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Intravitreal Aflibercept Injection for Macular Edema Due to Central Retinal Vein Occlusion

Two-Year Results from the COPERNICUS Study

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Purpose: To evaluate the efficacy and safety of intravitreal aflibercept injection (IAI) for the treatment of macular edema secondary to central retinal vein occlusion (CRVO).

Design: Randomized, double-masked, phase 3 trial.

Participants: A total of 188 patients with macular edema secondary to CRVO.

Methods: Patients received IAI 2 mg (IAI 2Q4) (n = 114) or sham injections (n = 74) every 4 weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed, or pro re nata (PRN) (IAI 2Q4 + PRN and sham + IAI PRN). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI PRN.

Main Outcome Measures: The primary efficacy end point was the proportion of patients who gained ≥15 letters in best-corrected visual acuity (BCVA) from baseline to week 24. This study reports week 100 results.

Results: The proportion of patients gaining ≥15 letters was 56.1% versus 12.3% ($P<0.001$) at week 24, 55.3% versus 30.1% ($P<0.001$) at week 52, and 49.1% versus 23.3% ($P<0.001$) at week 100 in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + PRN group compared with the sham + IAI PRN group at week 24 (+17.3 vs. −4.0 letters; $P<0.001$), week 52 (+16.2 vs. +3.8 letters; $P<0.001$), and week 100 (+13.0 vs. +1.5 letters; $P<0.0001$). The mean reduction from baseline in central retinal thickness was 457.2 versus 144.8 μm ($P<0.001$) at week 24, 413.0 versus 381.8 μm at week 52 ($P = 0.546$), and 390.0 versus 343.3 μm at week 100 ($P = 0.366$) in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively. The mean number (standard deviation) of PRN injections in the IAI 2Q4 + PRN and sham + IAI PRN groups was 2.7±1.7 versus 3.9±2.0 during weeks 24 to 52 and 3.3±2.1 versus 2.9±2.0 during weeks 52 to 100, respectively. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9% vs. 6.8% in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively).

Conclusions: The visual and anatomic improvements after fixed dosing through week 24 and PRN dosing with monthly monitoring from weeks 24 to 52 were diminished after continued PRN dosing, with a reduced monitoring frequency from weeks 52 to 100. *Ophthalmology 2014;121:1414-1420 © 2014 by the American Academy of Ophthalmology.*

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

Macular edema is the most common cause of decreased vision in patients with central retinal vein occlusion (CRVO).[1,2] Despite some reduction in macular edema, grid laser photocoagulation provides no visual benefit in patients with macular edema secondary to CRVO.[3] In contrast, treatment with intravitreal corticosteroid injections or implants has met with some clinical success.[4–6] Clarification of the central role of vascular endothelial growth factor (VEGF) in the pathophysiology of vascular permeability led to the use of anti-VEGF therapies for treatment of macular edema.[7–9] More recently, clinical trials have demonstrated the efficacy of intravitreal anti-VEGF agents for treatment of macular edema secondary to CRVO.[10–13]

Intravitreal aflibercept (known in the scientific literature as VEGF Trap-Eye; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; and Bayer HealthCare Pharmaceuticals, Berlin, Germany) is a fusion protein comprising key domains of human VEGF receptors 1 and 2 with immunoglobulin-G Fc.[14] Intravitreal aflibercept binds multiple isoforms of human VEGF-A and placental growth factor with high affinity and has demonstrated efficacy for the treatment of wet age-related macular degeneration and diabetic macular edema.[15,16] Two parallel trials, the COPERNICUS and GALILEO studies, evaluated the efficacy and safety of intravitreal aflibercept injection (IAI) for the treatment of macular edema secondary to CRVO.[10–12] The primary efficacy end point of the COPERNICUS study was at week 24, and the results for weeks 24 and 52 were reported.[10,11] We present the 100-week results of the COPERNICUS study.

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Methods

Study Design

The COPERNICUS study was a 2-year, phase 3, randomized, double-masked clinical trial conducted across 61 sites in the United States, Canada, Colombia, India, and Israel (see Appendix 1 for a list of study investigators). The respective institutional review boards/ethics committees approved the protocol, which was carried out in compliance with ethical guidelines of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. All participants provided written informed consent before the initiation of the study-specific procedures. The study was registered with ClinicalTrials.gov (identifier no. NCT00943072). Data for this report were collected between July 2009 and April 2012.

The design and eligibility criteria for the COPERNICUS study have been reported previously.[10,11] Only 1 eye from each patient was included in the study. Patients with macular edema secondary to CRVO who had a central retinal thickness (CRT) of ≥250 μm and a best-corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) were randomly assigned in a 3:2 ratio to receive IAI 2 mg (IAI 2Q4) or sham injections every 4 weeks up to week 24. From week 24 to 52, all patients were evaluated monthly and received IAI on an as-needed, or pro re nata (PRN), basis if they had a >50 μm increase in CRT compared with the lowest previous measurement, new or persistent cystic retinal changes or subretinal fluid, persistent diffuse edema >250 μm in the central subfield, loss of ≥5 letters from the best prior measurement in conjunction with any increase in CRT, or an increase of ≥5 letters in BCVA from the most recent visit (suggesting a patient may not have reached maximal response yet). If none of the re-treatment criteria were met, patients received a sham injection. From week 52 to 100, patients from both study arms were evaluated at least quarterly and received IAI PRN according to the same re-treatment criteria. Patients could be evaluated and dosed as frequently as every 4 weeks if deemed necessary by the investigators. Masking was not performed during weeks 52 to 100. All patients were eligible to receive panretinal laser photocoagulation at any time during the study if they progressed to clinically significant ocular neovascularization.

Study End Point Assessments

The primary efficacy end point was the proportion of patients who gained ≥15 letters in BCVA from baseline to week 24. We report the 100-week results of the COPERNICUS study. Efficacy end points at week 100 were all exploratory and included the proportion of patients who gained ≥15 letters in BCVA; change from baseline in the mean BCVA and CRT; proportion of patients progressing to neovascularization of the anterior segment, optic disc, or elsewhere in the fundus; and change from baseline in the mean National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score.

The efficacy and safety end points were assessed as described previously.[10,11] The BCVA and CRT were assessed every 4 weeks from baseline to week 52, and every 12 weeks from week 52 to 100. Fundus photography and fluorescein angiography were performed at screening and weeks 12, 24, 36, 52, and 100. Vision-related quality of life was assessed at baseline and weeks 24, 52, and 100 using the NEI VFQ-25, which was administered by site personnel before intravitreal injections.

Statistical Analyses

The full analysis set included all randomized patients who received any study medication and had a baseline BCVA assessment and at least 1 BCVA assessment after baseline. Proportions were analyzed using a 2-sided Cochran–Mantel–Haenszel test. Continuous variables were analyzed with an analysis of covariance, with treatment group, region, and baseline BCVA as fixed factors and the respective baseline variable as a covariate. In the analysis of the proportion of patients who gained ≥15 letters, patients who discontinued before week 24 and had fewer than 5 injections were considered nonresponders; otherwise, missing values were imputed using the last-observation-carried-forward method. In the analysis of the proportion of patients with no retinal fluid, observed values were used. For all other efficacy end points, missing data were imputed using the last-observation-carried-forward method. Time to first injection was analyzed using Kaplan–Meier methodology. Safety was analyzed in the safety analysis set, which included all randomized patients who received any study treatment. Ocular and nonocular treatment-emergent serious adverse events (SAEs) from week 52 to 100 were analyzed among week 24 completers within the safety analysis set.

Results

Patient Disposition, Demographics, and Baseline Characteristics

A total of 115 patients were randomized to receive IAI, and 74 patients were randomized to receive sham. With the exception of 1 patient in the IAI group, all randomized patients were treated in the study and included in the safety analysis set (n = 114 for the IAI group and n = 74 for the sham group). As reported previously, 1 sham patient was excluded from the full analysis set (n = 114 for the IAI group and n = 73 for the sham group) because of the lack of a postbaseline BCVA assessment.[10] The percentages of patients completing the study in the IAI 2Q4 + PRN and sham + IAI PRN groups were 95.7% versus 81.1% at week 24, 93.0% versus 77.0% at week 52, and 88.7% versus 67.6% at week 100, respectively. Major reasons for discontinuation before week 100 in the IAI 2Q4 + PRN group were adverse events (3.5%), consent withdrawal (4.3%), loss to follow-up (1.7%), and protocol deviation (0.9%). No patient in the IAI 2Q4 + PRN group discontinued because of treatment failure. Major reasons for discontinuation before week 100 in the sham + IAI PRN group were adverse events (5.4%), lack of efficacy (5.4%), loss to follow-up (6.8%), death (5.4%), withdrawal of consent (4.1%), and protocol deviations (2.7%).

Demographic and baseline characteristics of patients were similar in both treatment groups.[10,11] Overall, 56.1% of patients in the IAI group and 71.2% of sham patients had CRVO for less than 2 months. Most patients were judged to have <10 disc areas of capillary nonperfusion at baseline (67.5% in the IAI group and 68.5% in the sham group) and a baseline BCVA of ≥35 letters (>20/200; 75.4% in the IAI group and 75.3% in the sham group).

Efficacy

The proportion of patients who gained ≥15 letters was significantly higher in the IAI 2Q4 + PRN group compared with the sham + IAI PRN group at week 24 (56.1% vs. 12.3%; $P<0.001$), week 52 (55.3% vs. 30.1%; $P<0.001$), and week 100 (49.1% vs. 23.3%; $P<0.001$) (Fig 1A). The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + PRN group compared with the sham + IAI PRN group at week 24 (+17.3 vs. −4.0 letters; $P<0.001$), week 52 (+16.2 vs. +3.8 letters; $P<0.001$), and week 100 (+13.0 vs. +1.5 letters; $P<0.0001$) (Fig 1B).

The mean reduction from baseline in CRT was 457.2 versus 144.8 μm at week 24 ($P<0.001$), 413.0 versus 381.8 μm at week 52, and 390.0 versus 343.3 μm at week 100 in the IAI 2Q4 + PRN and

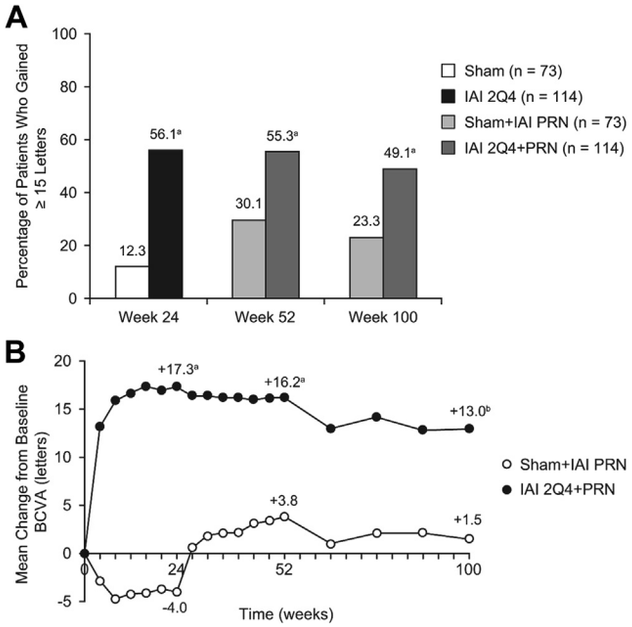

Figure 1. Visual outcomes of the full analysis set. **A,** Proportion of patients who gained ≥15 letters from baseline to weeks 24, 52, and 100. **B,** Mean change from baseline best-corrected visual acuity (BCVA) over 100 weeks. Patients received intravitreal aflibercept injection (IAI) or sham every 4 weeks up to week 24. From week 24 to 52, all patients were evaluated monthly and received IAI pro re nata (PRN). From week 52 to 100, all patients were evaluated at least quarterly and received IAI PRN. In the analysis of the proportion of patients who gained ≥15 letters at week 24 (primary efficacy end point), patients who discontinued before week 24 and had <5 injections were considered nonresponders; otherwise, missing values were imputed using the last-observation-carried-forward method. For all other efficacy end points, missing data were imputed using the last-observation-carried-forward method. [a]$P < 0.001$ and [b]$P < 0.0001$ versus sham. 2Q4 = 2 mg every 4 weeks.

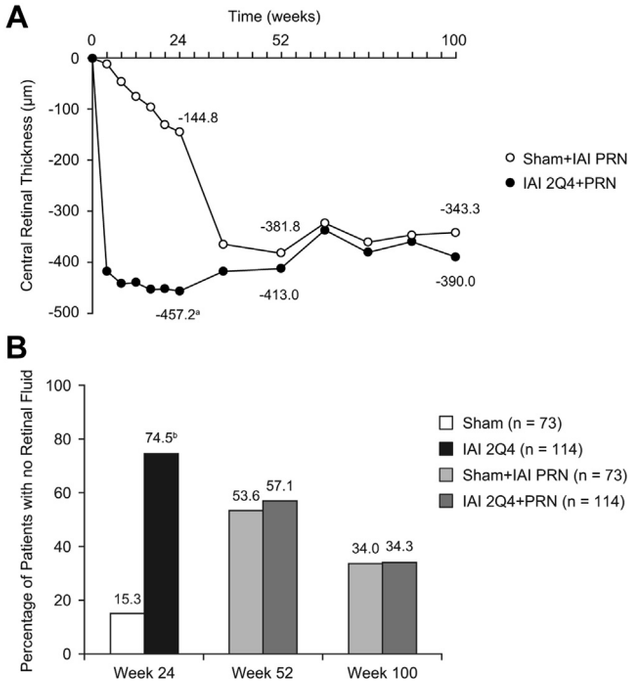

Figure 2. Anatomic outcomes of the full analysis set. **A,** Mean change from baseline central retinal thickness (CRT) over 100 weeks. **B,** Proportion of patients with no retinal fluid at weeks 24, 52, and 100. Patients received intravitreal aflibercept injection (IAI) or sham every 4 weeks up to week 24. From week 24 to 52, all patients were evaluated monthly and received IAI pro re nata (PRN). From week 52 to 100, all patients were evaluated at least quarterly and received IAI PRN. Missing values were imputed using the last-observation-carried-forward method in **(A)**; observed values were used in **(B)**. [a]$P < 0.001$ and [b]$P < 0.0001$ versus sham. 2Q4 = 2 mg every 4 weeks.

sham + IAI PRN groups, respectively (Fig 2A). The proportion of patients with no retinal fluid in the IAI 2Q4 + PRN and sham + IAI PRN groups was 74.5% versus 15.3% ($P<0.0001$) at week 24, 57.1% versus 53.6% at week 52, and 34.3% versus 34.0% at week 100, respectively (Fig 2B). During the first 52 weeks of the study, no eyes in the IAI 2Q4 + PRN group developed neovascularization, compared with 5 eyes (6.8%) developing neovascularization of anterior segment in the sham + IAI PRN group ($P = 0.006$). Between weeks 52 and 100, neovascularization developed in 6 patients (5.3%) in the IAI 2Q4 + PRN group and 6 patients (8.2%) in the sham + IAI PRN group. In the IAI 2Q4 + PRN group, 5 patients (4.4%) developed optic disc neovascularization and 1 patient (0.9%) developed both optic disc and anterior segment neovascularization. In the sham + IAI PRN group, 3 patients (4.1%) developed optic disc neovascularization and 3 patients (4.1%) developed anterior segment neovascularization. From baseline to week 100, a significantly smaller percentage of the IAI 2Q4 + PRN group received panretinal photocoagulation than did the sham + IAI PRN group (1.8% vs. 8.1%, respectively; $P = 0.0355$).

The mean change from baseline NEI VFQ-25 total score for the IAI 2Q4 + PRN and sham + IAI PRN groups was 7.2 versus 0.8 at week 24 ($P<0.001$), 7.5 versus 5.1 at week 52 ($P = 0.2164$), and 6.3 versus 3.6 at week 100, respectively ($P = 0.2628$).

Treatment Experience

The mean (standard deviation) number of PRN injections in the IAI 2Q4 + PRN and sham + IAI PRN groups was 6.0 (3.4) and 7.1 (3.4) from weeks 24 to 100 (week 100 completers), 2.7 (1.7) and 3.9 (2.0) from weeks 24 to 52 (week 24 completers), and 3.3 (2.1) and 2.9 (2.0) from weeks 52 to 100 (week 100 completers), respectively. The distribution of injections from week 24 to 100 is presented in Figure 3. For patients completing week 100, the median time (range) to the first PRN injection after week 24 was 81 (22−553) days in the IAI 2Q4 + PRN group and 28 (21 to 567) days in the sham + IAI PRN group. Between week 52 and week 100, 42.7% of the IAI 2Q4 + PRN group received no PRN injection or received PRN injections always with an interval of ≥8 weeks. The remaining 57.3% received an injection after a 4-week interval at least once, although other treatment intervals may have been longer (Table 1). The mean (standard deviation) time between PRN injections was 87.1 (46.6) and 83.8 (42.7) days in the IAI 2Q4 + PRN and sham + IAI PRN groups from week 52 to week 100, respectively (Table 1).

Safety

From baseline to week 100, the percentage of patients experiencing at least 1 ocular treatment-emergent adverse event (TEAE) in the study eye was similar in the IAI 2Q4 + PRN and sham + IAI PRN

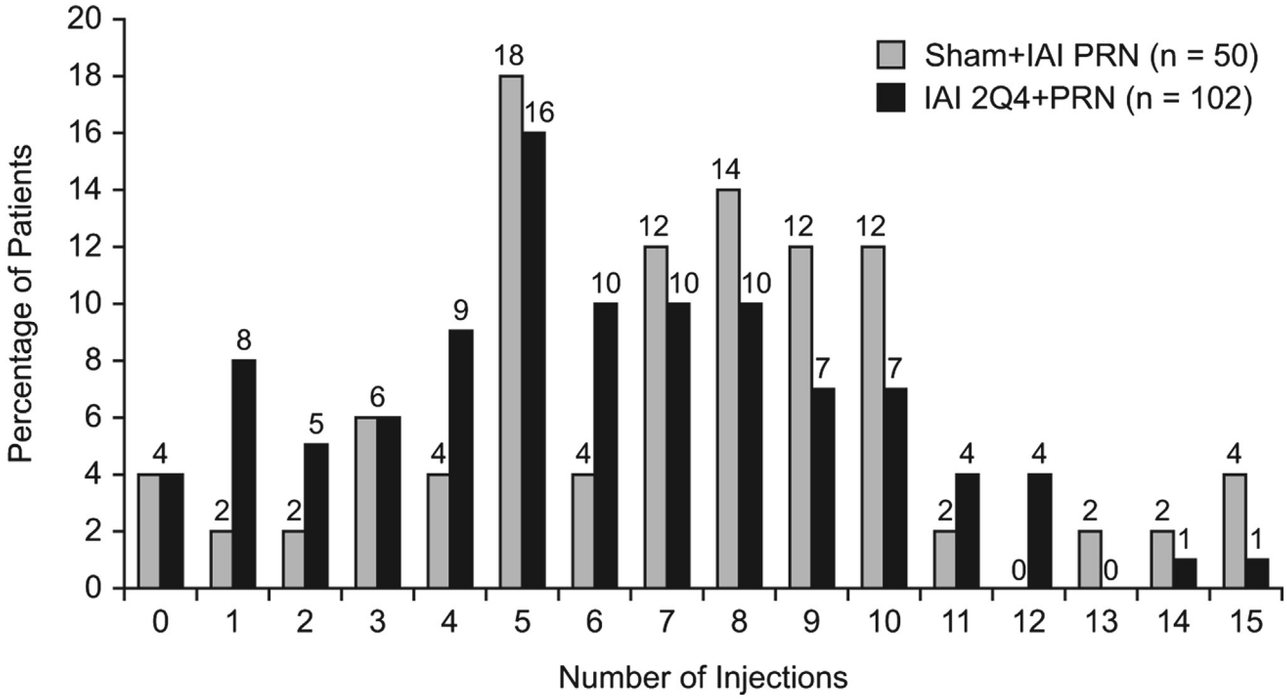

Figure 3. Proportion of patients receiving the indicated number of injections from week 24 to 100. Patients completing week 100 were included in this analysis. IAI = intravitreal aflibercept injection; PRN = pro re nata; 2Q4 = 2 mg every 4 weeks.

groups (87.7% and 85.1%, respectively). During weeks 52 to 100, ocular TEAEs occurring in ≥10% of patients in the IAI 2Q4 + PRN and sham + IAI PRN groups were reduced visual acuity (16.7% vs. 10.8%, respectively) and macular edema (11.4% vs. 2.7%, respectively). The incidence of ocular treatment-emergent SAEs was 8.8% in the IAI 2Q4 + PRN group and 16.2% in the sham + IAI PRN group from baseline to week 100. Ocular SAEs occurring from week 52 to week 100 are shown in Table 2. Most ocular SAEs were related to the disease state or injection procedure, and there were no clinically relevant differences between the treatment groups in terms of frequency or pattern of ocular SAEs.

Table 1. Interval of Pro Re Nata Intravitreal Aflibercept Injections from Week 52 to 100

	Sham + IAI PRN (N = 60)	IAI 2Q4 + PRN (N = 110)
Mean time between PRN injections, days (SD)	83.8 (42.7)	87.1 (46.6)
Patients receiving PRN injections, n (%)	45 (75.0)	94 (85.5)
Always with an interval of ≥12 wks	14 (23.3)	22 (20.0)
Always with an interval of ≥8 wks	18 (30.0)	31 (28.2)
At least one 4-wk interval	27 (45.0)	63 (57.3)
Patients not receiving PRN injections, n (%)	15 (25.0)	16 (14.5)

IAI = intravitreal aflibercept injection; PRN = pro re nata; SD = standard deviation; 2Q4 = 2 mg once every 4 weeks.
These values are from week 24 completers in the safety analysis set.

The incidence of nonocular TEAEs was similar in the IAI 2Q4 + PRN and sham + IAI PRN groups from baseline to week 100 (77.2% and 81.1%, respectively). Hypertension was the only systemic adverse event that occurred in ≥10% of patients in the IAI 2Q4 + PRN and sham + IAI PRN groups (19.3% vs. 16.2%, respectively). Nonocular SAEs occurred with a similar frequency in both IAI 2Q4 + PRN and sham + IAI PRN groups from baseline to week 100 (21.1% and 25.7%, respectively). Pneumonia was the only nonocular SAE that was reported for more than 1 patient (3 patients [5.0%] in the sham + IAI PRN group) from week 52 to 100. Nonocular SAEs occurring from week 52 to 100 are shown in Table 3 (available at www.aaojournal.org). Antiplatelet Trialists' Collaboration–defined arterial thromboembolic events occurred in 2 patients (1.8%) in the IAI 2Q4 + PRN group from baseline to week 100 (Table 4): One patient in the IAI group had 2 incidents of nonfatal myocardial infarction, the first between weeks 24 and 52 and the second between weeks 52 and 100; 1 patient in the IAI group had a nonfatal stroke between weeks 52 and 100. Antiplatelet Trialists' Collaboration events occurred in 2 patients (2.7%) in the sham group (1 fatal myocardial infarction and 1 fatal arrhythmia) from baseline to week 24 (Table 4).

Two additional patients in the sham + IAI PRN group died during the study: 1 of arrhythmia (between weeks 24 and 52) and 1 of pneumonia (between weeks 52 and 100). No deaths occurred in the IAI 2Q4 + PRN group during the study.

Discussion

Treatment with fixed monthly IAI over 24 weeks resulted in rapid and sustained improvements in visual and anatomic end points. These improvements were largely maintained after PRN dosing with monthly evaluations through week 52 (a mean loss of 1.1 letters in BCVA and a mean increase

Table 2. Ocular Serious Adverse Events in the Study Eye from Week 52 to 100

	Sham + IAI PRN (N = 60)	IAI 2Q4 + PRN (N = 110)
Patients with ≥1 ocular SAE, n (%)	0 (0)	7 (6.4)
Cataract	0 (0)	3 (2.7)
Cystoid macular edema	0 (0)	2 (1.8)
Retinal vein occlusion	0 (0)	1 (0.9)
Macular edema	0 (0)	1 (0.9)
Retinal vascular disorder	0 (0)	1 (0.9)
Reduced visual acuity	0 (0)	1 (0.9)

IAI = intravitreal aflibercept injection; PRN = pro re nata; SAE = serious adverse event; 2Q4 = 2 mg once every 4 weeks.
These values are from week 24 completers in the safety analysis set.

of 44.2 μm in CRT compared with week 24). After PRN dosing with at least quarterly evaluations, patients in the IAI 2Q4 + PRN group had a decline in the visual and anatomic improvements at week 100 from those gained at weeks 24 and 52 (mean losses of 4.3 and 3.2 letters in BCVA along with mean increases of 67.2 and 23.0 μm in CRT compared with weeks 24 and 52, respectively). Likewise, the proportion of patients with no retinal fluid decreased after changing the treatment regimen from fixed dosing to PRN dosing, with further declines when the monitoring frequency was decreased from monthly to at least quarterly. These findings suggest that a PRN dosing regimen with at least quarterly evaluations, treating disease only after it has recurred, may not be sufficient for at least some patients to maintain the visual and anatomic improvements gained after a fixed monthly dosing regimen. It remains to be elucidated whether other factors, such as disease progression, play a role in the decline in visual and anatomic gains seen after PRN dosing with infrequent monitoring.

Similar to the COPERNICUS study, Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety (CRUISE) trial investigated the efficacy of ranibizumab for treatment of CRVO, starting with monthly intravitreal injections for 6 months and continuing with PRN injections and monthly monitoring for an additional 6 months, which was then followed by PRN dosing and less-than-monthly monitoring for up to 2 years in HORIZON, an extension study of CRUISE.[13,17,18] Visual and anatomic outcomes of the CRUISE study are similar to those of the COPERNICUS study, with gains achieved during the fixed monthly dosing phase largely maintained under PRN dosing with monthly monitoring.[13,17] Also similar to the COPERNICUS study, lengthening of the monitoring intervals after the first year in HORIZON resulted in a decrease of gains over the second year.[18]

Table 4. Anti-Platelet Trialists' Collaboration–Defined Arterial Thromboembolic Events from Baseline to Week 100

	Sham + IAI PRN (N = 74)	IAI 2Q4 + PRN (N = 114)
Patients with any APTC-defined arterial thromboembolic event, n (%)	2 (2.7)	2 (1.8)
Nonfatal myocardial infarction	0 (0)	1 (0.9)
Nonfatal stroke	0 (0)	1 (0.9)
Vascular death	2 (2.7)	0 (0)

APTC = Anti-Platelet Trialists' Collaboration; IAI = intravitreal aflibercept injection; PRN = pro re nata; 2Q4 = 2 mg once every 4 weeks.
Values are from patients in the afety analysis set.

Several lines of evidence suggest that early treatment after the presentation of CRVO might be important for optimal visual outcomes with anti-VEGF agents. In the CRUISE study, sham patients crossing over to ranibizumab 0.5 mg had significantly less improvement from baseline BCVA at month 12 compared with those receiving ranibizumab 0.5 mg from the beginning of study.[17] Likewise, in the COPERNICUS study, sham patients treated with IAI PRN during weeks 24 to 100 did not gain vision as robustly as patients in the IAI group who started the study with fixed monthly doses of IAI, despite receiving a higher mean number of injections. A less pronounced vision gain in sham patients switching to therapy with anti-VEGF agents is at least partly due to a delay in initiating anti-VEGF treatment, highlighting the importance of early diagnosis and treatment. Nevertheless, it should be noted that sham patients in both the CRUISE[17] and COPERNICUS (Fig 2A) studies benefitted from anatomic improvements after delayed treatment with anti-VEGF agents.

In the current study, IAI was generally well tolerated over the 100 weeks of study in both treatment groups, with most adverse events being attributable to those typically associated with intravitreal injections or the underlying disease. An increase in the rates of macular edema and reduced visual acuity seen in patients receiving IAI after changing the treatment regimen from fixed dosing to PRN dosing suggests that some patients would have benefited from regular dosing, and perhaps more frequent monitoring, rather than being treated in response to the recurrence of disease.[10,11] Although the incidence of neovascularization from week 52 to 100 was higher in the sham + IAI PRN group (8.2%), this event was still seen in the IAI 2Q4 + PRN group (5.3%), suggesting that the reduced treatment and monitoring frequency that was used between week 52 and 100 may not be sufficient to adequately control this sequelae of CRVO in all patients.

In conclusion, the COPERNICUS study, as well as the CRUISE and HORIZON studies, demonstrated that long-term dosing with anti-VEGF agents is necessary to control macular edema in many patients with CRVO, likely because the continued ischemia leads to continued excessive production of VEGF.[17,18] The COPERNICUS study results at week 100 corroborate the loss of visual and anatomic improvements after a quarterly or more frequent PRN dosing regimen with this protocol, suggesting that more frequent monitoring may be necessary, at least in some patients, for

optimal outcomes. Thus, from a practical perspective, the suitability of PRN dosing with quarterly monitoring seems to be questionable. Given that outside of a clinical study setting a close monitoring schedule might not always be practicable, a "treat and extend regimen" or a fixed every 2 months dosing regimen of IAI after an initial period of monthly doses could be a viable treatment option to reduce the monitoring burden in the treatment of macular edema secondary to CRVO, while still potentially maintaining the gains achieved with monthly injections.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CRT** = central retinal thickness; **CRUISE** = Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety; **CRVO** = central retinal vein occlusion; **IAI** = intravitreal aflibercept injection; **NEI VFQ-25** = National Eye Institute 25-item Visual Function Questionnaire; **PRN** = pro re nata; **SAE** = serious adverse event; **TEAE** = treatment-emergent adverse event; **2Q4** = 2 mg every 4 weeks; **VEGF** = vascular endothelial growth factor

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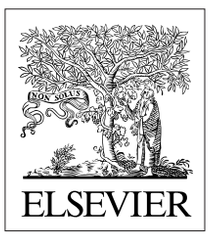
Table 3. Nonocular Serious Adverse Events by Primary System Organ Class and Preferred Term in the Study Eye from Week 52 to 100

	Sham + IAI PRN (N = 60)	IAI 2Q4 + PRN (N = 110)
Patients with ≥1 nonocular SAE,* n (%)	10 (16.7)	15 (13.6)
Blood and lymphatic system disorders	1 (1.7)	0 (0)
Cardiac disorders	1 (1.7)	6 (5.5)
Gastrointestinal disorders	4 (6.7)	1 (0.9)
General disorders and administration site conditions	1 (1.7)	0 (0)
Infections and infestations	3 (5.0)	3 (2.7)
Injury, poisoning, and procedural complications	1 (1.7)	3 (2.7)
Metabolism and nutrition disorders	2 (3.3)	0 (0)
Musculoskeletal and connective tissue disorders	2 (3.3)	2 (1.8)
Neoplasms (including cysts and polyps)	1 (1.7)	1 (0.9)
Nervous system disorders	0 (0)	4 (3.6)
Renal and urinary disorders	1 (1.7)	0 (0)
Reproductive system and breast disorders	1 (1.7)	0 (0)
Respiratory, thoracic, and mediastinal disorders	1 (1.7)	3 (2.7)
Skin and subcutaneous tissue disorders	0 (0)	1 (0.9)
Vascular disorders	0 (0)	1 (0.9)

IAI = intravitreal aflibercept injection; PRN = pro re nata; SAE = serious adverse event; 2Q4 = 2 mg once every 4 weeks.
*Week 24 completers in the safety analysis set.



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