity (BCVA) from baseline to month 24 (full analysis set [FAS], last observation carried forward [LOCF]). 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 who were included even without receiving study treatment. Patients form the laser arm could receive ranibizumab after month 6. D8 = day 8; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation; SE = standard error; VA = visual acuity.

month 23 in the patients with ischemia receiving ranibizumab monotherapy, ranibizumab + laser, and laser + ranibizumab from month 6 was 11.4 (6.01) 12.2 (5.77), and 8.0 (4.62), respectively, and 11.0 (5.72), 9.5 (6.04), and 9.4 (6.04), respectively, in patients without ischemia.

In the second year, provided that treatment was interrupted because of meeting the stabilization criteria, monitoring could become bimonthly (skipped visit). Overall, 47.8% (n = 86) of patients in the ranibizumab monotherapy arm and 39.9% (n = 71) in the ranibizumab + laser arm skipped at least 1 visit. The proportion of patients whose stability allowed successfully skipping at least 1 visit was 35.6% and 34.3% in the ranibizumab monotherapy and ranibizumab + laser arms, respectively, whereby success was defined as persisting stabilization in BCVA from the last visit before a skipped visit to the visit after a skipped visit (i.e., retreatment was not required at the visit after a skipped visit). The proportion of patients who successfully skipped at least 3 visits was 21.7% and 19.1% in the ranibizumab monotherapy and ranibizumab + laser arms, respectively.

Laser Treatments. The mean (SD) number of laser treatments administered up to month 23 was 1.0 (0.57), 0.9 (0.64), and 1.5 (0.74) in patients receiving ranibizumab + laser, laser monotherapy, and laser + ranibizumab from month 6, respectively (Fig 11, available at www.aaojournal.org).

Safety

Adverse Events. Over the 24-month study period, ocular AEs (in the study eye) were reported in 48.3%, 53.6%, 28.0%, and 46.0% of patients receiving ranibizumab monotherapy, ranibizumab + laser, laser monotherapy, and laser + ranibizumab from month 6, respectively (Table 3). Eye pain, increased intraocular pressure, and conjunctival hemorrhage were the most frequently reported ocular AEs (Table 3). There were no reports of neovascular glaucoma or iris neovascularization. The incidence of nonocular AEs up to month 24 was 64.4%, 62.3%, 40.0%, and 55.6% in patients receiving ranibizumab monotherapy, ranibizumab + laser, laser monotherapy, and laser + ranibizumab from month 6, respectively (Table 3). Hypertension, nasopharyngitis, influenza, and headache were the most common nonocular AEs (Table 3).

Ocular AEs suspected to be related to treatment or the ocular injection procedure were reported in 27.8%, 31.1%, and 19.0% of the patients receiving ranibizumab monotherapy, ranibizumab + laser, and laser + ranibizumab from month 6, respectively

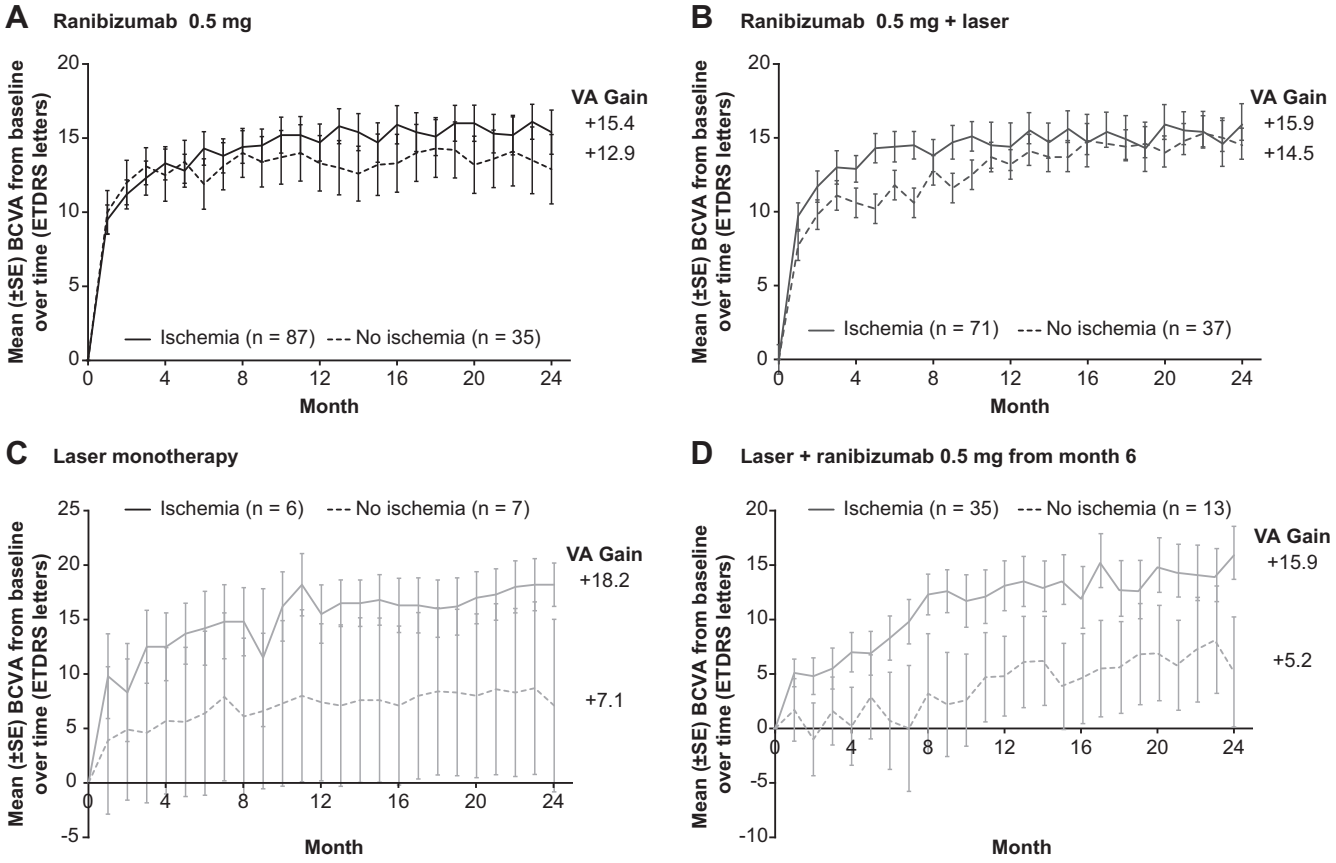


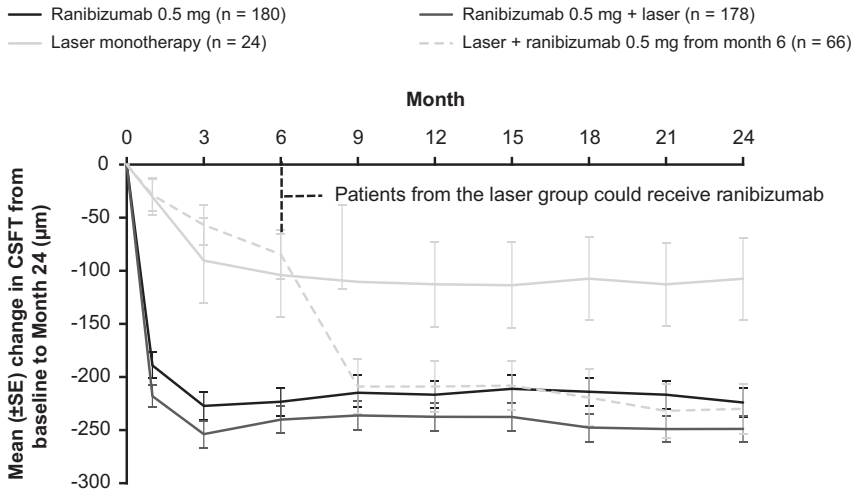
Figure 4. Mean change in best-corrected visual acuity (BCVA) from baseline to month 24 based on Central Reading Center (CRC)–assessed macular ischemia status at baseline (full analysis set [FAS], last observation carried forward [LOCF]). The FAS consisted of all randomized patients who had ≥1 postbaseline assessment for BCVA in the study eye and who received ≥1 administration of study treatment, except patients randomized to laser, who were included even without receiving study treatment. ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error; VA = visual acuity.

(Table 4, available at www.aaojournal.org). Nonocular AEs suspected to be related to treatment or the ocular injection procedure were reported in 4.4%, 5.5%, 4.0%, and 4.8% of the patients receiving ranibizumab monotherapy, ranibizumab + laser, laser monotherapy, and laser + ranibizumab from month 6, respectively (Table 4, available at www.aaojournal.org). Overall, 6 patients (ranibizumab + laser [n = 3], laser monotherapy [n = 2], and laser + ranibizumab from month 6 [n = 1]) experienced ocular AEs that led to treatment discontinuation. Nonocular AEs leading to treatment discontinuation were reported in 12 patients (ranibizumab monotherapy [n = 3], ranibizumab + laser [n = 6], and laser + ranibizumab from month 6 [n = 3]) (Table 5, available at www.aaojournal.org).

Serious Adverse Events. The incidence of ocular SAEs was low over the 24-month study period across the treatment arms (ranibizumab monotherapy, 2 [1.1%]; ranibizumab + laser, 4 [2.2%]; and laser + ranibizumab from month 6, 1 [1.6%]) (Table 6, available at www.aaojournal.org). Nonocular SAEs were reported in 28 patients (15.6%), 28 patients (15.3%), 3 patients (12.0%), and 9 patients (14.3%) receiving ranibizumab monotherapy, ranibizumab with laser, laser monotherapy, and laser with ranibizumab from month 6, respectively (Table 6, available at www.aaojournal.org). Overall, 5 deaths were reported during the study: 2 (1.1%), 1 (0.5%), and 2 (3.2%) among patients receiving ranibizumab monotherapy, ranibizumab with laser, and laser with ranibizumab from month 6, respectively. The reasons for deaths were acute respiratory failure and head injury (1 each in the ranibizumab arm); respiratory tract infection (1 in the ranibizumab + laser arm), and cardiac arrest and malignant lung neoplasm (1 each; both in the laser + ranibizumab from month 6–treated patients). None of them were suspected to be related to the study drug or procedure by the investigator.

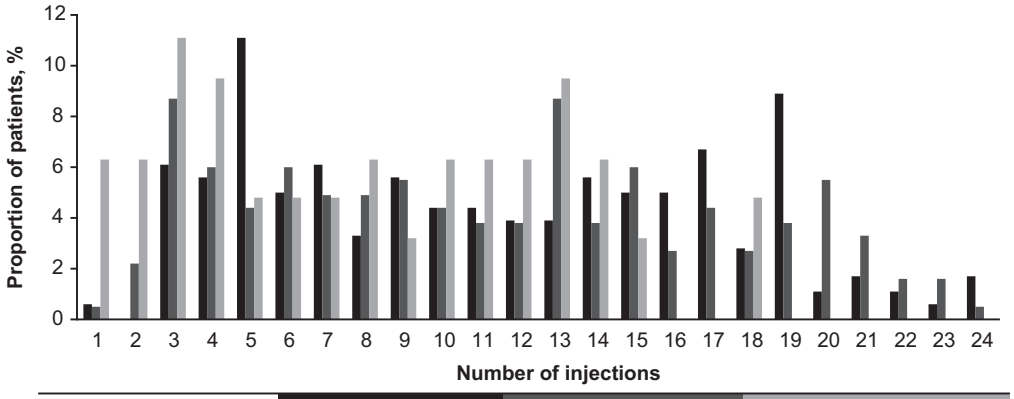
Discussion

BRIGHTER was a long-term study to evaluate the efficacy and safety of a PRN regimen driven by VA stabilization comparing ranibizumab with or without laser versus laser monotherapy in a broad population of patients with BRVO. The study population, which included patients with variable degree of retinal ischemia and disease duration, is likely to represent individuals from real-life settings. The 6-month primary outcomes of the BRIGHTER study demonstrated that the PRN regimen driven by VA stabilization using ranibizumab with or without laser led to statistically significant BCVA gains compared with laser alone.[7] The 24-month results presented further strengthen the evidence for long-term visual benefits with ranibizumab with a PRN regimen driven by VA stabilization and support the



Mean (±SD) CSFT, µm (absolute value)	Baseline	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Ranibizumab 0.5 mg	529.5 (144.97)	308.6 (95.55)	312.6 (104.61)	321.0 (101.57)	319.1 (99.32)	323.5 (115.69)	320.6 (118.26)	317.8 (105.85)	309.9 (100.03)
Ranibizumab 0.5 mg + laser	553.8 (170.06)	299.6 (88.13)	313.2 (86.38)	317.2 (102.71)	315.8 (98.42)	315.0 (95.69)	304.9 (88.17)	303.5 (84.36)	303.6 (84.68)
Laser monotherapy	528.2 (190.28)	437.8 (214.70)	424.1 (219.60)	417.8 (223.10)	415.5 (224.34)	414.6 (224.40)	420.8 (223.37)	415.4 (224.38)	420.7 (222.33)
Laser + ranibizumab 0.5 mg from month 6	549.4 (176.19)	489.4 (143.83)	461.5 (148.69)	337.2 (129.41)	337.1 (124.63)	338.0 (111.46)	326.7 (117.25)	314.2 (104.17)	316.2 (98.42)

Figure 9. Mean change in Central Reading Center (CRC)-assessed central subfield thickness (CSFT) from baseline to month 24 (full analysis set [FAS], last observation carried forward [LOCF]). The FAS consisted of all randomized patients who had ≥1 postbaseline assessment for best-corrected visual acuity (BCVA) in the study eye and who received ≥1 administration of study treatment, except patients randomized to laser, who were included even without receiving study treatment. SD = standard deviation; SE = standard error.



	Ranibizumab 0.5 mg (n = 180)	Ranibizumab 0.5 mg + laser (n = 183)	Laser + ranibizumab 0.5 mg from month 6 (n = 63)
Number of injections			
Mean (SD)	11.4 (5.81)	11.3 (6.02)	8.1 (4.86)
Median	11.0	11.0	8.0

Figure 10. Ranibizumab treatment exposure up to month 24 (safety set). The safety set consisted of all patients who had ≥1 postbaseline safety assessment and received ≥1 administration of study treatment, except patients randomized to laser, 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.

Table 3. Key Ocular and Nonocular Adverse Events up to Month 24 (Safety Set)*

Preferred Term, n (%)	Ranibizumab 0.5 mg (n = 180)	Ranibizumab 0.5 mg + Laser (n = 183)	Laser Monotherapy (n = 25)	Laser + Ranibizumab 0.5 mg from Month 6 (n = 63)
Ocular AEs, total	87 (48.3)	98 (53.6)	7 (28.0)	29 (46.0)
Eye pain	18 (10.0)	21 (11.5)	0	3 (4.8)
IOP increased	17 (9.4)	18 (9.8)	0	2 (3.2)
Conjunctival hemorrhage	15 (8.3)	15 (8.2)	0	5 (7.9)
Dry eye	10 (5.6)	3 (1.6)	0	2 (3.2)
Cataract	8 (4.4)	3 (1.6)	0	1 (1.6)
Macular fibrosis	8 (4.4)	7 (3.8)	0	2 (3.2)
Vitreous detachment	8 (4.4)	7 (3.8)	0	1 (1.6)
Ocular hyperemia	7 (3.9)	8 (4.4)	0	0
Vitreous floaters	7 (3.9)	10 (5.5)	1 (4.0)	4 (6.3)
Visual acuity reduced	6 (3.3)	7 (3.8)	1 (4.0)	4 (6.3)
Ocular hypertension	5 (2.8)	4 (2.2)	2 (8.0)	0
Retinal hemorrhage	5 (2.8)	3 (1.6)	1 (4.0)	2 (3.2)
Vitreous hemorrhage	5 (2.8)	6 (3.3)	0	1 (1.6)
Eye irritation	4 (2.2)	7 (3.8)	0	1 (1.6)
Macular edema	4 (2.2)	5 (2.7)	1 (4.0)	3 (4.8)
Blepharitis	3 (1.7)	11 (6.0)	0	1 (1.6)
Nonocular AEs, total	116 (64.4)	114 (62.3)	10 (40.0)	35 (55.6)
Hypertension	19 (10.6)	22 (12.0)	2 (8.0)	7 (11.1)
Nasopharyngitis	15 (8.3)	17 (9.3)	1 (4.0)	4 (6.3)
Influenza	13 (7.2)	13 (7.1)	1 (4.0)	2 (3.2)
Headache	11 (6.1)	9 (4.9)	0	6 (9.5)
Sinusitis	8 (4.4)	2 (1.1)	0	1 (1.6)
Edema peripheral	6 (3.3)	2 (1.1)	0	2 (3.2)
Osteoarthritis	6 (3.3)	8 (4.4)	1 (4.0)	3 (4.8)
Upper respiratory tract infection	6 (3.3)	6 (3.3)	0	3 (4.8)
Urinary tract infection	6 (3.3)	4 (2.2)	0	3 (4.8)
Back pain	5 (2.8)	9 (4.9)	2 (8.0)	1 (1.6)
Diarrhea	5 (2.8)	2 (1.1)	0	3 (4.8)
Arthralgia	4 (2.2)	6 (3.3)	0	1 (1.6)
Cough	4 (2.2)	6 (3.3)	0	4 (6.3)
Pain in extremity	4 (2.2)	7 (3.8)	0	0
Dizziness	3 (1.7)	6 (3.3)	1 (4.0)	0
Fall	2 (1.1)	6 (3.3)	0	3 (4.8)

AE = adverse event; IOP = intraocular pressure.
The safety set consisted of all patients who had ≥1 postbaseline safety assessment and received ≥1 administration of study treatment, except patients randomized to laser who were included even without receiving study treatment.
A patient with multiple occurrences of an AE under 1 treatment was counted only once in the AE category for that treatment.
The Medical Dictionary for Regulatory Activities v17.1 was used for coding of study AEs.
*Adverse events that occurred in ≥2% of the safety set. Adverse events were sorted in descending frequency, as reported in the ranibizumab 0.5 mg column.

treatment recommendations compiled by an international expert panel.[9] The BRIGHTER study results add to the findings from other studies in patients with BRVO, such as BRAVO,[3] HORIZON,[10] SHORE,[11] and RETAIN,[12] that have reported benefits with long-term ranibizumab treatment.

Looking at the overall population, addition of laser to ranibizumab had no impact on BCVA changes or re-treatment need, suggesting that additional laser, at least over a period of 24 months, does not provide any benefit. However, patients receiving ranibizumab + laser and laser + ranibizumab from month 6 with a longer duration (≥12 months) of BRVO had higher mean change in BCVA (Figs 7 and 8, available at www.aaojournal.org) compared with patients from the ranibizumab monotherapy arm. Of note, these patients receiving ranibizumab + laser and laser + ranibizumab from month 6 had a lower baseline BCVA (5.5 and 9.8 letters lower compared with patients in the ranibizumab monotherapy arm, respectively). The absolute BCVA at month 24 for patients with a BRVO duration of ≥12 months was 72.5, 72.4, and 66.7 letters for patients receiving ranibizumab monotherapy, ranibizumab + laser, and laser + ranibizumab from month 6, respectively.

The BCVA improvement and CSFT reduction observed at month 6 in the ranibizumab monotherapy and ranibizumab + laser arms were sustained over the 24-month study period. Patients from the laser + ranibizumab from month 6 arm had numerically higher BCVA improvements compared with those who received laser monotherapy. Patients receiving laser with or without ranibizumab from month 6 had numerically lower BCVA improvements compared with those who received ranibizumab since inclusion. These results do not favor delaying ranibizumab

treatment by initially treating with laser monotherapy in general in patients with BRVO.

The presence of macular ischemia is an important prognostic factor for final VA outcomes in patients with BRVO.[2,13] Whether some ischemia in the macular area could affect the final results and whether it may change with the treatment are debatable. In the BRIGHTER study, ranibizumab with or without laser provided BCVA improvements irrespective of the ischemia status at baseline with a similar number of injections, demonstrating that the presence of some macular ischemia at baseline with BCVA >19 ETDRS letters (~20/400) does not affect BCVA gains over 24 months.

Disease duration is another factor that can affect treatment outcomes. In this study, patients experienced visual benefits regardless of the baseline disease duration. In ranibizumab monotherapy and ranibizumab + laser-treated patients, the BCVA outcomes were numerically higher in patients with BRVO duration of <3 months and 3 to 6 months compared with those with a longer disease duration (6−<9 months, 9−<12 months, and >12 months). These results are in favor of early treatment with ranibizumab. Moreover, these results corroborate findings from the previous studies in which patients with BRVO who received early treatment with anti-vascular endothelial growth factor with or without laser showed better visual outcomes.[14,15]

Baseline BCVA is an important predictor of final visual outcomes.[16] Among the patients in the ranibizumab monotherapy and ranibizumab + laser arms in BRIGHTER, patients with lower baseline BCVA (≤39 letters) had numerically higher BCVA gains compared with those with higher baseline BCVA (40−59 and ≥60 letters). However, at month 24, the final absolute BCVA values were lower in patients with poor baseline VA, further highlighting the need for early treatment initiation.

Overall, the number of ranibizumab injections required during the 24-month study duration was comparable between patients receiving ranibizumab monotherapy and ranibizumab + laser. Over the 24-month study period, patients from the ranibizumab monotherapy and ranibizumab + laser arms received 11.4 and 11.3 injections, respectively (including 3 initial monthly injections mandated per protocol). This suggests that the individualized PRN regimen reduced the treatment requirement compared with monthly treatment and the initial BCVA gain at month 6 was sustained over next 18 months with fewer injections. Therefore, the individualized, VA stability criteria-driven, PRN dosing regimen of ranibizumab may help reduce the treatment burden while maintaining visual and anatomic benefits.

In the second year of the BRIGHTER study, if VA was stable and disease activity was absent, the visit interval could be extended to bimonthly. Approximately 35% of the patients had ≥1 successful skipped visit in the ranibizumab with or without laser arms. This suggests that most patients with BRVO may require frequent monitoring for at least the initial 24 months of treatment; alternative approaches such as treat and extend may be appropriate to adjust the monitoring frequency individually.

The incidence of AEs and SAEs was similar in the ranibizumab monotherapy and ranibizumab + laser arms. There were no reports of neovascular glaucoma or iris neovascularization. The BRIGHTER study results further strengthen the well-established safety profile of ranibizumab 0.5 mg in patients with BRVO.[3,4,7,8,10−12]

The BRIGHTER study had a few limitations. As per protocol, patients from the laser monotherapy arm were eligible to receive adjunctive ranibizumab only after month 6. The visit skipping algorithm used in the study was complicated and may be difficult for physicians to follow in their routine practice. Comparisons of the efficacy based on baseline characteristics between treatment arms were exploratory and not sufficiently powered.

The BRIGHTER study results confirmed the long-term efficacy and safety profile of PRN dosing driven by individualized VA stabilization criteria using ranibizumab 0.5 mg in patients with BRVO. Addition of laser did not lead to better functional outcomes or lower treatment need. The study findings support early ranibizumab treatment. The safety results add to the well-established safety profile of ranibizumab.

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Footnotes and Financial Disclosures

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*Appendix 1 lists the contributing investigators in the BRIGHTER Study Group (available at www.aaojournal.org).

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Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **BRVO** = branch retinal vein occlusion; **CI** = confidence interval; **CRC** = Central Reading Center; **CSFT** = central subfield thickness; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **LS** = least squares; **OCT** = optical coherence tomography; **PRN** = pro re nata; **SAE** = serious adverse event; **SD** = standard deviation; **VA** = visual acuity.

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