

Individualized Ranibizumab Regimen Driven by Stabilization Criteria for Central Retinal Vein Occlusion

Twelve-Month Results of the CRYSTAL Study

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Purpose: To assess the 12-month efficacy and safety profile of an individualized regimen of ranibizumab 0.5 mg driven by stabilization criteria in patients with macular edema secondary to central retinal vein occlusion (CRVO).

Design: A 24-month, prospective, open-label, single-arm, multicenter study.

Participants: Three hundred fifty-seven patients.

Methods: Patients were treated with monthly ranibizumab 0.5-mg injections (minimum of 3 injections) until stable visual acuity (VA) was maintained for 3 consecutive months. Thereafter, ranibizumab 0.5 mg was dosed as needed if monthly monitoring indicated a loss of VA resulting from disease activity.

Main Outcome Measures: Mean change from baseline at month 12 in best-corrected VA (BCVA; primary end point) and safety over 12 months. The efficacy of this regimen in subgroups categorized by baseline BCVA score, CRVO duration, or presence of macular ischemia (exploratory analysis).

Results: At baseline, the mean BCVA was 53.0 letters and mean CRVO duration was 8.9 months (median, 2.4 months). Ranibizumab 0.5-mg treatment resulted in a statistically significant mean gain in BCVA from baseline at month 12 of 12.3 letters (standard deviation [SD], 16.72 letters; $P < 0.0001$). The mean number of ranibizumab injections up to month 12 was 8.1 (SD, 2.77). At month 12, mean BCVA gains were similar with or without macular ischemia at baseline (11.6 vs. 12.1 letters); the mean BCVA gain was higher with baseline CRVO duration of less than 3 months (13.4 letters) than with a longer duration (≥ 3 – < 9 months, 11.1 letters; ≥ 9 months, 10.9 letters). Patients with lower baseline BCVA had larger mean BCVA gains at month 12 than those with higher baseline BCVA ($\leq 39/40$ – $\geq 59/\geq 60$ and 18.0/12.7/8.9 letters, respectively), although the absolute BCVA at month 12 was higher with higher baseline BCVA. No new ocular or nonocular safety events were observed.

Conclusions: An individualized dosing regimen of ranibizumab 0.5 mg driven by stabilization criteria for up to 12 months resulted in significant BCVA gain in a broad population of patients with macular edema secondary to CRVO, including those with macular ischemia at baseline. The safety findings were consistent with those reported in previous ranibizumab studies in patients with CRVO. *Ophthalmology* 2016;123:1101-1111 © 2016 by the American Academy of Ophthalmology. 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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Central retinal vein occlusion (CRVO) is a common retinal vascular disorder with a prevalence of approximately 1 per 1000 persons.¹ Macular edema is a major complication in CRVO that can lead to legal blindness.^{2–4} Intravitreal anti-vascular endothelial growth factor (VEGF) agents have proven efficacy and are considered the first-line treatment option for macular edema secondary to CRVO.^{3,5–8}

The results from the Central Retinal vein occlusion Study: Evaluation of efficacy and safety trial (CRUISE)

study contributed significantly in defining anti-VEGF agents as a treatment option for patients with macular edema secondary to CRVO. In the CRUISE study, 392 patients received monthly injections of ranibizumab (0.3 or 0.5 mg) or sham for the first 6 months, followed by ranibizumab pro re nata (PRN) treatment (based on prespecified criteria) for the next 6 months. The improvements in best-corrected visual acuity (BCVA) and central foveal thickness observed with a monthly dosing regimen of ranibizumab 0.5 mg in

the first 6 months were maintained with a PRN dosing regimen until month 12.^{9,10}

The CRUISE study results showed that 6 initial monthly injections were successful in the treatment of patients with macular edema secondary to CRVO. However, it is possible that macular edema resulting from CRVO may resolve in some patients without the need for monthly injections.² In the CRUISE study, during the PRN treatment period, patients received a mean number of 3.3 injections, and 15% of patients did not require any treatment. Furthermore, in the HORIZON-retinal vein occlusion (HORIZON-RVO) trial (cohort II),¹¹ an open-label extension of the CRUISE study,⁹ the need for retreatment in patients with CRVO decreased to a mean of 3.5 injections per year, although patients required more frequent follow-ups than every 3 months.

The CRYSTAL study was designed to assess the long-term efficacy and safety of an individualized visual acuity (VA) dosing regimen of ranibizumab 0.5 mg driven by stabilization criteria. The CRYSTAL study was a 24-month phase 3b, open-label, single-arm, multicenter study conducted in a broad patient population with visual impairment resulting from macular edema secondary to CRVO, including those with macular ischemia or longer disease duration. Herein, we report the efficacy and safety results from the first 12 months of the CRYSTAL study.

Methods

Study Design

The CRYSTAL study was a 24-month phase 3b, open-label, single-arm, multicenter study assessing the efficacy and safety of an individualized dosing regimen of ranibizumab 0.5 mg driven by VA stabilization criteria in patients with visual impairment resulting from macular edema secondary to CRVO. The study was conducted at 86 sites across 18 countries worldwide (Appendix 2, available at www.aaojournal.org). The study began in February 2012 and was completed in April 2015. The results of the first 12 months of the CRYSTAL study were obtained in April 2014.

The CRYSTAL study was designed to assess the treatment posology for CRVO according to the 2011 Lucentis European Union Summary of Product Characteristics (EU SmPC)¹² that deviated from the posology of the pivotal CRUISE trial.⁹ A sham arm was not used in the CRYSTAL study because the superiority of ranibizumab treatment versus sham was established in the CRUISE study. Laser could not be used as an active comparator because it was shown to be ineffective in improving VA in patients with macular edema secondary to CRVO in the Central Vein Occlusion study.¹³ No other approved treatments for macular edema secondary to CRVO were available at the time of study initiation.

The study was conducted in accordance with the Declaration of Helsinki and the protocol was reviewed and approved by the independent ethics committee or institutional review board for each contributing center. Patients provided written informed consent before entering the study. The study is registered with ClinicalTrials.gov (identifier, NCT01535261).

Patients

The study population consisted of patients 18 years of age or older with visual impairment resulting from macular edema secondary to

CRVO. The key inclusion criterion was a BCVA between 73 and 19 (inclusive) Early Treatment Diabetic Retinopathy Study (ETDRS) letters (approximate Snellen equivalents, 20/40 and 20/400, respectively) at screening and baseline.

The key exclusion criteria were use of intravitreal anti-VEGF injections 3 months or less before baseline (either eye) and systemic anti-VEGF agents 6 months or less before baseline, panretinal laser photocoagulation 3 months or less before baseline, focal or grid laser photocoagulation 4 months or less before baseline, topical ocular or systemic corticosteroids administered for 30 consecutive days or more within 6 months before screening, intraocular or periocular corticosteroid use 3 months or less before screening (study eye), use of intraocular corticosteroid implants, and the following conditions in either eye: active periocular or ocular infection or inflammation at screening or baseline, uncontrolled glaucoma (intraocular pressure [IOP] \geq 30 mmHg with medication or according to the investigator's judgment) at the time of screening or baseline or diagnosis within 6 months before baseline, and iris neovascularization or neovascular glaucoma. Additional exclusion criteria are provided in Appendix 3 (available at www.aaojournal.org).

Treatment

Administration of an intravitreal ranibizumab 0.5-mg injection was as recommended in the EU SmPC.¹² The treatment was initiated with monthly consecutive intravitreal ranibizumab 0.5-mg injections starting on day 1 (baseline). Per design, at least 3 initial injections were required (baseline, month 1, month 2) until a stable maximum VA (based on the investigator's judgment) was observed over 3 consecutive visits with treatment (months 1, 2, and 3; Fig 1, available at www.aaojournal.org).

The investigators then monitored the patients for VA and disease activity on a monthly basis. Monthly ranibizumab 0.5-mg injections were reinitiated if monitoring indicated a loss of VA resulting from disease activity and were continued until VA stabilization (defined as 3 consecutive visits with stable VA [based on investigator's judgment], implying a minimum of 2 monthly injections). Per protocol (and 2011 EU SmPC¹²), retreatment was required upon observation of VA loss resulting from disease activity (i.e., worsening of macular edema). Visual acuity loss not accompanied by increased disease activity did not warrant retreatment, and changes in retinal anatomic features—for example, on optical coherence tomography (OCT) images—not causing VA loss likewise did not warrant treatment. If VA did not improve after the first 3 mandatory injections, continued treatment with ranibizumab was not recommended, and the patient could receive alternative treatment at the investigator's discretion.

If both eyes were eligible for treatment, the study eye was selected based on the investigators' judgment. The nonstudy eye, labeled the "fellow eye," was allowed to receive ranibizumab treatment within the study according to the local label, based on the investigator's judgment. However, both eyes were not treated with ranibizumab on the same day, as recommended in the 2011 EU SmPC.¹²

The use of rescue medication was not permitted. Panretinal laser photocoagulation was permitted during the study in either eye, but only later than month 3 in the study eye.

Study Objectives

The primary objective was to evaluate the efficacy of an individualized dosing regimen of ranibizumab 0.5 mg driven by VA stabilization criteria in patients with visual impairment resulting from macular edema secondary to CRVO according to the 2011

EU SmPC for ranibizumab. This was assessed by the mean change in BCVA from baseline at month 12.

There were 2 secondary objectives. The first was to evaluate the efficacy of an individualized dosing regimen of ranibizumab 0.5 mg driven by stabilization criteria as assessed by (1) the mean average change in BCVA from baseline to month 1 through month 12 (i.e., the sum of each patient's average BCVA changes from month 1 through month 12 divided by the total number of patients, compared with baseline, an expression for the area under the change-in-BCVA curve); (2) the proportion of patients with a BCVA improvement of 1 or more, 5 or more, 10 or more, 15 or more, and 30 or more letters and loss of fewer than 15 letters from baseline to month 12; (3) the proportion of patients attaining a BCVA of 73 letters or more (approximate Snellen equivalent, 20/40) at month 12; and (4) the mean change in central reading center (CRC)-assessed central subfield thickness (CSFT) from baseline to month 1 through month 12. The second was to assess safety over 12 months. An exploratory objective of the study was to evaluate the efficacy of ranibizumab 0.5-mg treatment based on baseline ocular characteristics such as presence of macular ischemia, duration of CRVO, and BCVA scores.

Efficacy Assessments

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

Best-Corrected Visual Acuity. Best-corrected visual acuity was assessed at every study visit by certified investigators or designated staff using an ETDRS VA testing chart 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 4 letters or more on the ETDRS chart at this distance, the refraction or VA testing was attempted at 1 m.

Optical Coherence Tomography. Optical coherence tomography assessment was performed by certified operators at every visit using spectral-domain OCT equipment, and the same machine was used for assessment of the same patient throughout the study. The investigator or the designated study staff evaluated the images according to the standard practice and recorded the required variables in the clinical database. The images also were reviewed by a CRC to ensure a standardized evaluation of CSFT (which is the average retinal thickness of the circular area with a 1-mm diameter around the foveal center), central foveal thickness, and the retinal thickness at the foveal centerpoint and to capture the presence or absence of qualitative parameters (i.e., intraretinal cystoid fluid and subretinal fluid). Definitions of these quantitative and categorical spectral-domain OCT parameters are provided in [Appendix 4](#) (available at www.aajournal.org). Image raw data were evaluated using validated CRC software. The inner and outer retinal boundaries were segmented at predefined standardized locations to ensure standardization across the spectral-domain OCT instruments used. Quality control for the OCT grading procedure has been described previously.¹⁴

Fluorescein Angiography and Color Fundus Photography. Fluorescein angiography, in conjunction with 7-field color fundus photography, was performed by certified operators at screening, month 3, and month 12 (additional evaluation during the other monthly visits was at the investigator's discretion). The CRC evaluated the images and captured the degree of ischemia at baseline and during the study ([Appendix 5](#), available at www.aajournal.org). Retinal ischemia was defined by the extent of retinal capillary loss (presence or absence of nonperfusion) in the ETDRS grid center subfield, as well as inner and outer subfields. We defined macular ischemia as present if the CRC scored capillary loss as mild, moderate, severe, or completely destroyed in 1 or more location of the center, inner, or outer

subfields of the ETDRS grid. Here, we report the efficacy results for CRC-assessed macular ischemia. The CRC provided each study site with an OCT manual as well as a retinal fluorescein angiography and photography manual, providing instructions and guidance on how to capture and transfer images to ensure standardization across the sites. In case of loss of VA stabilization, the investigators assessed all image methods to judge disease activity, warranting retreatment.

Treatment Exposure. Information was collected on the number of ranibizumab injections in the first 12 visits, that is, baseline to month 11.

Safety Assessments. Safety assessments comprised recording of all adverse events (AEs) and serious AE (SAEs), with their type, frequency, severity, and relationship to the study drug, ocular injection procedure, or both, at all visits over the course of 12 months. Vital signs were measured and ophthalmic examination was performed at each study visit.

Statistical Analysis

The sample size calculation was based on the primary efficacy end point using the full analysis set (FAS) last observation carried forward. The estimate of the standard deviation (SD) for the change in BCVA from baseline to month 12 was based on the results from the CRUISE study.^{9,10} The sample size was calculated using PASS 2002 sample size software (NCSS, LLC, Kaysville, UT). Assuming an SD of 15.2 letters for the change (normally distributed) in BCVA from baseline at month 12, a sample size of 315 patients produced a 2-sided 95% confidence interval equal to the mean change in BCVA from baseline at month 12 of ± 1.7 letters. Assuming a 10% dropout rate for the 12-month analysis, the final sample size was 350 patients. Unless otherwise specified, all 95% confidence intervals and *P* values were 2 sided and were based on an α significance level of 0.05.

All analyses were descriptive. The 95% confidence intervals and *P* values for the primary (related to the null hypothesis that this mean change is equal to 0) and secondary efficacy analyses comparing response to baseline were calculated based on a *t* distribution/*t* test. The last observation carried forward approach was used to impute missing variables. The CRC-assessed categorical OCT parameters were summarized using the observed data for the study eye in the FAS.

All efficacy analyses were performed using the FAS, which included all patients who received 1 or more administrations of study treatment and had 1 or more postbaseline assessments for BCVA in the study eye. Safety analyses were performed using the safety set, which included all patients who received 1 or more administrations of study treatment and had 1 or more postbaseline safety assessments. All other analyses were performed using the eligible set that comprised all patients who were deemed eligible to receive the study treatment according to the investigator. The statistical analysis was performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Patient Disposition and Baseline Characteristics

Three hundred fifty-seven patients were enrolled, and 333 (93.3%) completed the first 12 months of the study. Treatment discontinuations were low, with no predominant reason for discontinuation. The most common reasons for discontinuation were withdrawal of consent (*n* = 8 [2.2%]) and AEs (*n* = 7 [2.0%]). The eligible set and safety set included 357 patients, and the FAS included 356

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

Parameter	Ranibizumab 0.5 mg (n = 357)
Age (yrs), mean (SD)	65.5 (12.68) [†]
Gender, no. (%)	
Male	229 (64.1)
Female	128 (35.9)
Predominant race, no. (%)	
White	337 (94.4)
Black	4 (1.1)
Asian	5 (1.4)
Other	11 (3.1)
Study eye, no. (%)	
Right	174 (48.7)
Left	183 (51.3)
Visual acuity (letters)	
Mean (SD)	53.0 (15.00)
Median	55.0
Visual acuity stratification group (letters), no. (%)	
<39	75 (21.0)
40–59	134 (37.5)
≥60	148 (41.5)
Duration of CRVO (mos)	
Mean (SD)	8.9 (20.66)
Median	2.4
Duration of CRVO (mos), no. (%)	
<3	193 (54.1)
≥3–<6	50 (14.0)
≥6–<9	26 (7.3)
≥9–<12	20 (5.6)
≥12	68 (19.0)
Intraocular pressure (mmHg), mean (SD)	15.7 (3.18)
Investigator-reported perfusion type, no. (%)	
Ischemic	54 (15.1)
Nonischemic	300 (84.0)
Missing	3 (0.8)
CRC-assessed macular ischemia, no. (%)	107 (30.0)
CRC-assessed CSFT (μm), mean (SD)	692.8 (231.93)

CRC = central reading center; CRVO = central retinal vein occlusion; CSFT = central subfield thickness; SD = standard deviation.

Percentages are based on the total number of patients in the eligible set. Baseline was defined as the last available nonmissing value recorded just before the start of treatment.

*Comprised all patients who were deemed to be eligible to receive study treatment according to the investigator.

[†]n = 355.

patients (1 patient was excluded from the FAS for not having 1 or more postbaseline assessments).

At baseline, the mean age of the enrolled patients was 65.5 years (SD, 12.68 years), two-thirds were men (n = 229 [64.1%]), and most were white (n = 337 [94.4%]; Table 1). The mean BCVA at baseline was 53.0 letters (SD, 15.00 letters; Table 1). Investigator-assessed ischemic perfusion type was present in 54 patients (15.1%) and CRC-assessed macular ischemia was present in 107 patients (30.0%). In 138 patients (38.7%), macular ischemia could not be assessed by the CRC, mainly because of severe intraretinal hemorrhage. The mean duration of CRVO was 8.9 months (SD, 20.66 months), and the median duration was 2.4 months (quartile 1–quartile 3, 0.9–8.7 months; Table 1). The CRC-assessed mean CSFT at baseline was 692.8 μm (SD, 231.93 μm). The mean IOP at baseline was 15.7 mmHg (SD, 3.18 mmHg).

Efficacy

Best-Corrected Visual Acuity. At month 12, ranibizumab 0.5-mg treatment resulted in a statistically significant mean gain in BCVA from baseline of 12.3 letters (SD, 16.72 letters; $P < 0.0001$; Fig 2). Improvement in vision was observed to occur rapidly; at the first examination after the baseline injection (day 8), a mean gain in BCVA from baseline of 8.9 letters (SD, 8.08 letters) was observed ($P < 0.0001$; Fig 2). The mean average change in BCVA from baseline to months 1 through 12 with ranibizumab 0.5-mg treatment was +11.8 letters (SD, 12.44 letters; $P < 0.0001$).

With ranibizumab 0.5-mg treatment, 63.8% of patients (n = 227) gained 10 letters or more, 49.2% (n = 175) gained 15 letters or more, and 9.0% (n = 32) gained 30 letters or more from baseline at month 12. Most patients (94.1%; n = 335) avoided loss of 15 letters or more from baseline at month 12. Approximately half of the patients (47.5%; n = 169) attained a BCVA score of 73 letters or more (Snellen equivalent, 20/40) at month 12.

The exploratory analysis showed that treatment with ranibizumab 0.5 mg resulted in BCVA gains from baseline at month 12 regardless of the baseline BCVA score, prior CRVO duration, or presence of CRC-assessed macular ischemia at baseline. The mean change in BCVA from baseline at month 12 was similar in patients with macular ischemia at baseline (+11.6 letters; SD, 14.92 letters) or without it (+12.1 letters; SD, 18.10 letters; Fig 3). The mean change in BCVA from baseline at month 12 was higher in patients with a lower baseline BCVA compared with those with a higher baseline BCVA. The mean BCVA gain was 18.0 letters in patients with a baseline BCVA of 39 letters or less, 12.7 letters in those with a baseline BCVA between 40 and 59 letters, and 8.9 letters in those with a baseline BCVA of 60 letters or more (Fig 4). However, patients with higher baseline BCVA had a higher absolute BCVA at month 12 compared with those with a lower baseline BCVA. The mean change in BCVA from baseline at month 12 was higher in patients with a shorter duration of CRVO at baseline compared with those with a longer duration of CRVO at baseline. The mean BCVA gain was 13.4 letters in patients with a prior CRVO duration of less than 3 months, 11.1 letters in those with CRVO duration between 3 and 9 months, and 10.9 letters in those with CRVO duration of at least 9 months (Fig 5).

Anatomic Outcomes. The mean CSFT decreased in a statistically significant manner from baseline to month 12 with ranibizumab 0.5 mg (693.7 μm [SD, 231.64 μm] vs. 358.0 μm [SD, 203.38 μm]; difference from baseline to month 12, 335.7 μm [SD, 285.02 μm]; $P < 0.0001$; Fig 6). Most of the reduction in CSFT from baseline was reached by month 3 (361.5 μm [SD, 246.30 μm]), and the reduction was maintained up to month 12 (Fig 6). With ranibizumab 0.5-mg treatment, there was an increase in the proportion of patients with CSFT and central foveal thickness of 450 μm or less (predefined cutoff value based on a subgroup analysis of the CRUISE study) and a decrease in the proportion of patients with visible intraretinal cystoid fluid and subretinal fluid from baseline at month 12 (Table 2, available at www.aaojournal.org).

Treatment Exposure. Patients received a mean of 8.1 ranibizumab injections (SD, 2.77 injections; median, 9.0 injections) in the study eye before month 12. Stable VA was achieved in 132 patients (37%) after the 3 initial mandatory injections, in 51 patients (14.3%) after 4 injections, in 23 patients (6.4%) after 5 injections, and in 33 patients (9.2%) after 6 injections. During the first 12 monthly visits of the study, 35 patients (9.8%) received only 3 injections, whereas 22 patients (6.2%) received the maximum exposure of 12 injections (Fig 7). The mean number of ranibizumab injections was similar in patients with macular ischemia (7.5 [SD, 2.90]) and those without macular ischemia

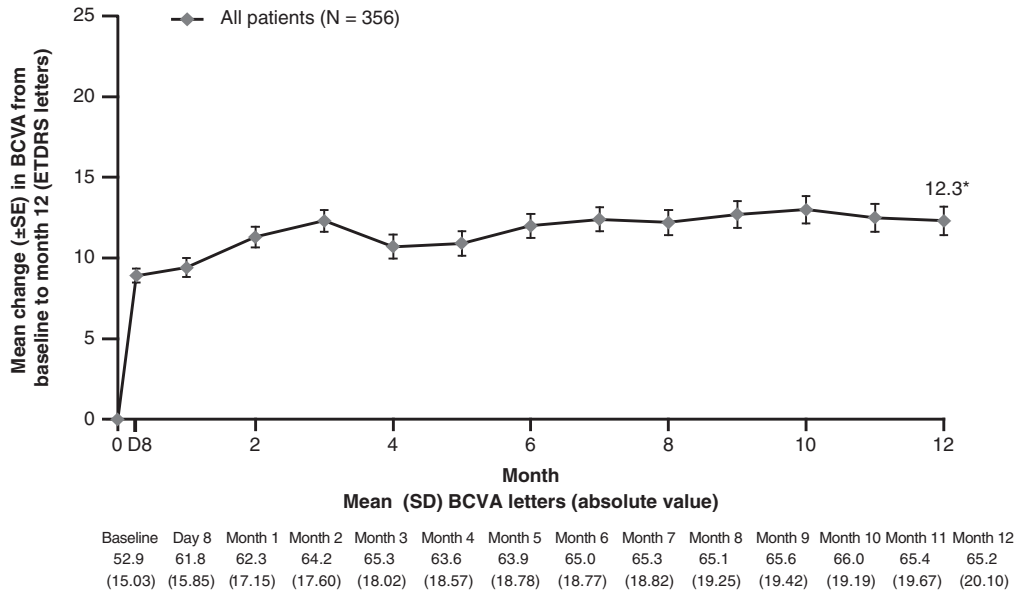


Figure 2. Graph showing mean change in best-corrected visual acuity (BCVA) from baseline to month 12 (full analysis set [last observation carried forward]). * $P < 0.0001$ (related to the null hypothesis that this mean change is equal to 0) at month 12 versus baseline. All postbaseline comparisons for individual time points up to month 12 versus baseline showed $P < 0.0001$. ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation; SE = standard error of the mean.

(8.0 [SD, 2.88]). A total of 5 patients (1.4%) received treatment in the fellow eye at any time during the 12 months, and 2 of the 5 patients (0.6%) had been treated already at baseline.

Safety

Serious Adverse Events up to Month 12. Ocular SAEs in the study eye were reported in 8 patients (2.2%; Table 3, available at

www.aaojournal.org). Reduced VA was reported as an SAE in 2 patients (0.6%). All other ocular SAEs were reported in 1 patient (0.3%) each. Retinal hemorrhage and retinal ischemia were reported as SAEs in 1 patient each; both events were considered by the investigator to be not related to the study treatment, ocular injection, or both (Table 3, available at www.aaojournal.org). Four SAEs reported in 2 patients were suspected by the investigator to be related to the ocular injection:

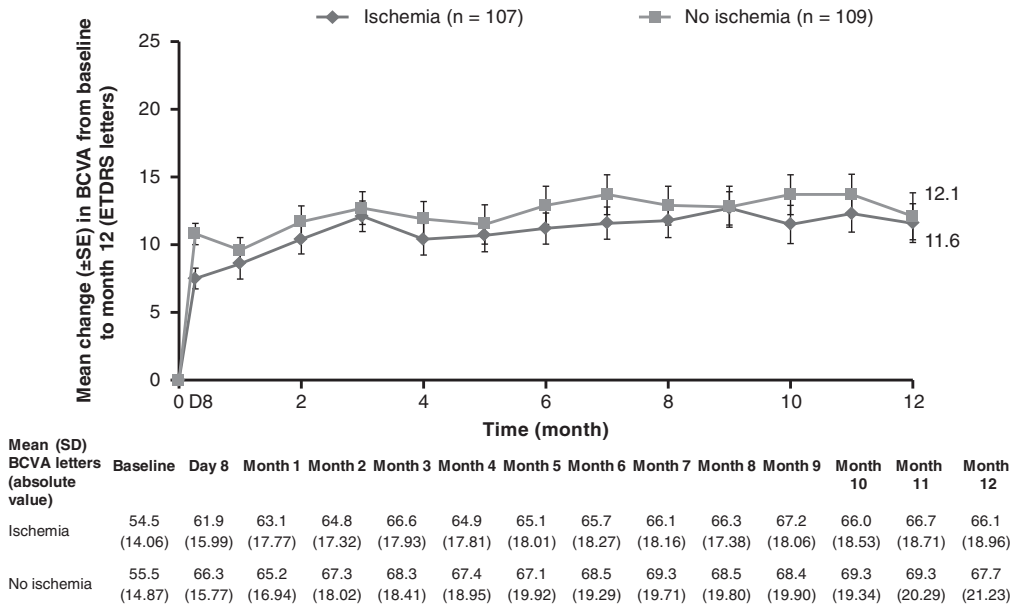


Figure 3. Graph showing mean change in best-corrected visual acuity (BCVA) from baseline to month 12 by presence of macular ischemia at baseline (full analysis set [last observation carried forward]). ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation; SE = standard error of the mean.

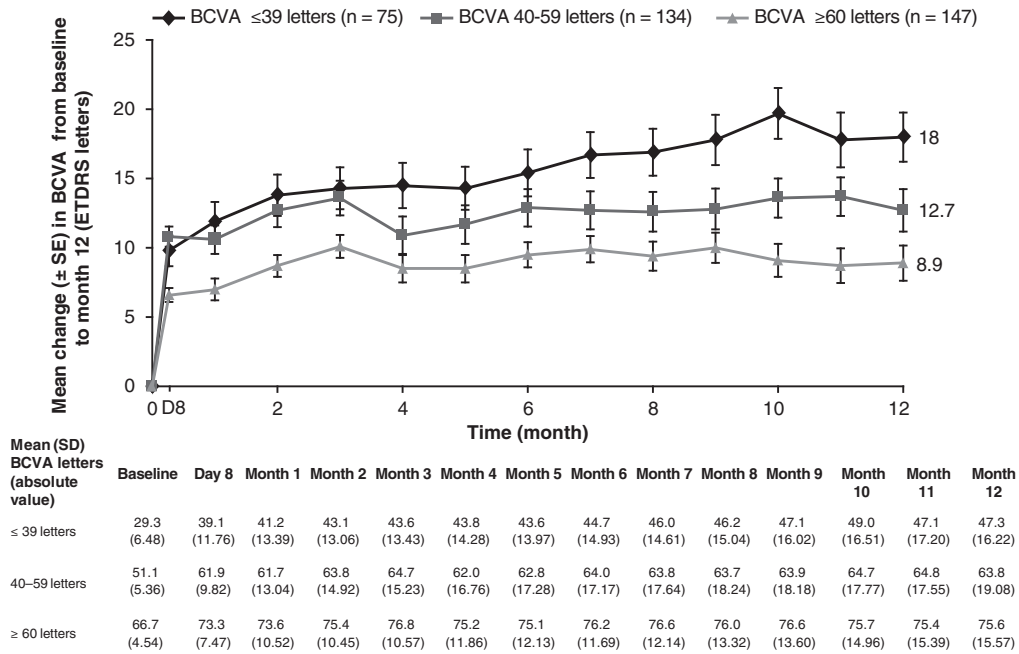


Figure 4. Graph showing mean change in best-corrected visual acuity (BCVA) from baseline to month 12 by baseline BCVA (full analysis set [last observation carried forward]). ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation; SE = standard error of the mean.

hyphema, increased IOP, and vitreous hemorrhage (all severe and reported in the same patient), and myopia (moderate severity and reported in 1 patient). No action was taken because of hyphema or myopia; paracentesis was performed once for increased IOP, and concomitant treatment was given for increased IOP and vitreous hemorrhage.

Nonocular SAEs were reported in 29 patients (8.1%; Table 3, available at www.aaojournal.org). Anxiety, lower respiratory tract infection, and pneumonia were reported in 2 patients (0.6%) each. All other nonocular SAEs were reported in 1 patient (0.3%) each. There was 1 case each of severe cardiac failure (resulting in hospitalization and concomitant medication

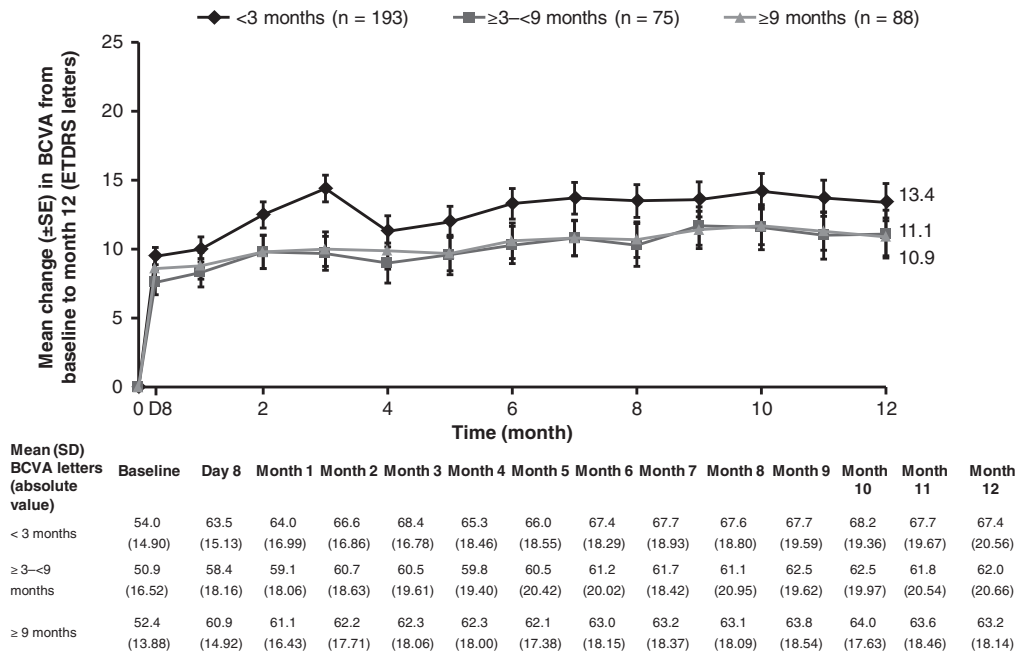


Figure 5. Graph showing mean change in best-corrected visual acuity (BCVA) from baseline to month 12 by duration of central retinal vein occlusion at baseline (full analysis set [last observation carried forward]). ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation; SE = standard error of the mean.

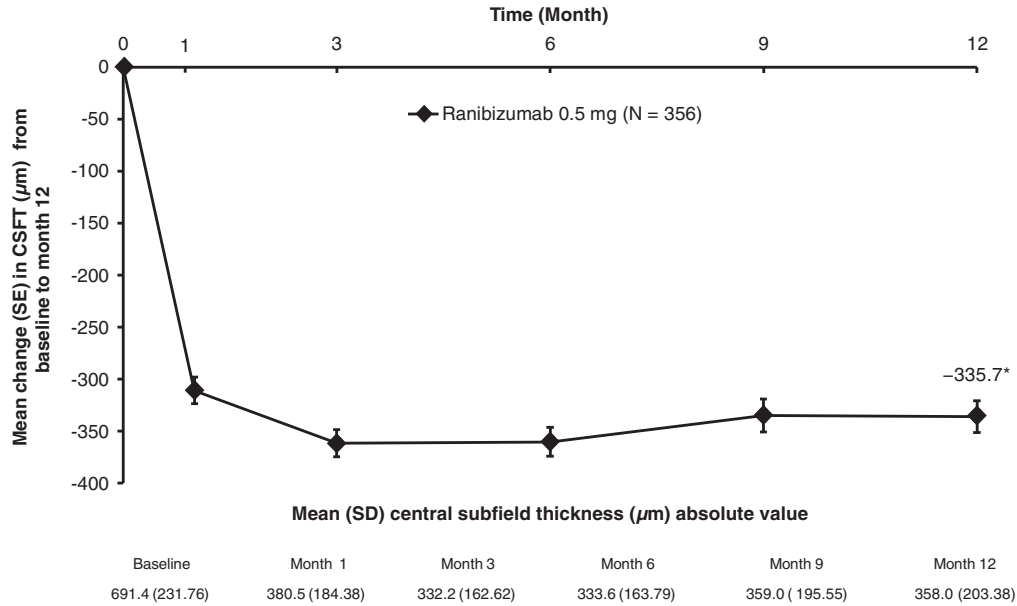


Figure 6. Graph showing mean change in central subfield thickness (CSFT) from baseline to month 12 (full analysis set [last observation carried forward]). * $P < 0.0001$ at month 12 versus baseline, assessed by central reading center. Average CSFT in a healthy individual is 212 µm.³¹ SD = standard deviation; SE = standard error.

administration) and severe cerebrovascular accident (resulting in study drug discontinuation, hospitalization, and concomitant medication administration); these 2 nonocular SAEs were suspected by the investigator to be related to the study treatment. Two patients died during the study: 1 of an unknown cause and the other of causes secondary to gangrene of the foot (Table 3, available at www.aajournal.org). Both the deaths were considered by the investigator to be not related to either the study treatment or ocular injection.

Adverse Events up to Month 12. Ocular AEs in the study eye were reported in 164 patients (45.9%; Table 4). Increased IOP (28 patients [7.8%]) and eye pain (19 patients [5.3%]) were the most commonly reported ocular AEs (Table 4). Nonocular AEs were reported in 190 patients (53.2%), of which nasopharyngitis was

most common (33 patients [9.2%; Table 4]). Overall, most (>90%) of all reported ocular and nonocular AEs were mild or moderate.

Overall, ocular AEs reported in 93 patients (26.1%) and nonocular AEs reported in 14 patients (3.9%) were suspected to be related to the study treatment, ocular injections, or both (Table 5, available at www.aajournal.org). Increased IOP (25 patients [7.0%]) and eye pain (patients 17 [4.8%]) were the most commonly reported ocular AEs suspected to be related to the study treatment, ocular injection, or both. Headache (7 patients [2.0%]) was the most commonly reported nonocular AE suspected to be related to the study treatment, ocular injection, or both.

Ocular and nonocular AEs leading to study treatment discontinuation are shown in Table 6 (available at www.aajournal.org). Five ocular AEs reported in 2 patients (0.6%) resulted in study treatment discontinuation; none were suspected by the investigator to be related to the study treatment, ocular injection, or both. Eight nonocular AEs reported in 8 patients (2.2%) resulted in study treatment discontinuation; of these AEs, 2 (the SAE of cerebrovascular accident mentioned above and transient ischemic attack) were suspected by the investigator to be related to the study treatment, ocular injection, or both.

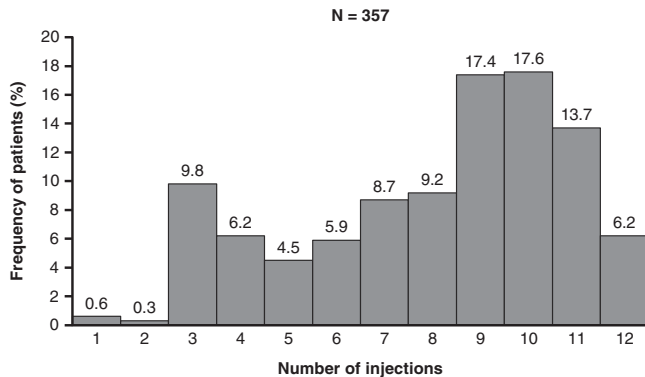


Figure 7. Bar graph showing ranibizumab treatment exposure during the study (safety set, comprising all patients who had 1 or more safety assessments after baseline and received 1 or more administrations of study treatment). The total number of injections per patient was calculated and the per-patient values are summarized. Injections at month 12 are not included.

Discussion

The CRYSTAL study evaluated an individualized dosing regimen of ranibizumab 0.5 mg driven by VA stabilization criteria in patients with visual impairment resulting from macular edema secondary to CRVO. This study showed that treatment of CRVO with ranibizumab according to the 2011 EU SmPC leads to VA gains versus baseline at all time points from day 8 (the first examination after ranibizumab 0.5-mg injection at baseline) to month 12. At month 12, approximately half of the patients attained a BCVA of 73

Table 4. Ocular (Study Eye) and Nonocular Adverse Events Regardless of Study Drug Relationship Reported in 2% or More of Patients (Safety Set*)

Preferred Term	Ranibizumab 0.5 mg (n = 357)
Ocular AEs, total	164 (45.9)
Intraocular pressure increased	28 (7.8)
Eye pain	19 (5.3)
Ocular hypertension	18 (5.0)
Macular edema	15 (4.2)
Conjunctival hemorrhage	14 (3.9)
Vitreous floaters	14 (3.9)
Dry eye	11 (3.1)
Macular fibrosis	11 (3.1)
Visual acuity reduced	12 (3.4)
Cataract	9 (2.5)
Vision blurred	11 (3.1)
Injection site pain	10 (2.8)
Vitreous detachment	7 (2.0)
Ocular discomfort	8 (2.2)
Blepharitis	8 (2.2)
Nonocular AEs, total	190 (53.2)
Nasopharyngitis	33 (9.2)
Influenza	8 (2.2)
Back pain	8 (2.2)
Headache	15 (4.2)
Hypertension	29 (8.1)
Dizziness	7 (2.0)
Diarrhea	7 (2.0)
Lower respiratory tract infection	7 (2.0)

AE = adverse event.

Data are no. (%). The values in bold are the total number (%) of ocular and nonocular AEs reported during the study. Preferred terms are sorted in descending frequency. A patient with multiple occurrences of an AE under 1 treatment is counted only once in the AE category for that treatment. A patient with multiple AEs within the primary system organ class (eye disorders) is counted only once in the total row. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

*Comprised all patients who had 1 or more safety assessments after baseline and received 1 or more administrations of study treatment.

letters or more (Snellen equivalent, 20/40), and there was a statistically significant reduction in mean CSFT from baseline.

The numerical difference in mean BCVA gain at month 12 between the CRYSTAL and CRUISE studies (CRYSTAL, 12.3 letters vs. CRUISE, 13.9 letters¹⁰; Fig 8, available at www.aaojournal.org) could be related to differences in baseline characteristics. The demographics (e.g., male-to-female ratio) and baseline characteristics of patients included in the CRYSTAL study are more representative of those with CRVO in the general population.^{15,16} In the CRYSTAL study, patients had a higher mean BCVA score than in CRUISE (53.0 vs. 48.1 letters). Patients in the CRYSTAL study also had a longer prior duration of CRVO compared with patients in the CRUISE study (8.9 vs. 3.3 months in the ranibizumab 0.5-mg arm). Both baseline BCVA and timely treatment initiation were shown to be important predictors of VA gain at later time points in ranibizumab studies in the context of retinal vein occlusion and other indications.^{9,17–24} Consistent with these

observations, the exploratory subgroup analysis in the CRYSTAL study showed that the BCVA gain with ranibizumab 0.5 mg was higher in patients with a lower baseline BCVA score compared with those with a higher baseline BCVA score. It was also higher in patients with a shorter duration of CRVO at baseline than those with a longer duration (although the mean gains with ranibizumab 0.5 mg were still >10 letters in patients with a CRVO duration of ≥ 9 months), stressing the need for early treatment initiation. The effect of delayed treatment initiation also was observed previously in the CRUISE study among patients initially randomized to sham who received ranibizumab 0.5 mg after 6 months. In these patients, although overall improvement in BCVA was observed at month 12, the gain was significantly lower than that observed in patients receiving ranibizumab throughout the study.¹⁰ A VA loss of 15 letters or more at month 12 was reported in a higher percentage (5.9%) of patients in the CRYSTAL study than in the CRUISE study (2.3%),¹⁰ possibly related to the differences in the patient population. A VA loss of 15 letters or more was reported in a similar percentage (5.3%) of patients receiving aflibercept at week 52 in the COPERNICUS study, which included patients with retinal nonperfusion at baseline.²⁵

Moreover, in the CRYSTAL study, at least in some patients, withdrawal of initial monthly treatments and switch to an individualized dosing regimen driven by VA stabilization criteria may have occurred too early, because the stability and retreatment criteria were based on VA loss as a consequence of disease activity. Retreatments could not be applied when CSFT remained abnormal or increased but VA was still unchanged (as recommended in the 2011 EU SmPC).¹² The numerical difference in BCVA gain, in addition to the lower CSFT response observed in the CRYSTAL study compared with the CRUISE study (in which both VA and OCT were considered as retreatment criteria),^{9,10} highlighted the need to make retreatment decisions on the basis of OCT findings and VA changes. The ranibizumab EU SmPC, modified in 2014,²⁶ recommends anatomic parameters as well as VA stabilization to guide treatment decisions by physicians.

Overall, the efficacy results from the CRYSTAL study add to the existing data from other ranibizumab studies in patients with macular edema secondary to CRVO. The HORIZON-RVO¹¹ and bRanch rETinal vein occlusion or central retinal vein occlusion-retinal vein occlusion (RETAIN-RVO)²⁷ (an open-label extension study that included patients who completed HORIZON-RVO [cohort II]¹¹) studies showed that VA gains were sustained up to 48 months with ranibizumab 0.5-mg PRN dosing. The SHORE study,²⁸ which assessed monthly versus PRN dosing of ranibizumab 0.5 mg, showed similar BCVA gains with 2 dosing regimens at month 15 in patients with macular edema secondary to CRVO. The COMRADE-C study, the first head-to-head study that compared the efficacy and safety of ranibizumab PRN versus dexamethasone implant, showed the superior efficacy of ranibizumab compared with dexamethasone in patients with CRVO, and the treatment schedule in COMRADE-C was similar to that of the CRYSTAL study. The positive results from all of these

studies validate the benefits of flexible ranibizumab 0.5-mg therapy in patients with CRVO.

The mean number of injections during the 12-month period in the CRYSTAL study (8.1; 3 initial mandatory injections until stable VA was achieved and sustained over 3 consecutive monthly assessments) was similar to the mean number of injections during the 12-month period in the CRUISE study (7.9; 6 initial mandatory injections). The mean number of injections decreased with continued ranibizumab treatment in other studies: 4.7 during an average of 18.2 months of follow-up in the HORIZON study and 4.1 and 2.5 in the first and second year, respectively, of the RETAIN study.²⁷ However, it should be noted that in the RETAIN study, 56% of patients still required an average of 6 injections during the last year of follow-up, and slightly more than half of the patients showed VA loss, suggesting a guarded prognosis in these patients; patients without edema resolution in general were older and had hypertension and possibly retinal ischemia that could have caused a positive feedback loop promoting chronicity resulting from high levels of VEGF.²⁷ In the CRYSTAL study, during the 12-month period, the mean number of ranibizumab injections was similar in patients with or without macular ischemia, although the study was not powered to detect a difference.

Similar sustained efficacy with an individualized, as-needed regimen also has been reported with other anti-VEGF agents. In the COPERNICUS and GALILEO studies, VA gains achieved with 6 monthly aflibercept injections largely were maintained up to 1 year with PRN injections.^{25,29} However, in the COPERNICUS study, the visual and anatomic gains decreased during the second year with PRN dosing and during quarterly evaluations, suggesting that more frequent monitoring may be necessary to prevent disease recurrence.³⁰ Because monthly monitoring was used in the first 12 months of the CRYSTAL study, an important observation from this study may be that regular monitoring plays an essential role in achieving successful outcomes from individualized dosing. The next 12 months of the CRYSTAL study will assess the feasibility of bimonthly monitoring in patients with stable VA.

The visual prognosis is reported generally to be poorer in CRVO eyes with macular ischemia than in nonischemic eyes.^{2,31} In the exploratory analysis in the CRYSTAL study, the BCVA gains with ranibizumab 0.5 mg were similar in patients with CRC-assessed macular ischemia and those without. Similarly, in the COPERNICUS and GALILEO studies, efficacy with PRN aflibercept was comparable in patients with or without retinal non-perfusion.^{25,29} In addition, a 6-month interventional case series with bevacizumab showed that mean VA gains at 6 months were similar in patients with or without macular ischemia.³² These results suggest anti-VEGF agents to be effective in CRVO patients with retinal ischemia. In the CRYSTAL study, the difference in the proportion of patients at baseline with CRC-assessed macular ischemia or investigator-assessed ischemic perfusion type could be related to the individual assessment method used, and this needs to be investigated in future studies. Visual outcomes

were similar between patients with or without macular ischemia at baseline. Further information on the impact of the severity (rather than just the presence or absence) of ischemia on VA would be valuable; indeed, these analyses have been performed and will form the basis of a separate publication.

Safety results in the CRYSTAL study were consistent with the well-established safety profile of ranibizumab in patients with CRVO.^{9–11,27} No new or unexpected AEs were reported during the study. Anti-VEGF therapy, when compared with lack of treatment, was reported to reduce the odds of progression of iris neovascularization and associated neovascular glaucoma, 2 recognized complications of untreated CRVO.³ The few AEs of iris neovascularization or neovascular glaucoma reported in this and other anti-VEGF studies^{10,29} suggest that these AEs, although rare, can occur despite anti-VEGF therapy.

The study had several limitations. It was open label and lacked a control group. Leaving the selection of the study eye to the discretion of the investigator could result in a potential bias toward selection of the eye most likely to benefit from treatment. However, the low percentage of patients (0.6%) who received bilateral treatment at baseline in this study renders any such bias influencing the overall study outcomes unlikely. The number of letters signifying loss of VA activity was not defined, but based on the investigator's judgment. This was based on the recommendations provided in the EU SmPC at that time, which were to be tested here.¹² Also, the investigators were not masked to the CSFT findings, although per protocol, retreatment could not be based on abnormal CSFT findings if VA was stable. Finally, the analysis of ranibizumab efficacy in the subgroups based on baseline ischemia, CRVO duration, or BCVA score was exploratory, and the analysis based on baseline ischemia focused only on macular ischemia, regardless of baseline ischemia severity.

In conclusion, the individualized dosing regimen of ranibizumab 0.5 mg driven by VA stabilization criteria (3 mandatory injections followed by dosing as needed) for 12 months resulted in statistically significant BCVA gains in patients with macular edema secondary to CRVO. The BCVA gains were observed in a broad population of patients, including those with macular ischemia at baseline. Overall, ranibizumab 0.5 mg up to 12 months was generally well tolerated in this patient population. No new or unexpected ocular or nonocular safety events were identified.

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*Members of the CRYSTAL Study Group 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; **CRC** = central reading center; **CRVO** = central retinal vein occlusion; **CSFT** = central subfield thickness; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **EU SmPC** = 2011 Lucentis European Union Summary of Product Characteristics; **FAS** = full analysis set; **IOP** = intraocular pressure; **OCT** = optical coherence tomography; **PRN** = pro re nata; **SAE** = serious adverse event; **SD** = standard deviation; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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