Intravitreal Aflibercept Injection for Macular Edema Secondary to Central Retinal Vein Occlusion: 1-Year Results From the Phase 3 COPERNICUS Study

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• PURPOSE: **To evaluate intravitreal aflibercept injections (IAI; also called VEGF Trap-Eye) for patients with macular edema secondary to central retinal vein occlusion (CRVO).**

• DESIGN: **Randomized controlled trial.**

• METHODS: **This multicenter study randomized 189 patients (1 eye/patient) with macular edema secondary to CRVO to receive 6 monthly injections of either 2 mg intravitreal aflibercept (IAI 2Q4) (n = 115) or sham (n = 74). From week 24 to week 52, all patients received 2 mg intravitreal aflibercept as needed (IAI 2Q4 + PRN and sham + IAI PRN) according to retreatment criteria. The primary endpoint was the proportion of patients who gained ≥15 ETDRS letters from baseline at week 24. Additional endpoints included visual, anatomic, and quality-of-life NEI VFQ-25 outcomes at weeks 24 and 52.**

• RESULTS: **At week 24, 56.1% of IAI 2Q4 patients gained ≥15 letters from baseline compared with 12.3% of sham patients ($P < .001$). At week 52, 55.3% of IAI 2Q4 + PRN patients gained ≥15 letters compared with 30.1% of sham + IAI PRN patients ($P < .001$). At week 52, IAI 2Q4 + PRN patients gained a mean of 16.2 letters of vision vs 3.8 letters for sham + IAI PRN ($P < .001$). The most common adverse events for both groups were conjunctival hemorrhage, eye pain, reduced visual acuity, and increased intraocular pressure.**

• CONCLUSIONS: **Monthly injections of 2 mg intravitreal aflibercept for patients with macular edema secondary to CRVO resulted in a statistically significant improvement in visual acuity at week 24, which was largely maintained through week 52 with intravitreal aflibercept PRN dosing. Intravitreal aflibercept injection was generally well tolerated. (Am J Ophthalmol 2013;155: 429–437. © 2013 by Elsevier Inc. All rights reserved.)**

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THE MANAGEMENT OF EYES WITH VISION LOSS FROM macular edema secondary to central retinal venous occlusion (CRVO) has been entirely transformed in recent years. Both anti–vascular endothelial growth factor (VEGF) and steroidal pharmacotherapies have been developed, tested, and put into clinical practice, targeting the vascular permeability and leakage that frequently develops following blockage of the central retinal vein.[1–7] Intravitreal aflibercept injection, also known as VEGF Trap-Eye (Regeneron Pharmaceuticals Inc, Tarrytown, New York, USA) is a 115-kDa decoy receptor fusion protein, composed of the second domain of human VEGF receptor 1 and the third domain of VEGF receptor 2 fused to the Fc domain of human IgG1.[8,9] The binding affinity of aflibercept for VEGF is substantially greater than that of either bevacizumab or ranibizumab,[10] and mathematical modeling has predicted its potential for a longer duration of action in the eye.[11]

The current phase 3 randomized, sham-controlled clinical trial (COPERNICUS) recently reported that aflibercept, given as a monthly intravitreal injection in eyes with macular edema attributable to CRVO, improved visual acuity (VA) and central retinal thickness, was associated with no progression to neovascularization, and had a low rate of ocular adverse events at 24 weeks.[6] Beginning at week 24, patients in both groups were eligible to receive 2 mg of intravitreal aflibercept injection (IAI) as needed (pro re nata; PRN). Therefore the patients in the sham + IAI PRN group received a different dosing regimen from weeks 24 onward compared with the start of treatment in those patients who had received intravitreal aflibercept initially (every 4 weeks). This report follows these patients to 1 year.

METHODS

THE COPERNICUS STUDY IS AN ONGOING 2-YEAR, PHASE 3, prospective, randomized, double-masked trial. This multicenter study was conducted across 70 sites in the United

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States, Canada, Colombia, India, and Israel. The study protocol of the COPERNICUS trial was approved by the institutional review board or ethics committee at each participating clinical center before the start of the study. This trial was registered with ClinicalTrials.gov (identifier #NCT00943072). All patients signed a written consent form before initiation of the study-specific procedures. This study was conducted in compliance with regulations of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

• **TREATMENTS:** Patients were randomly allocated using a 3:2 ratio to receive intravitreal aflibercept injections, 2 mg (IAI 2Q4), or sham injections, every 4 weeks for 24 weeks, for a total of 6 monthly treatments (Supplemental Figure 1, available at AJO.com).[6] Between weeks 24 and 52, patients in both treatment groups were evaluated monthly and were injected with intravitreal aflibercept as needed if they met protocol-specified retreatment criteria. They received a sham injection if retreatment was not indicated. After the first year of masked dosing, patients are continuing in a 1-year extension phase with PRN dosing. Data for this 52-week report were collected between July 2009 and April 2011.

Randomization was stratified by geographic region (North America [Canada and the United States] vs the rest of the world [Colombia, India, and Israel]) and by using a baseline best-corrected visual acuity (BCVA) score (>20/200, ie, 35 to 73 Early Treatment Diabetic Retinopathy Study [ETDRS] letters; and ≤20/200 ie, 24 to 34 ETDRS letters). Only 1 eye per patient was included in the randomization. All patients were eligible to receive panretinal photocoagulation at any time during the study if they progressed to neovascularization of the anterior or posterior segment.

• **PARTICIPANTS:** The study enrolled patients aged ≥18 years with center-involved macular edema secondary to CRVO diagnosed within 9 months of study initiation. All study eyes had mean central subfield retinal thickness ≥250 μm using optical coherence tomography (OCT) from Zeiss Stratus OCT (Version 4.0 or later; Carl Zeiss Meditec, Jena, Germany), and protocol refracted ETDRS[12] BCVA of 20/40 to 20/320 (73 to 24 letters).

Key exclusion criteria for the study eye included: any previous treatment with antiangiogenic drugs; prior panretinal or macular laser photocoagulation; and any ocular disorders that could confound interpretation of study results. Exclusion criteria with respect to both eyes included: previous use of intraocular corticosteroids or use of periocular corticosteroids within the 3 months prior to day 1; iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; history or presence of age-related macular degeneration (AMD; dry or wet form) that significantly affected central vision; diabetic macular edema or diabetic retinopathy, defined as eyes of diabetic subjects with more than 1 microaneurysm outside the area of the vein occlusion; and infectious blepharitis, keratitis, scleritis, or conjunctivitis.

• **ENDPOINTS AND ASSESSMENTS:** The primary efficacy endpoint was the proportion of eyes with a gain of ≥15 ETDRS letters in BCVA from baseline to week 24. Secondary efficacy endpoints (all assessed at week 24) were: change from baseline in BCVA scores; change from baseline in central retinal thickness (CRT); proportion of patients progressing to neovascularization of anterior segment, optic disc, or elsewhere in the retina; and change from baseline in the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) in total and subscale scores (distance activities, near activities, and vision dependency). The tertiary efficacy endpoints were all of the parameters mentioned above measured at 52 weeks.

A masked physician was assigned to assess adverse events (AEs), supervise the masked assessment of efficacy, and decide on the need for retreatment during the PRN phase. Visual acuity assessors were masked as to treatment assignment.

Assessments were conducted at regularly scheduled clinic visits on day 1 and every 4 weeks from weeks 4 to 52. BCVA was evaluated by certified examiners using the ETDRS refraction protocol. Retinal characteristics from OCT scans were assessed at a masked independent central reading center (Duke Reading Center, Durham, North Carolina, USA). Central retinal thickness was defined as the thickness of the center subfield (the area of the retina using a 1-mm diameter around the center of the macula). Fundus photography and fluorescein angiography were used to evaluate the anatomy of the retinal vasculature. Angiographic images were reviewed by masked graders at an independent reading center (Digital Angiographic Reading Center, New York, New York, USA). Vision-related quality of life was assessed using the NEI VFQ-25, which was administered by masked site personnel prior to intravitreal injection.

Eyes were evaluated, starting at week 24, for retreatment and received an injection of intravitreal aflibercept if any of the following retreatment criteria were met: a >50 μm increase in CRT on OCT compared with lowest previous measurement; new or persistent cystic retinal changes or subretinal fluid on OCT, or persistent diffuse edema ≥250 μm in the central subfield on OCT; a loss of ≥5 letters from the best prior measurement in conjunction with any increase in CRT on OCT; or an increase of VA between the current and most recent visit of ≥5 letters. If none of these retreatment criteria were met, patients received a sham injection.

Safety was monitored with the recording of ocular and nonocular AEs and laboratory measures.

• **STATISTICAL ANALYSES:** The full analysis set (FAS), on which the primary efficacy analyses were conducted, included all randomized patients who received any study medication, had a baseline efficacy assessment, and had at least 1 postbaseline efficacy assessment. In the primary endpoint analysis, patients who discontinued prematurely (prior to week 24) and had fewer than 5 injections were evaluated as nonresponders. The last-observation-carried-forward method was used to impute missing values. The proportions of patients who gained 15 letters were compared with a 2-sided Cochran-Mantel-Haenszel test and randomization was stratified by region and baseline BCVA. Secondary endpoint analyses were conducted sequentially according to the order in which the variables were predefined to preserve an alpha of 0.05. Proportions were analyzed using the Cochran-Mantel-Haenszel test. Time to first injection was analyzed using Kaplan-Meier methodology. The Cox proportional hazards model was used to quantify the differences in the rate of time to first injection between treatment groups.

Continuous variables were analyzed with an analysis of covariance main effects model with treatment group, region, and baseline BCVA as fixed factors, and the respective baseline variable as a covariate.

Ocular serious adverse events (SAEs) included any AE that: caused a decrease in VA of >30 letters (compared with the most recent assessment) or a decrease in VA to the level of light perception or worse that lasted >1 hour; required medical or surgical intervention to prevent permanent loss of sight; or was associated with severe intraocular inflammation.

The sample size calculation was based on the assumptions that the dropout rate would be 9% for each arm and the difference in the proportion of eyes gaining at least 15 letters of vision would be 25% (ie, 15% in the sham group[13] and 40% in the intravitreal aflibercept 2Q4 group.[14] Therefore, a total sample size of 165 eyes was required to detect a difference in the primary analysis with 90% power at a significance level of 5% using a 2-sided Fisher exact test or a Cochran-Mantel-Haenszel test.

RESULTS

• **PATIENT DISPOSITION:** A total of 189 patients were randomized to intravitreal aflibercept 2Q4 + PRN (n = 115) and sham + IAI PRN (n = 74). With the exception of 1 patient in the IAI 2Q4 + PRN group, all randomized patients received study drugs. The majority of patients (57/74, 77.0% sham + IAI PRN and 107/115, 93.0% IAI 2Q4 + PRN) completed the first 52 weeks of the study (Supplemental Figure 2, available at AJO.com). The primary reasons for premature discontinuation from the study before week 52 were withdrawal of consent (5/115, 4.3%) for the IAI 2Q4 + PRN group and adverse event (4/74, 5.4%) and treatment failure (4/74, 5.4%) in the sham + IAI PRN group. Treatment failures and AEs were the main reasons for the larger proportion of discontinuations in the sham + IAI PRN group compared with the IAI 2Q4 + PRN patient group, which had no discontinuations attributable to AEs or treatment failures during the first 52 weeks of the study. Adverse events resulting in the study discontinuation in the sham + IAI PRN group included vitreous and retinal hemorrhages, reduced visual acuity, and iris neovascularization, which all occurred before week 24 and were consistent with the complications of CRVO.

• **DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS:** Most patients were male (107/187; 57%), white (147/187; 78.6%), and originating from North America (159/187; 85%) (Table 1). The majority of patients (127/187; 67.9%) had fewer than 10 disc areas of nonperfusion on reading center evaluation.

• **EFFICACY:** At week 52, the proportion of patients who gained at least 15 letters in BCVA was 55.3% in the IAI 2Q4 + PRN group vs 30.1% in the sham + IAI PRN group (Figure 1), demonstrating that IAI 2Q4 + PRN continued to be superior at week 52. For comparison, at week 24, 56.1% of patients in the IAI 2Q4 group had gained ≥15 letters from baseline compared with 12.3% of patients in the sham group ($P < .001$). The majority of patients in both groups gained ≥0 letters of vision (92.1% of patients in the IAI 2Q4 + PRN group compared with 68.5% of those in the sham + IAI PRN group at week 52) (Table 2).

At week 52, patients in the IAI 2Q4 + PRN group showed a mean change from baseline BCVA of 16.2 ETDRS letters (Figure 2). For comparison, at week 24, the mean change from baseline BCVA was 17.3 ETDRS letters in the IAI 2Q4 + PRN group and −4.0 ETDRS letters in the sham group ($P < .001$). When the sham group was later eligible to receive intravitreal aflibercept (following an as-needed dosing regimen), mean change from baseline in BCVA improved in this group from −4.0 letters at week 24 to +3.8 letters at week 52, a gain of 7.8 letters. The waterfall analysis (Supplemental Figure 3, Top and Bottom panels) (Supplemental Material available at AJO.com) of individual patient responses found that only 7.9% of patients who were originally randomized to the IAI 2Q4 treatment group experienced a loss of vision at week 52 (vs baseline) compared with 31.5% of patients in the sham + IAI PRN group.

At week 52, a gain of ≥15 letters was noted in 60.7% vs 22.2% of patients with a baseline BCVA ≤20/200 in the IAI 2Q4 + PRN group vs the sham + IAI PRN group and in 53.5% vs 32.7% of patients, respectively, with a baseline BCVA >20/200. For patients with a baseline BCVA ≤20/200, the mean change from baseline at week 52 in BCVA letter score was +19.9 vs +5.1 letters for IAI 2Q4 + PRN compared with sham + IAI PRN. Patients who had a baseline BCVA of >20/200 had improvements in BCVA of +14.9 compared with +3.5 letters.

TABLE 1. Demographics and Baseline Characteristics of Patients With Macular Edema Secondary to Central Retinal Vein Occlusion

	IAI 2Q4 + PRN (n = 114)[d]	Sham + IAI PRN (n = 73)	Total (n = 187)[e]
Age (y), mean (SD)	65.5 (13.57)	67.5 (14.29)	66.3 (13.85)
Sex, n (%)			
Female	45 (39)	35 (48)	80 (43)
Male	69 (61)	38 (52)	107 (57)
Race, n (%)			
White	88 (77.2)	59 (80.8)	147 (78.6)
Black	5 (4.4)	5 (6.8)	10 (5.3)
Asian	7 (6.1)	2 (2.7)	9 (4.8)
Other[a]	14 (12.3)	7 (9.6)	21 (11.2)
Geographic region, n (%)			
North America	95 (83.3)	64 (87.7)	159 (85.0)
Rest of world	19 (16.7)	9 (12.3)	28 (15.0)
Visual acuity (ETDRS)			
Mean (SD)	50.7 (13.90)	48.9 (14.42)	50.0 (14.09)
BCVA >20/200 (letters read ≥35)	86 (75.4)	55 (75.3)	141 (75.4)
BCVA ≤20/200 (letters read ≤34)	28 (24.6)	18 (24.7)	46 (24.6)
Retinal perfusion status, n (%)			
Perfused[b]	77 (67.5)	50 (68.5)	127 (67.9)
Nonperfused	17 (14.9)	12 (16.4)	29 (15.5)
Indeterminate	20 (17.5)	11 (15.1)	31 (16.6)
Retinal thickness (μm)			
Mean (SD)	661.7 (237.37)	672.4 (245.33)	665.8 (239.82)
IOP (mm Hg), mean (SD)	15.1 (3.26)	15.0 (2.81)	15.1 (3.08)
Time since CRVO diagnosis (mo)			
Mean (SD)	2.73 (3.09)	1.88 (2.19)	2.40 (2.796)
≤2 months	64 (56.1)	52 (71.2)	116 (62.0)
>2 months	49 (43.0)	21 (28.8)	70 (37.4)
NEI VFQ-25 total score,[c] *mean (SD)*	77.39 (16.176)	77.38 (16.602)	77.39 (16.299)
NEI VFQ-25 near activities score,[c] *mean (SD)*	69.96 (21.939)	70.72 (20.222)	70.25 (21.234)
NEI VFQ-25 distance activities score, mean (SD)	75.99 (21.255)	78.08 (21.258)	76.80 (21.224)
Vision dependency score, mean (SD)	83.26 (25.511)	82.76 (27.405)	83.07 (26.195)

2Q4 = 2 mg once every 4 weeks; BCVA = best-corrected visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection; IOP = intraocular pressure; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire – 25; PRN = as needed; SD = standard deviation.

[a]Included not reported and multiple races.

[b]Less than 10 disc areas of nonperfusion.

[c]Baseline total and near activities subscale scores changed slightly from weeks 24 to 52 as a result of multiple-choice options in the questionnaires changing from 4 possible responses at week 24 to 5 possible responses at week 52.

[d]113 for the time since CRVO diagnosis.

[e]186 for the time since CRVO diagnosis.

Full analysis set.

In eyes with over 10 disc areas of posterior nonperfusion (that seen on 7 standard field fluorescein angiogram) at baseline, the proportion of eyes gaining ≥15 letters at week 24 was 51.4% vs 4.3% for IAI 2Q4 + PRN vs sham + IAI PRN treatment and 58.4% vs 16.0% in eyes with less than 10 disc areas of posterior nonperfusion at baseline, respectively. At 52 weeks, these proportions were 48.6% vs 30.4% for IAI 2Q4 + PRN vs sham + IAI PRN treatment in eyes with posterior nonperfusion, and 58.4% vs 30.0% in eyes without posterior nonperfusion eyes, respectively.

If the diagnosis was within 2 months of treatment, the proportions of eyes gaining ≥15 letters were 64.1% vs 34.6% for IAI 2Q4 + PRN vs sham + IAI PRN treatment at 52 weeks (difference of 29.4%), and 42.9% vs 19.0% (difference of 23.8%) if the time since diagnosis was greater than 2 months.

The rapid reduction in CRT observed in the IAI 2Q4 + PRN group through week 24 was largely maintained through week 52 (−457.2 μm and −413.0 μm, respectively) (Figure 3). At week 52, mean CRT reductions

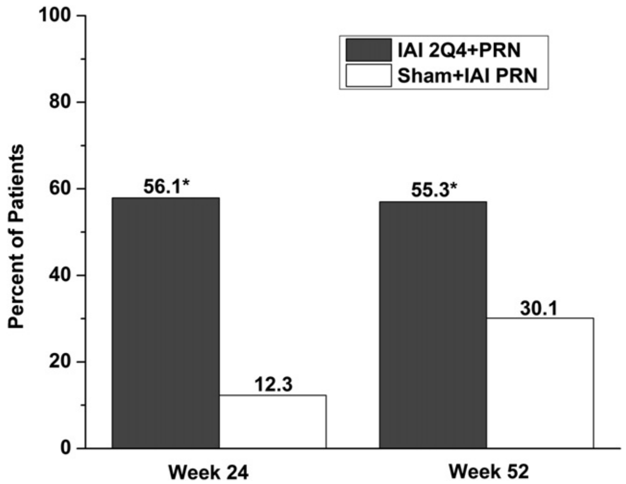

FIGURE 1. Proportion of patients with best-corrected visual acuity improvement ≥15 letters at weeks 24 and 52 following intravitreal aflibercept and/or sham injections for the treatment of macular edema secondary to central retinal vein occlusion. *$P < .001$. Missing data were imputed using the last-observation-carried-forward method. 2Q4 = 2 mg every 4 weeks; IAI = intravitreal aflibercept injection; PRN = as needed.

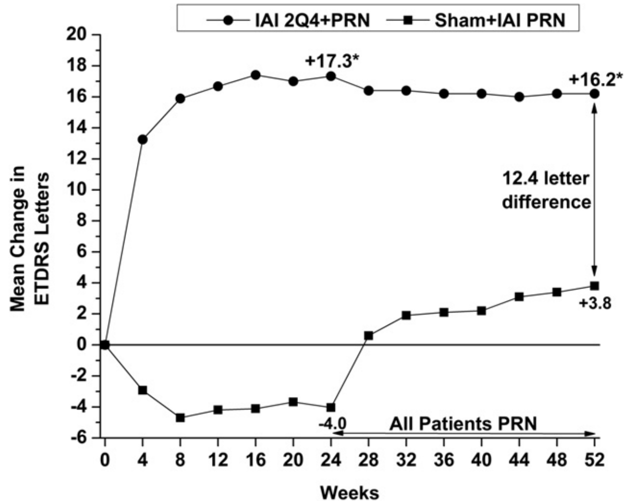

FIGURE 2. Mean change from baseline in best-corrected visual acuity over 52 weeks after intravitreal aflibercept and/or sham injections for the treatment of macular edema secondary to central retinal vein occlusion. *$P < .001$. Missing data were imputed using the last-observation-carried-forward method. 2Q4 = 2 mg every 4 weeks; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection; PRN = as needed.

TABLE 2. Proportions of Patients With Vision Gains and Losses at Weeks 24 and 52 Following Sham and/or Intravitreal Aflibercept Injections for the Treatment of Macular Edema Secondary to Central Retinal Vein Occlusion

	Week 24		Week 52	
	IAI 2Q4 + PRN (n = 114)	Sham + IAI PRN (n = 73)	IAI 2Q4 + PRN (n = 114)	Sham + IAI PRN (n = 73)
Letter gain, n (%)				
≥15 letters[a]	64 (56.1)	9 (12.3)	63 (55.3)	22 (30.1)
≥10 letters	87 (76.3)	16 (21.9)	88 (77.2)	34 (46.6)
≥5 letters	97 (85.1)	29 (39.7)	93 (81.6)	43 (58.9)
≥0 letters	107 (93.9)	38 (52.1)	105 (92.1)	50 (68.5)
Letter loss, n (%)				
>0 letter	7 (6.1)	35 (47.9)	9 (7.9)	23 (31.5)
≥5 letters	5 (4.4)	29 (39.7)	8 (7.0)	17 (23.3)
≥10 letters	2 (1.8)	22 (30.1)	6 (5.3)	13 (17.8)
≥15 letters	2 (1.8)	20 (27.4)	6 (5.3)	11 (15.1)

2Q4 = 2 mg once every 4 weeks; IAI = intravitreal aflibercept injection; PRN = as needed.
[a]Week 24 completers within full analysis set.
Full analysis set unless indicated otherwise.

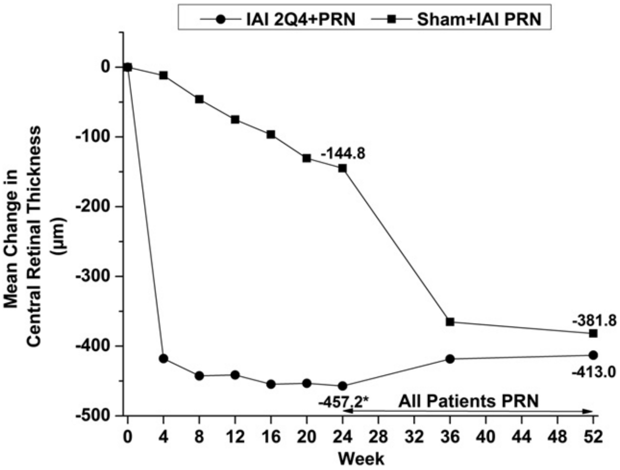

FIGURE 3. Mean change from baseline in central retinal thickness (CRT) over 52 weeks after intravitreal aflibercept and/or sham injections for the treatment of macular edema secondary to central retinal vein occlusion. CRT was measured with optical coherence tomography. A significant decrease from baseline in CRT was observed at week 24 in the IAI group compared with the sham-treated group (*$P < .001$). Missing data were imputed using the last-observation-carried-forward method. 2Q4 = 2 mg every 4 weeks; IAI = intravitreal aflibercept injection; PRN = as needed.

were similar in both treatment groups (413.0 µm for IAI 2Q4 + PRN vs 381.8 µm for sham + IAI PRN).

During the first 52 weeks, no eyes in the IAI 2Q4 + PRN group developed any neovascularization compared with 5 eyes (6.8%, all in the anterior segment) for the sham + IAI PRN group ($P = .006$ by Cochran-Mantel-Haenszel test). Panretinal photocoagulation was performed for 4 of the patients (5.5%) in the sham + IAI PRN group.

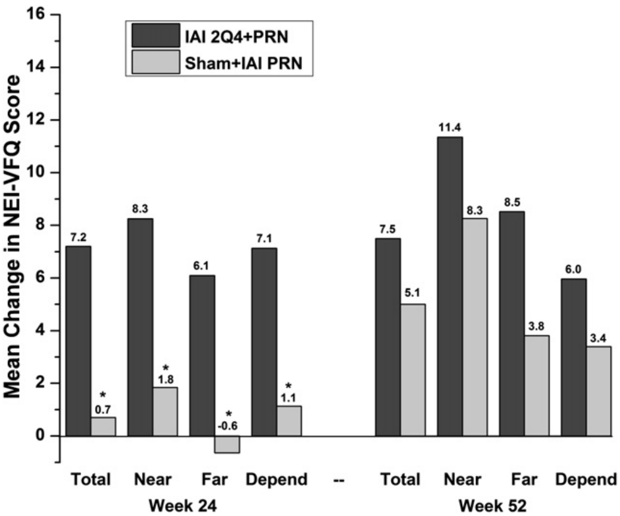

FIGURE 4. Mean change from baseline in NEI VFQ-25 scores at weeks 24 and 52 following intravitreal aflibercept and/or sham injections for the treatment of macular edema secondary to central retinal vein occlusion. Missing data were imputed using the last-observation-carried-forward method. Week 24, IAI 2Q4 + PRN n = 104, sham + IAI PRN n = 59. $^*P < .05$. P values for sham + IAI PRN vs IAI 2Q4 + PRN: Total, $P = .001$; near-activities subscores, $P = .071$; distance-activities subscores, $P = .032$; dependency subscores, $P = .083$. Week 52, IAI 2Q4 + PRN n = 109, sham + IAI PRN n = 59. P values for sham + IAI PRN vs IAI 2Q4 + PRN: Total, $P = .216$; near-activities subscores, $P = .338$; distance-activities subscores, $P = .085$; dependency subscores, $P = .415$. P values are based on least square mean changes using an analysis of covariance model. 2Q4 = 2 mg once every 4 weeks; IAI = intravitreal aflibercept injection; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire - 25; PRN = as needed.

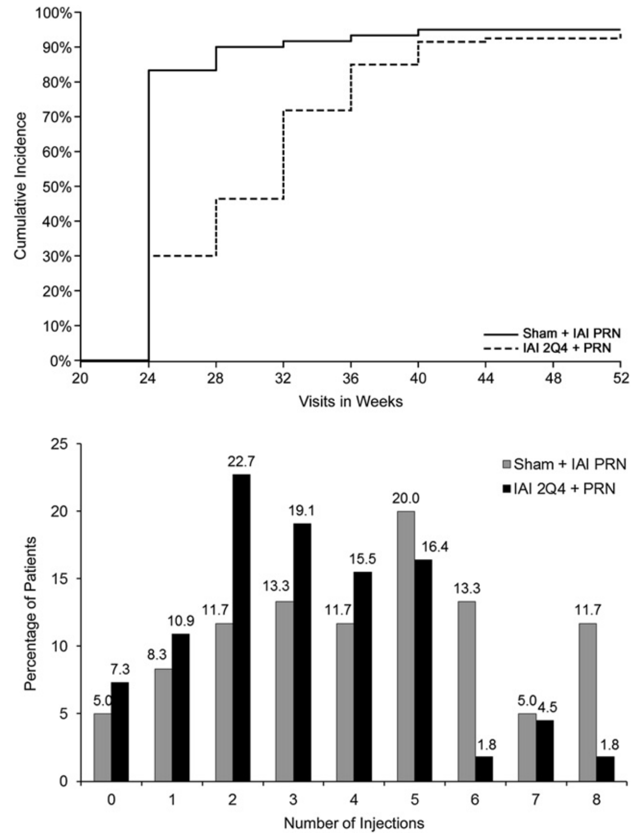

FIGURE 5. Cumulative incidence of time to first intravitreal aflibercept injection and distribution of injections in patients with macular edema secondary to central retinal vein occlusion. (Top panel) The cumulative incidence of time to first injection was compared between the treatment groups. The P value from the log-rank test was $< .01$. (Bottom panel) Exposure to study drug (excluding sham) from weeks 24 to 52 is shown for the week-24 completers within safety analysis set. 2Q4 = 2 mg once every 4 weeks; IAI = intravitreal aflibercept injection; PRN = as needed.

The between-group differences in the mean NEI VFQ-25 total and subscale scores were significant at week 24. A clinically relevant improvement in the mean NEI VFQ-25 total score was observed in both IAI 2Q4 + PRN (7.5 points) and sham + IAI PRN (5.1 points) groups at week 52 (Figure 4). A significant difference between the treatment arms was not seen at week 52 because of the crossover to intravitreal aflibercept PRN in the sham group.

• **TREATMENT EXPERIENCE:** Beginning at week 24, all patients were eligible to receive an injection of aflibercept if any of the protocol-defined retreatment criteria were met. During the PRN phase of the study, 57 of the 60 patients in the sham + IAI PRN group and 102 of the 110 patients in the IAI 2Q4 + PRN group had at least 1 injection (Figure 5, Top panel). Eighty-three percent of the sham + IAI PRN patients compared with 30% of IAI 2Q4 + PRN patients had their first injection at week 24. The median time to first injection in the PRN phase was 29 days for the sham + IAI PRN group and 68 days for the IAI 2Q4 + PRN group. The mean numbers of injections were 3.9 (SE = 0.3) and 2.7 (SE = 0.2) in the sham + IAI PRN and IAI 2Q4 + PRN groups, respectively (Figure 5, Bottom panel).

• **SAFETY:** From baseline to week 52, the proportion of patients that experienced at least 1 ocular treatment-emergent adverse event (TEAE) in the study eye was similar between treatment groups (Supplemental Table 1, available at AJO.com). The most common ocular TEAEs in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively, were reduced visual acuity (18.4% and 21.6%), conjunctival hemorrhage (16.7% and 18.9%), eye pain (15.8% and 9.5%), and increased intraocular pressure (12.3% and 13.5%).

Ocular-SAEs reported more than once in the study eye all occurred in the sham + IAI PRN group (Table 3). The 1 case of endophthalmitis in the intravitreal

TABLE 3. All Ocular Serious Adverse Events From Baseline to Weeks 24 and 52 Occurring in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion Who Were Treated With Sham and/or Intravitreal Aflibercept Injections

	Weeks 0-24[a]		Weeks 24-52[b]	
	IAI 2Q4 (n = 114)	Sham (n = 74)	IAI 2Q4 + PRN (n = 110)	Sham + IAI PRN (n = 60)
Number of patients with at least 1 ocular serious TEAE in study eye, n (%)	4 (3.5)	10 (13.5)	3 (2.7)	2 (3.3)
Eye disorders, n (%)	2 (1.8)	10 (13.5)	3 (2.7)	2 (3.3)
Vitreous hemorrhage	0	4 (5.4)	1 (0.9)	1 (1.7)
Glaucoma	0	2 (2.7)	0	1 (1.7)
Iris neovascularization	0	2 (2.7)	0	0
Retinal hemorrhage	0	2 (2.7)	0	0
Visual acuity reduced	1 (0.9)	1 (1.4)	0	0
Retinal artery occlusion	1 (0.9)	0	0	0
Retinal tear	0	1 (1.4)	0	1 (1.7)
Retinal vein occlusion	0	1 (1.4)	1 (0.9)	0
Cataract	0	0	1 (0.9)	1 (1.7)
Cystoid macular edema	0	0	1 (0.9)	0
Infections and infestations, n (%)	1 (0.9)	0	0	0
Endophthalmitis	1 (0.9)	0	0	0
Injury, poisoning and procedural complications, n (%)	1 (0.9)	0	0	0
Corneal abrasion	1 (0.9)	0	0	0

2Q4 = 2 mg once every 4 weeks; IAI = intravitreal aflibercept injection; PRN = as needed; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a]Safety analysis set.

[b]Week 24 completers within the safety analysis set.

aflibercept group was culture-positive for coagulase-negative *Staphylococcus* and was considered by the investigator to be related to the intravitreal injection. It occurred before week 24, 44 days after starting study medication, and 10 days after the last intravitreal injection. From weeks 24 to 52, only 3 patients in the IAI 2Q4 + PRN group and 2 in the sham + IAI PRN group experienced any ocular serious adverse events.

The incidence of nonocular TEAEs was similar in both treatment groups from baseline to week 52. In the sham + IAI PRN and IAI 2Q4 + PRN groups, the most commonly reported nonocular TEAEs were hypertension (9.5% vs 14.9%, respectively), nasopharyngitis (6.8% vs 7.9%, respectively), and upper respiratory infections (5.4% vs 7.9%, respectively). Nonocular SAEs occurred in a small group of patients with a similar frequency in the IAI 2Q4 and sham groups from weeks 0 to 24 (5.3% vs 8.1%, respectively) and in the IAI 2Q4 + PRN and sham + IAI PRN groups from weeks 24 to 52 (6.4% vs 8.3%, respectively) (Supplemental Table 2, available at AJO.com). The incidence of Anti-Platelet Trialists' Collaboration and arterial thromboembolic events were 2.7% in the sham group (1 acute myocardial infarction and 1 carotid artery stenosis) and 0.9% in the IAI 2Q4 + PRN group (1 myocardial infarction). There were 2 vascular deaths (2.7%) (1 attributable to acute myocardial infarction and 1 to arrhythmia), both occurring in the sham group before receiving intravitreal aflibercept at week 24.

DISCUSSION

THE COPERNICUS STUDY RESULTS FROM WEEK 24 THROUGH week 52 demonstrate that the robust elimination of retinal edema on OCT and the concomitant BCVA gains achieved after 6 monthly intravitreal aflibercept injections in the IAI 2Q4group can be largely maintained with less frequent dosing of a mean 2.7 injections. It must be noted that patients continued to be evaluated monthly during the PRN phase. Careful monitoring in clinical practice may be critical to achieve this result in a reactive PRN treatment setting. In real-world practice, clinicians may choose a "treat and extend" regimen, although this has not been formally tested in CRVO to circumvent the requirement for monthly monitoring and to stay in a proactive treatment mode. A prolonged injection interval, ie, reduced injection frequency, after an initial period of monthly dosing is consistent with the use of intravitreal aflibercept injection in neovascular AMD, where a Q8-week dosing regimen has been shown to be as efficacious as a monthly regimen for the treatment of neovascular AMD (Nguyen QD et al. IOVS 2011;52:ARVO E-Abstract 3073;

Schmidt-Erfurth U et al. IOVS 2011;52:ARVO E-Abstract 1650). Similarly, the DA VINCI study also reported significant gains in BCVA and reductions in CRT at 24 and 52 weeks for patients with diabetic macular edema who were treated with 3 initial monthly 2 mg doses of intravitreal aflibercept followed by injections every 8 weeks or as needed.[15]

The eyes originally randomized to sham therapy benefited from crossover to active therapy both anatomically and with improvements in visual acuity. While the anatomic improvement experienced in the delayed sham + IAI PRN cohort appeared almost as robust as for those who were originally randomized to IAI 2Q4, none of the VA parameters (percent of 15-letter gainers, net letter gainers, and mean improvement from baseline) ever approached those seen with the proactive dosing regimen with an earlier treatment onset. In fact, all of these parameters were still statistically below those of the original IAI 2Q4 group at 52 weeks. This occurred even though from weeks 24 to 52, the sham + IAI PRN group of patients received 3.9 injections on average compared with 2.7 for those on the IAI 2Q4 + PRN regimen. The waterfall analysis demonstrates that the final disposition of the patients that were originally randomized to the IAI 2Q4 cohort was positive but the sham crossover group had mixed results, with over 30% of patients having a net vision loss at week 52 compared to baseline. The marked difference in outcomes implies that a 6-month delay in providing intravitreal aflibercept therapy may be too long and that irreversible damage from chronic edema may limit VA gains at 1 year. An alternative explanation for relative lack of efficacy in the crossover arm is that the sham group was treated with a reactive PRN regimen instead of 6 initial monthly doses in weeks 24 to 52. It is possible that VA gains could have been better in this group with a proactive, fixed dosing schedule of anti-VEGF suppression. However, higher proportions of eyes gained ≥15 letters at 52 weeks in the subgroup of patients who received intravitreal aflibercept ≤2 months after diagnosis compared with those who received treatment >2 months after diagnosis. These results, coupled with the differences between initial treatment and sham groups, suggest a benefit of prompt therapy on visual outcomes once CRVO has been diagnosed.

The COPERNICUS study (unlike the ranibizumab CRUISE study)[7] did not exclude patients with a brisk relative afferent pupillary defect. This may explain why, despite similar VA inclusion criteria, COPERNICUS had a much larger percentage of patients with posterior nonperfusion (15.5%) compared to CRUISE (1.5%). The COPERNICUS sham group also had a net loss of vision at 24 weeks (−4.0 letters) compared to a small net gain (+0.8 letters) in the sham arm of CRUISE.[7,16]

The COPERNICUS study is a 2-year trial, and further follow-up will determine if the visual acuity gains can be maintained with continued PRN therapy. CRVO and age-related macular degeneration studies have demonstrated a gradual decrease in efficacy with PRN regimens over 2 years compared with monthly regimens.[5,17] As the primary pathobiology in retinal vein occlusion is in the vasculature of the inner retina (unlike AMD), it is possible that CRVO eyes may be more resilient to intermittent edematous episodes and therefore less frequent than monthly dosing with intravitreal aflibercept may maintain vision gains, reducing the overall treatment and monitoring burden for patients with CRVO.

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Biosketch

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Biosketch

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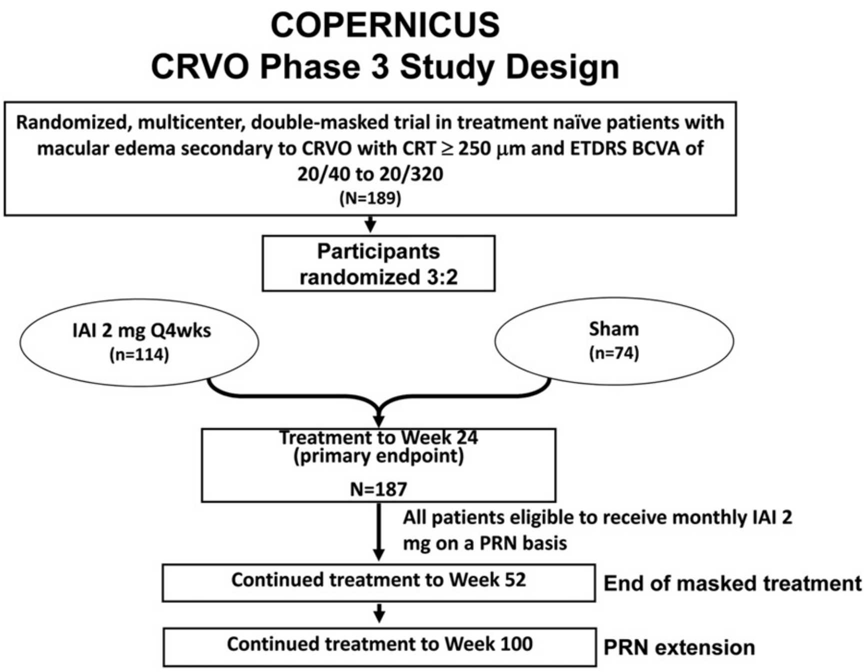
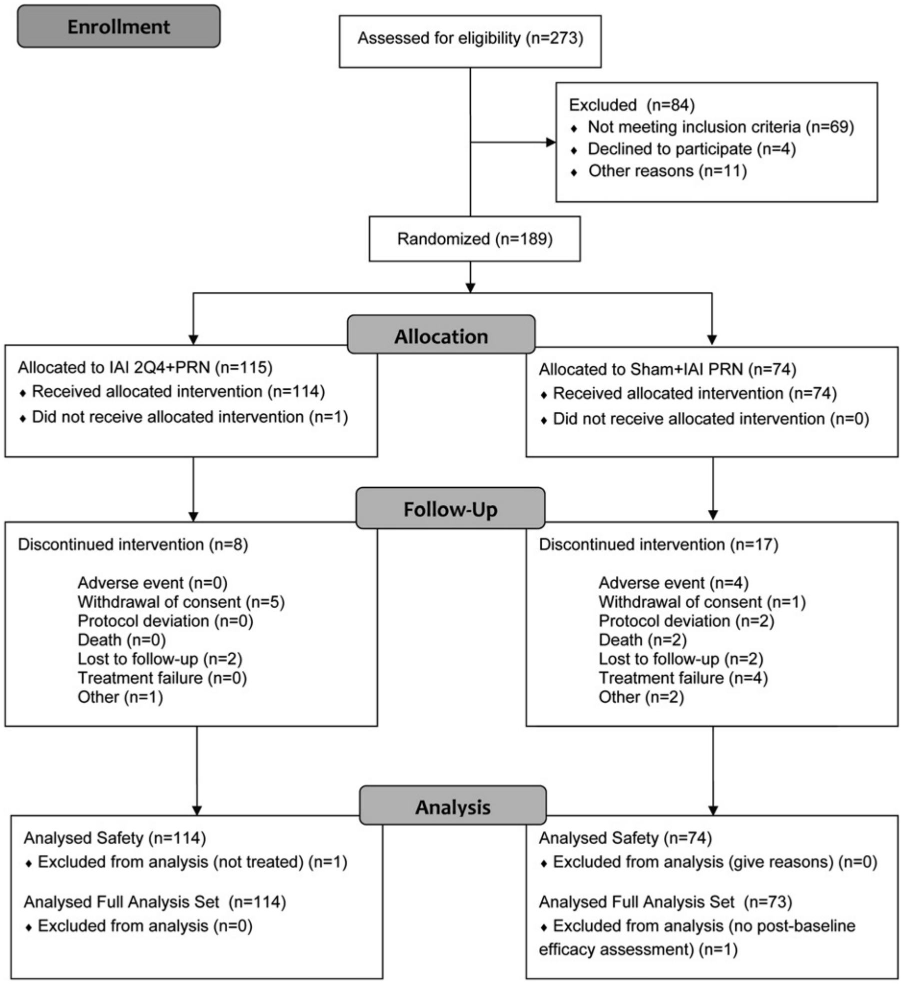
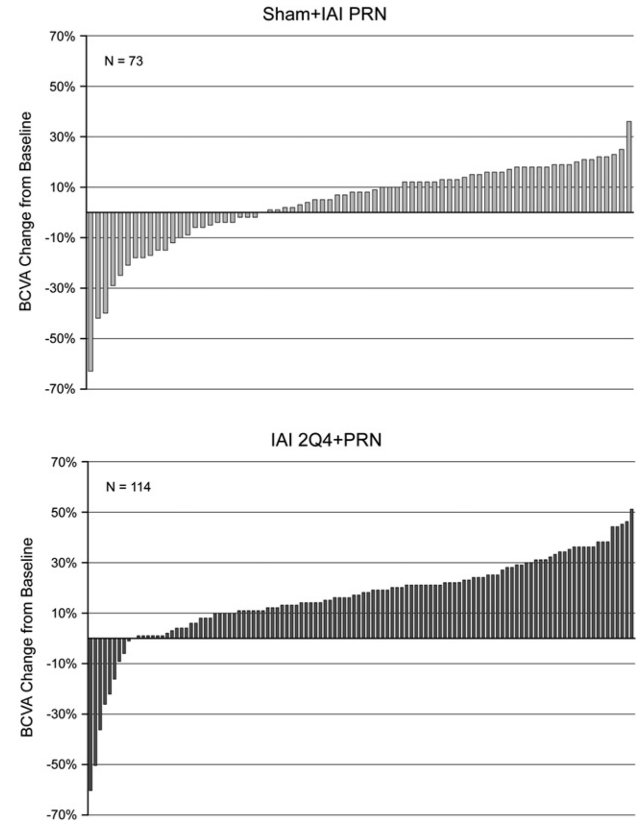


SUPPLEMENTAL FIGURE 1. Study design for evaluating the efficacy and safety of intravitreal aflibercept injection for the treatment of macular edema secondary to central retinal vein occlusion. Patients were randomized 3:2 to receive monthly injections of intravitreal aflibercept or sham for 24 weeks. One hundred eighty-nine patients were randomized; 188 patients received treatment. The full analysis set for 24 weeks comprised 187 patients (114 for IAI 2Q4 + PRN and 73 for sham + IAI PRN). Between weeks 24 and 52, masking was maintained and all patients were dosed on an as-needed basis according to predetermined criteria. Between weeks 24 and 52, patients received a sham injection if retreatment was not indicated. The primary endpoint, proportion of eyes with a gain of ≥15 letters in BCVA from baseline, and secondary endpoints were assessed at week 24. BCVA = best-corrected visual acuity; CRT = central retinal thickness; CRVO = central retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; IAI = intravitreal aflibercept injection; PRN = as needed; Q4wks = 2 mg every 4 weeks.



SUPPLEMENTAL FIGURE 2. Consort flow diagram of patients who were screened and enrolled in the study of intravitreal aflibercept injection for the treatment of macular edema secondary to central retinal vein occlusion. Patients were randomized 3:2 to receive monthly injections of intravitreal aflibercept or sham for 24 weeks. One hundred eighty-nine patients were randomized; 188 patients received treatment. The primary reasons for premature discontinuation from the study before week 52 were withdrawal of consent for the IAI 2Q4 + PRN group and adverse events and treatment failure in the sham + IAI PRN group. 2Q4 = 2 mg every 4 weeks; IAI = intravitreal aflibercept injection; PRN = as needed.



SUPPLEMENTAL FIGURE 3. Waterfall plot of individual changes in best-corrected visual acuity (BCVA) from baseline to week 52 after sham (Top panel) and/or intravitreal aflibercept (Bottom panel) injections for the treatment of macular edema secondary to central retinal vein occlusion. Missing data were imputed using the last-observation-carried-forward method. 2Q4 = 2 mg every 4 weeks; IAI = intravitreal aflibercept injection; PRN = as needed.

SUPPLEMENTAL TABLE 1. Ocular Treatment Emergent Adverse Events in the Study Eye From Baseline to Week 52 Occurring in At Least 3% of Patients Treated With Sham and/or Intravitreal Aflibercept Injections for Macular Edema Secondary to Central Retinal Vein Occlusion

	Weeks 0-24[a]		Weeks 24-52[b]	
	IAI (n = 114)	Sham (n = 74)	IAI 2Q4 + PRN (n = 110)	Sham + IAI PRN (n = 60)
Number of subjects with at least 1 ocular TEAE in study eye, n (%)	72 (63.2)	49 (66.2)	62 (56.4)	33 (55.0)
Eye disorders, n (%)	62 (54.4)	49 (66.2)	60 (54.5)	30 (50.0)
Conjunctival hemorrhage	17 (14.9)	13 (17.6)	9 (8.2)	8 (13.3)
Visual acuity reduced	8 (7.0)	13 (17.6)	16 (14.5)	3 (5.0)
Eye pain	16 (14.0)	4 (5.4)	6 (5.5)	3 (5.0)
Maculopathy	10 (8.8)	1 (1.4)	6 (5.5)	4 (6.7)
Retinal hemorrhage	5 (4.4)	6 (8.1)	3 (2.7)	3 (5.0)
Retinal vascular disorder	6 (5.3)	4 (5.4)	3 (2.7)	1 (1.7)
Vitreous detachment	5 (4.4)	5 (6.8)	6 (5.5)	1 (1.7)
Eye irritation	6 (5.3)	3 (4.1)	4 (3.6)	2 (3.3)
Optic disc vascular disorder	8 (7.0)	1 (1.4)	5 (4.5)	2 (3.3)
Vitreous floaters	6 (5.3)	2 (2.7)	2 (1.8)	1 (1.7)
Vitreous hemorrhage	2 (1.8)	6 (8.1)	1 (0.9)	2 (3.3)
Retinal exudates	7 (6.1)	0	1 (0.9)	4 (6.7)
Iris neovascularization	0	6 (8.1)	0	2 (3.3)
Ocular discomfort	5 (4.4)	1 (1.4)	2 (1.8)	2 (3.3)
Punctate keratitis	3 (2.6)	3 (4.1)	1 (0.9)	1 (1.7)
Retinal pigment epitheliopathy	3 (2.6)	2 (2.7)	3 (2.7)	5 (8.3)
Lacrimation increased	3 (2.6)	1 (1.4)	3 (2.7)	3 (5.0)
Ocular hyperemia	4 (3.5)	0	4 (3.6)	0
Foreign body sensation in eyes	1 (0.9)	2 (2.7)	0	2 (3.3)
Macular edema	1 (0.9)	1 (1.4)	10 (9.1)	0
Cystoid macular edema	0	1 (1.4)	8 (7.3)	2 (3.3)

2Q4 = 2 mg once every 4 weeks; IAI = intravitreal aflibercept injection; PRN = as needed; TEAE = treatment-emergent adverse event.
[a]Safety analysis set.
[b]Week 24 completers within the safety analysis set.

SUPPLEMENTAL TABLE 2. All Nonocular Serious Adverse Events by Primary System Organ Class From Baseline to Weeks 24 and 52 Occurring in Patients Treated With Sham and/or Intravitreal Aflibercept Injections for Macular Edema Secondary to Central Retinal Vein Occlusion

	Weeks 0-24[a]		Weeks 24-52[b]	
	IAI 2Q4 (n = 114)	Sham (n = 74)	IAI 2Q4 + PRN (n = 110)	Sham + IAI PRN (n = 60)
Number of patients with at least 1 nonocular serious TEAE, n (%)	6 (5.3)	6 (8.1)	7 (6.4)	5 (8.3)
Neoplasms	1 (0.9)	4 (5.4)	1 (0.9)	1 (1.7)
Gastrointestinal disorders	2 (1.8)	1 (1.4)	1 (0.9)	2 (3.3)
Cardiac disorders	1 (0.9)	1 (1.4)	1 (0.9)	0
Infections and infestations	1 (0.9)	1 (1.4)	3 (2.7)	1 (1.7)
Respiratory, thoracic, and mediastinal disorders	1 (0.9)	1 (1.4)	0	0
Blood and lymphatic system disorders	1 (0.9)	0	0	1 (1.7)
Hepatobiliary disorders	0	1 (1.4)	0	1 (1.7)
Metabolism and nutrition disorders	1 (0.9)	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.9)	0	0	0
Nervous system disorders	0	1 (1.4)	0	0
Psychiatric disorders	0	1 (1.4)	0	0
Renal and urinary disorders	0	1 (1.4)	0	0
General disorders and administration site conditions	0	0	2 (1.8)	0
Injury, poisoning, and procedural complications	0	0	0	1 (1.7)
Reproductive system and breast disorders	0	0	1 (0.9)	0

2Q4 = 2 mg once every 4 weeks; IAI = intravitreal aflibercept injection; PRN = as needed; TEAE = treatment-emergent adverse event.
[a]Safety analysis set.
[b]Week 24 completers within the safety analysis set.