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Intravitreal Aflibercept for Macular Edema Secondary to Central Retinal Vein Occlusion: 18-Month Results of the Phase 3 GALILEO Study

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• PURPOSE: To evaluate intravitreal aflibercept for treatment of macular edema secondary to central retinal vein occlusion (CRVO).
• DESIGN: Randomized, double-masked, phase 3 study.
• METHODS: A total of 177 patients with macular edema secondary to CRVO were randomized to receive 2 mg intravitreal aflibercept (n = 106) or sham (n = 71) every 4 weeks for 20 weeks. From weeks 24 to 48, patients were monitored every 4 weeks; the former group received intravitreal aflibercept as needed (PRN), and the sham group received sham. From weeks 52 to 76, patients were monitored every 8 weeks, and both groups received intravitreal aflibercept PRN. The primary endpoint (proportion of patients who gained ≥15 letters) was at week 24. This study reports exploratory outcomes at week 76.
• RESULTS: The proportion of patients who gained ≥15 letters in the intravitreal aflibercept and sham groups was 60.2% vs 22.1% at week 24 (patients discontinued before week 24 were considered nonresponders; $P < .0001$), 60.2% vs 32.4% at week 52 (last observation carried forward, $P < .001$), and 57.3% vs 29.4% at week 76 (last observation carried forward; $P < .001$). Mean μm change from baseline central retinal thickness was −448.6 vs −169.3 at week 24 ($P < .0001$), −423.5 vs −219.3 at week 52 ($P < .0001$), and −389.4 vs −306.4 at week 76 ($P = .1122$). Over 76 weeks, the most common ocular serious adverse event in the intravitreal aflibercept group was macular edema (3.8%).
• CONCLUSIONS: The visual and anatomic improvements seen after fixed, monthly dosing at week 24 were largely maintained when treatment intervals were extended. Patients with macular edema following CRVO benefited from early treatment with intravitreal aflibercept. (Am J Ophthalmol 2014;158: 1032–1038. © 2014 by Elsevier Inc. All rights reserved.)

MACULAR EDEMA IS THE LEADING CAUSE OF vision loss in patients with central retinal vein occlusion (CRVO).[1] The pathophysiology of CRVO is incompletely understood, but a partial obstruction in blood flow, likely caused by venous thrombosis, increases retinal capillary pressure and results in transudation of fluid into the extravascular space, ultimately leading to macular edema.[2] The proangiogenic protein, vascular endothelial growth factor (VEGF), plays an important role in the pathogenesis of macular edema following CRVO, as evidenced by its ability to initiate intraocular neovascularization and to induce vascular hyperpermeability.[3] Moreover, vitreous levels of VEGF are positively correlated with the severity of macular edema in patients with CRVO.[4] Accordingly, blockade of VEGF following intravitreal injection of anti-VEGF agents improves both visual and anatomic outcomes in patients with macular edema secondary to CRVO.[5–10]

Intravitreal aflibercept injection (also known in the scientific literature as IAI, IVT-AFL, or VEGF Trap-Eye; Regeneron Pharmaceuticals, Inc; Tarrytown, New York, USA and Bayer HealthCare Pharmaceuticals, Berlin, Germany) is a fusion protein composed of key extracellular domains from human VEGF receptors 1 and 2 and the constant region from human IgG1.[11] The molecule functions as a soluble decoy receptor, binding to multiple VEGF-A isoforms and placental growth factor, thereby preventing these proangiogenic ligands from binding to and activating endothelial VEGF receptors.[11,12] Intravitreal aflibercept was first approved in the United States for the treatment of neovascular age-related macular degeneration (AMD),

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based on clinical evidence that it was as effective and safe as ranibizumab in improving visual and anatomic outcomes over a 1-year period.[13] Intravitreal aflibercept has also been investigated for the treatment of macular edema secondary to CRVO in 2 parallel trials, with the COPERNICUS study performed in the United States and the GALILEO study performed in Europe and Asia/Pacific. Twenty-four-week, 52-week, and 100-week results of the COPERNICUS study have been reported, as have the 24-week and 52-week results from the GALILEO study.[7–10,14] This report describes the 76-week results of the GALILEO study.

METHODS

• **STUDY DESIGN:** The GALILEO study was a 76-week, randomized, double-masked, phase 3 trial comparing intravitreal aflibercept to sham for the treatment of macular edema secondary to CRVO. The study was carried out at 63 sites across Europe and Asia/Pacific (a list of study investigators is provided in the Appendix, available as Supplemental Material at AJO.com). Institutional Review Board/Ethics Committee approval was prospectively obtained for the study protocol at each site. All patients signed a written consent form before initiation of the study-specific procedures. The study was registered with ClinicalTrials.gov (identifier no. NCT01012973) and was conducted in compliance with ethical guidelines from the Declaration of Helsinki and International Conference on Harmonization. Data for this 76-week report were collected between October 2009 and February 2012.

The design and eligibility criteria for the GALILEO study have previously been described.[9] Briefly, patients were randomized in a 3:2 ratio to receive either 2 mg intravitreal aflibercept injection (2Q4) or sham in the study eye once every 4 weeks for 20 weeks, for a total of 6 doses. From week 24 to week 48, patients in the intravitreal aflibercept group were evaluated every 4 weeks and received intravitreal aflibercept as needed (2Q4 → PRN) if they met prespecified retreatment criteria. Patients in the sham group continued to receive sham at all scheduled visits through week 48. From week 52 through week 68, patients in both intravitreal aflibercept (2Q4 → PRN) and sham (sham → PRN) groups were monitored every 8 weeks and received intravitreal aflibercept PRN according to the prespecified retreatment criteria. No treatment was administered at week 76 in either group. The prespecified retreatment criteria were as follows: (1) a >50 μm increase in central retinal thickness compared with the lowest previous measurement, (2) new or persistent cystic changes within the neurosensory retina or subretinal fluid, (3) persistent diffuse edema ≥250 μm in the central subfield, (4) loss of ≥5 letters from the best prior measurement in conjunction with any increase in central retinal thickness, or (5) an increase of ≥5 letters in best-corrected visual acuity (BCVA) from the most recent visit in the absence of retinal edema in the central subfield, suggesting potentially further improvements upon a subsequent injection. If none of the retreatment criteria were met, patients received sham to maintain masking. All patients were eligible to receive panretinal laser photocoagulation at any time during the study if they progressed to neovascularization of the anterior segment, optic disc, or elsewhere in the fundus. Only 1 eye from each patient was included in the study and treated as described here.

• **OUTCOME MEASURES:** The primary efficacy endpoint was the proportion of patients achieving a gain of ≥15 letters in BCVA from baseline to week 24. Efficacy endpoints at week 76 were all exploratory and included the proportion of patients who gained ≥15 letters in BCVA from baseline; mean change from baseline in BCVA and central retinal thickness; 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 scores. Safety assessments included ophthalmic examinations, adverse events, laboratory measurements, and vital signs. The efficacy and safety endpoints were assessed as described previously.[9] Retinal characteristics were evaluated using time-domain optical coherence tomography.

• **STATISTICAL ANALYSES:** The efficacy endpoints were analyzed using the full analysis set, which included all randomized patients who received any study treatment and had a baseline and at least 1 post-baseline BCVA assessment. In a prespecified analysis of the primary efficacy endpoint (the proportion of patients who gained ≥15 letters at week 24), patients who discontinued before week 24 were considered to be nonresponders. In the exploratory analysis of proportion of patients with no retinal fluid, observed values were used. In all other efficacy analyses, missing values were imputed by the last observation carried forward method. Between-group differences in the proportion of patients who gained ≥15 letters were evaluated with a 2-sided Cochran-Mantel-Haenszel test. Continuous variables were analyzed with an analysis of covariance, except for BCVA, which was assessed using an analysis of variance. Safety from baseline to week 76 was analyzed in the safety analysis set, which included all randomized patients who received any study treatment. Safety from week 52 to week 76 was analyzed in patients from the safety analysis set who completed week 52.

RESULTS

• **PATIENT DISPOSITION, DEMOGRAPHICS, AND BASELINE CHARACTERISTICS:** Of 240 patients screened, 106 patients were randomized to the intravitreal aflibercept group and 71

patients were randomized to the sham group.[9] A total of 104 patients (104/106, 98.1%) in the intravitreal aflibercept group and 68 patients (68/71, 95.8%) in the sham group received treatment and were included in the safety analysis set. The full analysis set included 103 patients (103/106, 97.2%) in the intravitreal aflibercept group (1 patient did not have any post-baseline BCVA score and was therefore excluded from the full analysis set) and 68 patients (68/71, 95.8%) in the sham group. A total of 16 patients (16/106, 15.1%) in the 2Q4 → PRN group and 19 patients (19/71, 26.8%) in the sham → PRN group discontinued the study before week 76. Major reasons for discontinuation in the 2Q4 → PRN group were adverse event (5 of 106 patients, 4.7%), protocol violation (5 of 106 patients, 4.7%), and withdrawal of consent (4 of 106 patients, 3.8%). Major reasons for discontinuation in the sham → PRN group were withdrawal of consent (6 of 71 patients, 8.5%), adverse event (5 of 71 patients, 7.0%), and lack of efficacy (5 of 71 patients, 7.0%). No patient in the 2Q4 → PRN group discontinued the study treatment because of a lack of efficacy. As previously described, demographics and baseline disease characteristics of patients were similar in both treatment groups.[9]

• **EFFICACY:** The proportion of patients in the 2Q4 → PRN and sham → PRN groups who gained ≥15 letters in BCVA was 60.2% vs 22.1% at week 24 (patients who discontinued before week 24 were considered to be nonresponders; $P < .0001$), 60.2% vs 32.4% at week 52 (last observation carried forward; $P < .001$), and 57.3% vs 29.4% at week 76 (last observation carried forward; $P < .001$). The mean change from baseline BCVA in the 2Q4 → PRN and sham → PRN groups was 18.0 vs 3.3 letters ($P < .0001$) at week 24, 16.9 vs 3.8 letters ($P < .0001$) at week 52, and 13.7 vs 6.2 letters ($P < .01$) at week 76 (Figure 1).

The mean change from baseline central retinal thickness in the 2Q4 → PRN and sham → PRN groups was −448.6 vs −169.3 μm ($P < .0001$) at week 24, −423.5 vs −219.3 μm ($P < .0001$) at week 52, and −389.4 vs −306.4 μm ($P = .1122$) at week 76 (Figure 2, Top). The proportion of patients in the 2Q4 → PRN and sham → PRN groups who had no retinal fluid was 80.4% vs 25.5% at week 24, 66.7% vs 30.0% at week 52, and 60.2% vs 52.0% at week 76 (Figure 2, Bottom).

During the 76-week study, 8 patients (7.8%) in the 2Q4 → PRN group and 6 patients (8.8%) in the sham → PRN group developed neovascularization. In the 2Q4 → PRN group, neovascularization occurred in the anterior segment in 7 patients (6.8%), in the optic disc in 1 patient (1.0%), and elsewhere in the fundus in 2 patients (1.9%) (neovascularization occurred in more than 1 location in 2 patients). In the sham → PRN group, neovascularization occurred in the anterior segment in 1 patient (1.5%), in the optic disk in 2 patients (2.9%), and elsewhere in the fundus in 4 patients (5.9%) (neovascularization occurred in more than 1 location in 1 patient). Panretinal photocoagulation was performed for 2 patients (1.9%) in the 2Q4 → PRN group and for 3 patients (4.4%) in the sham → PRN group.

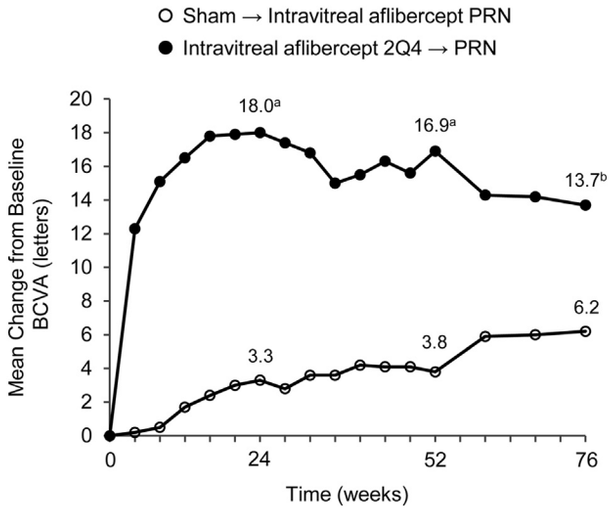
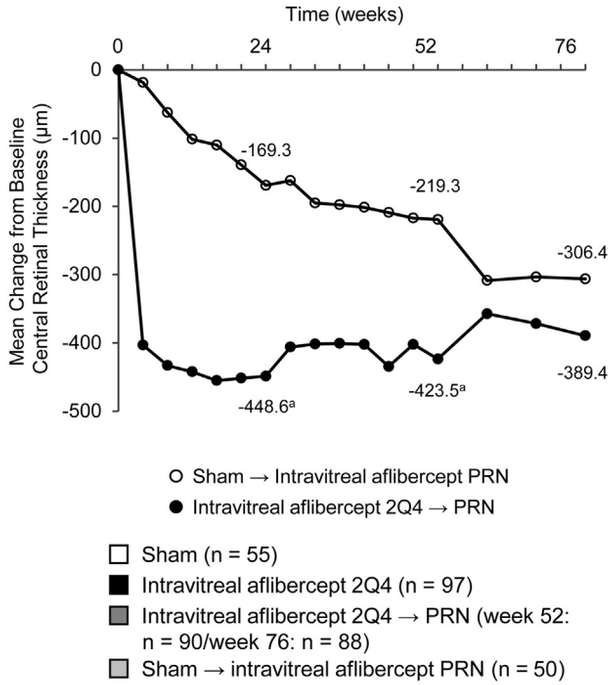


FIGURE 1. Mean change from baseline best-corrected visual acuity during the 76 weeks of study in patients with macular edema secondary to central retinal vein occlusion. Treatment frequency with intravitreal aflibercept was every 4 weeks and as needed, respectively, before and after week 24 for the intravitreal aflibercept group, and as needed from week 52 for the sham → PRN group. Monitoring frequency was every 4 weeks until week 52 and every 8 weeks from week 52 to week 76 in both treatment arms. [a]$P < .0001$ and [b]$P < .01$. Full analysis set; last observation carried forward. 2Q4 = 2 mg intravitreal aflibercept every 4 weeks; PRN = pro re nata (as needed).

Vision-related quality of life, as measured by mean changes in NEI VFQ-25 total scores from baseline, demonstrated a clinically relevant improvement (≥4-point increase) in the 2Q4 → PRN group at weeks 24, 52, and 76 (7.5, 7.8, and 7.4 points, respectively). In the sham → PRN group, improvements in NEI VFQ-25 total scores were 3.5 points at week 24, 4.5 points at week 52, and 4.9 points at week 76. The between-group differences in these scores significantly favored the 2Q4 → PRN group at all 3 visits ($P = .0013$ at week 24; $P = .0049$ at week 52; $P = .0445$ at week 76).

• **STUDY DRUG INJECTIONS:** Between week 24 and week 52, the 2Q4 → PRN group received a mean (±SD) of 2.5 ± 1.7 injections (safety analysis set) (Table 1). Between week 52 and week 76, the mean (±SD) number of intravitreal aflibercept injections in the 2Q4 → PRN group was 1.3 ± 1.1, compared with 1.7 ± 1.1 in the sham → PRN group (safety analysis set). Distribution of injections from week 52 to week 76 is presented in Figure 3.

• **SAFETY:** The percentage of patients experiencing at least 1 ocular adverse event in the study eye was



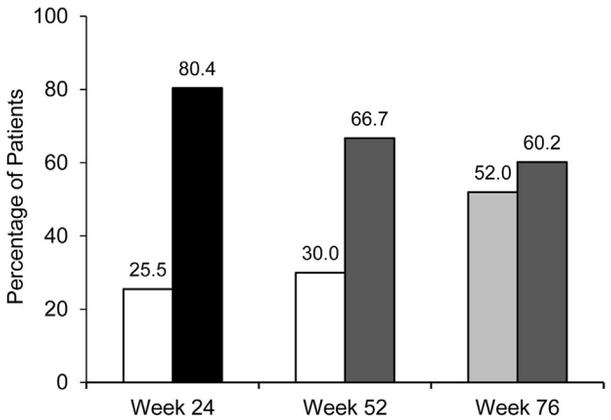


FIGURE 2. Anatomic outcomes of patients with macular edema secondary to central retinal vein occlusion during the 76 weeks of study. Mean change from baseline central retinal thickness across study visits (Top) (full analysis set; last observation carried forward), and percentage of patients without retinal fluid at weeks 24, 52, and 76 (Bottom) (full analysis set; observed values) are shown. Treatment frequency with intravitreal aflibercept was every 4 weeks and as needed, respectively, before and after week 24 for the intravitreal aflibercept group and as needed from week 52 for the sham → PRN group. Monitoring frequency was every 4 weeks until week 52 and every 8 weeks from week 52 to week 76 in both treatment arms. [a]P < .0001. 2Q4 = 2 mg intravitreal aflibercept every 4 weeks; PRN = pro re nata (as needed).

TABLE 1. Number of Intravitreal Aflibercept Injections in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion

	Mean Number of Intravitreal Aflibercept Injections		
	Baseline to Week 24	Week 24 to Week 52	Week 52 to Week 76
Sham → intravitreal aflibercept PRN	NA	NA	1.7 ± 1.1[c]
Intravitreal aflibercept 2Q4 → PRN	5.7 ± 0.9[a]	2.5 ± 1.7[b]	1.3 ± 1.1[c]

2Q4 → PRN = intravitreal aflibercept injection administered every 4 weeks from baseline to week 20 and as needed from week 24 to week 76; NA = not applicable; Sham → PRN = sham administered every 4 weeks from baseline to week 48 and intravitreal aflibercept injection administered as needed from week 52 to week 76.

[a]Full analysis set, n = 103.

[b]Safety analysis set, n = 97.

[c]Safety analysis set, n = 52 for Sham → PRN, and n = 91 for 2Q4 → PRN.

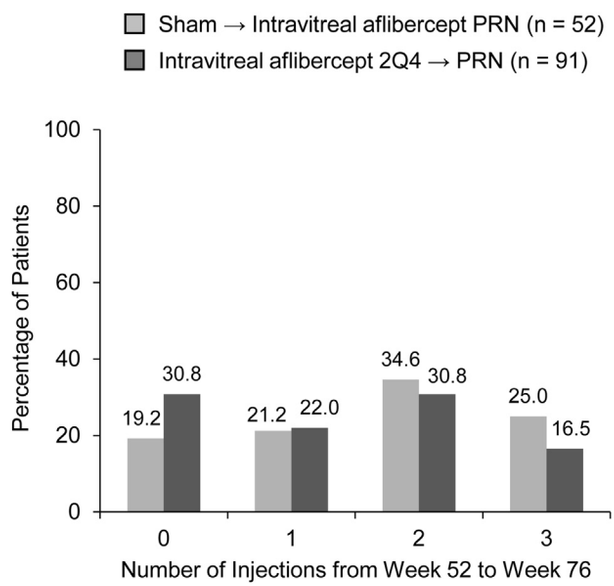


FIGURE 3. Distribution of patients with macular edema secondary to central retinal vein occlusion who received 0, 1, 2, and 3 intravitreal aflibercept injections from week 52 to week 76. During this period, patients were monitored every 8 weeks, and intravitreal aflibercept was administered to both treatment groups as needed. Safety analysis set. 2Q4 = 2 mg intravitreal aflibercept every 4 weeks; PRN = pro re nata (as needed).

78.8% in the 2Q4 → PRN group and 75.0% in the sham → PRN group from baseline to week 76, and 48.4% and 48.1%, respectively, from week 52 to week 76. The most common ocular adverse events reported for the study eye in the 2Q4 → PRN group as compared with the sham → PRN group were macular edema

TABLE 2. Ocular Serious Adverse Events Occurring From Baseline to Week 76 and From Week 52 to Week 76 in Study Eyes of Patients With Macular Edema Secondary to Central Retinal Vein Occlusion

	Baseline to Week 76[a]		Week 52 to Week 76[b]	
	Sham → Intravitreal Aflibercept PRN (n = 68)	Intravitreal Aflibercept 2Q4 → PRN (n = 104)	Sham → Intravitreal Aflibercept PRN (n = 52)	Intravitreal Aflibercept 2Q4 → PRN (n = 91)
Patients with ≥1 ocular serious adverse event in study eye, n (%)	6 (8.8)	11 (10.6)	0 (0)	2 (2.2)
Macular edema	2 (2.9)	4 (3.8)	0 (0)	1 (1.1)
Reduced visual acuity	1 (1.5)	2 (1.9)	0 (0)	2 (2.2)
Glaucoma	2 (2.9)	0 (0)	0 (0)	0 (0)
Vitreous hemorrhage	1 (1.5)	1 (1.0)	0 (0)	0 (0)
Unilateral blindness	0 (0)	1 (1.0)	0 (0)	0 (0)
Iris neovascularization	0 (0)	1 (1.0)	0 (0)	0 (0)
Macular fibrosis	0 (0)	1 (1.0)	0 (0)	0 (0)
Macular ischemia	0 (0)	1 (1.0)	0 (0)	0 (0)
Retinal vein occlusion	0 (0)	1 (1.0)	0 (0)	0 (0)
Vitreous detachment	0 (0)	1 (1.0)	0 (0)	0 (0)

2Q4 → PRN = intravitreal aflibercept injection administered every 4 weeks from baseline to week 20 and as needed from week 24 to week 76; Sham → PRN = sham administered every 4 weeks from baseline to week 48 and intravitreal aflibercept injection administered as needed from week 52 to week 76.

[a]Safety analysis set.

[b]Week 52 completers within safety analysis set.

(39.4% vs 25.0%, respectively), conjunctival hemorrhage (17.3% vs 7.4%, respectively), and retinal hemorrhage (15.4% vs 11.8%, respectively) from baseline to week 76, and macular edema (23.1% vs 5.8%, respectively), reduced visual acuity (9.9% vs 1.9%, respectively), conjunctival hemorrhage (8.8% vs 5.8%, respectively), and retinal hemorrhage (8.8% vs 5.8%, respectively) from week 52 to week 76. Ocular serious adverse events are shown in Table 2.

The percentage of patients experiencing at least 1 nonocular adverse event was 68.3% in the 2Q4 → PRN group and 73.5% in the sham → PRN group from baseline to week 76, and 27.5% and 38.5%, respectively, from week 52 to week 76. Nasopharyngitis was the most commonly reported nonocular adverse event in both 2Q4 → PRN and sham → PRN groups from baseline to week 76 (15.4% vs 25.0%, respectively) and from week 52 to week 76 (3.3% vs 5.8%, respectively). Nonocular serious adverse events occurred with a similar frequency in both the 2Q4 → PRN and sham → PRN groups from baseline to week 76 (11.5% and 14.7%, respectively) and from week 52 to week 76 (2.2% and 5.8%, respectively). Nonocular serious adverse events reported for more than 1 patient were syncope (1 patient in the 2Q4 → PRN group and 2 patients in the sham → PRN group), pneumonia (1 patient in each treatment group), and humerus fracture (1 patient in each treatment group) from baseline to week 76. There were no adverse events adjudicated as Antiplatelet Trialists' Collaboration–defined arterial thromboembolic events during the course of study. No deaths occurred during the 76 weeks of this study.

DISCUSSION

TREATMENT OF MACULAR EDEMA SECONDARY TO CRVO with 6 monthly intravitreal aflibercept injections resulted in significant improvements in BCVA and central retinal thickness that were largely maintained with extension of treatment intervals. Up to week 52, the intervals were extended in increments of 1 month as patients were monitored every month. Beyond week 52, patients were monitored only every 2 months, meaning that the PRN treatment interval was extended at increments of 8 weeks at a minimum. This extended 8-week monitoring interval resulted in some decline in visual and anatomic gains from week 52 through week 76. A similar trend was also observed in the percentage of patients in the 2Q4 → PRN group with no retinal fluid. These findings suggest that (1) the treatment interval can be extended after treatment initiation with monthly doses, but (2) the monitoring and treatment interval should be chosen carefully on an individualized basis.

The COPERNICUS study was a parallel trial to GALILEO, differing in the timing of the intravitreal aflibercept administration in the sham group. In COPERNICUS, patients in the control group received sham for

only 20 weeks, after which they received intravitreal aflibercept PRN, whereas sham patients from the GALILEO study did not receive intravitreal aflibercept PRN until week 52. Overall, the COPERNICUS study demonstrated similar effects to those seen in the current study in visual and anatomic improvements with intravitreal aflibercept injections after switching from monthly dosing and PRN dosing with monthly monitoring to PRN dosing with less-than-monthly monitoring in patients with macular edema secondary to CRVO.[7,8,14] As with the current study, the COPERNICUS study showed a continued superiority of the 2Q4 → PRN group over the sham → PRN group in visual outcomes despite the improvement in visual outcomes seen in the sham group after PRN dosing with intravitreal aflibercept.[7,8,14] These findings suggest that patients with macular edema secondary to CRVO may benefit from receiving intravitreal aflibercept early following the initial event.

The approach of monthly intravitreal injections followed by PRN dosing with monthly monitoring and then less-than-monthly monitoring has also been used in the CRUISE trial, which evaluated intravitreal ranibizumab for treatment of macular edema secondary to CRVO.[5,6] Similar to the GALILEO and COPERNICUS studies of intravitreal aflibercept, the CRUISE trial demonstrated visual and anatomic improvements with monthly ranibizumab injections that were largely maintained during the period of PRN dosing, albeit with some decrease of gains over the second year with the introduction of extended monitoring intervals (HORIZON extension study).[5,6,15]

The very favorable outcomes from clinical trials of anti-VEGF agents in CRVO[14,15] requires the applied treatment algorithms to be translated into practice. While a clinical trial setting comes with certain requirements, such as fixed, predefined monitoring intervals in order to maintain masking, these constraints do not exist in routine clinical practice, and a treat-and-extend regimen may be an option to treat patients successfully, as in the clinical trials, with an extended interval without putting the burden of monthly office visits on patients and physicians. In a treat-and-extend regimen, the initial fixed monthly dosing phase is followed by a maintenance phase, once improvements in visual and anatomic outcomes have stabilized, where treatment intervals can be carefully extended in small increments, guided by the visual and anatomic measures. Ophthalmic examinations will still be performed, but they will be used to guide the decision regarding the length of the interval until the next treatment, rather than determining treatment at the same visit. This regimen constitutes a reasonable way to translate the trial regimen into practice, as it allows for a tailored approach for individual patients with a proactive component, while reducing the monitoring burden and maintaining visual and anatomic gains.

In this study, intravitreal aflibercept was generally well tolerated, and the most common adverse events were those typically associated with intravitreal injections or the underlying disease. The occurrence of serious adverse event of macular edema in patients treated with intravitreal aflibercept was likely attributable to the disease progression and/or lack of response to the treatment. Overall, there were no clinically relevant differences between the treatment groups in terms of frequency or pattern of ocular and nonocular serious adverse events.

In conclusion, GALILEO results show that intravitreal aflibercept injection is efficacious in the treatment of macular edema secondary to CRVO. Early treatment is important for optimal outcomes in patients with macular edema secondary to CRVO. After fixed initial monthly injections, the vision gains are largely maintained, if the treatment interval is extended based on visual and anatomic outcomes.

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A list of study investigators has been provided in an Appendix, as Supplemental Material, available at AJO.com.

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APPENDIX. GALILEO STUDY INVESTIGATORS AND LOCATIONS

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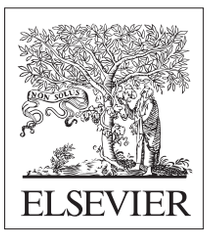

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