Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion

One-Year Results of the Phase 3 GALILEO Study

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

Design: A randomized, multicenter, double-masked phase 3 study.

Participants: A total of 177 treatment-naive patients with macular edema secondary to CRVO were randomized in a 3:2 ratio.

Methods: Patients received either 2-mg intravitreal aflibercept or sham injections every 4 weeks for 20 weeks. From week 24 to 48, the aflibercept group received aflibercept as needed (pro re nata [PRN]), and the sham group continued receiving sham injections.

Main Outcome Measures: The primary efficacy end point was the proportion of patients who gained 15 letters or more in best-corrected visual acuity (BCVA) at week 24. This study reports week 52 results including the proportion of patients who gained 15 letters or more in BCVA and the mean change from baseline BCVA and central retinal thickness. Efficacy end points at week 52 were all exploratory.

Results: At week 52, the mean percentage of patients gaining 15 letters or more was 60.2% in the aflibercept group and 32.4% in the sham group ($P = 0.0004$). Aflibercept patients, compared with sham patients, had a significantly higher mean improvement in BCVA (+16.9 letters vs. +3.8 letters, respectively) and reduction in central retinal thickness (−423.5 μm vs. −219.3 μm, respectively) at week 52 ($P < 0.0001$ for both). Aflibercept patients received a mean of 2.5 injections (standard deviation, 1.7 injections) during PRN dosing. The most common ocular adverse events in the aflibercept group were related to the injection procedure or the underlying disease, and included macular edema (33.7%), increased intraocular pressure (17.3%), and eye pain (14.4%).

Conclusions: Treatment with intravitreal aflibercept provided significant functional and anatomic benefits after 52 weeks as compared with sham. The improvements achieved after 6 monthly doses at week 24 largely were maintained until week 52 with as-needed dosing. Intravitreal aflibercept generally was well tolerated. *Ophthalmology 2014;121:202-208 © 2014 by the American Academy of Ophthalmology.*

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The most common cause of vision loss in patients with central retinal vein occlusion (CRVO) is macular edema, which resolves spontaneously in only 30% of nonischemic cases and may not resolve in ischemic cases.[1,2] Several lines of evidence indicate that vascular endothelial growth factor (VEGF) may play a key role in the pathophysiology of macular edema secondary to CRVO. Vascular endothelial growth factor is released in response to retinal hypoxia, which occurs in CRVO as a result of impaired capillary blood flow.[3] Vascular endothelial growth factor stimulates angiogenesis and may result in neovascularization of the retina, the anterior segment, or both, as well as vascular leakage resulting in macular edema.[3] In CRVO patients, the vitreous level of VEGF correlates with the severity of macular edema.[4] Furthermore, intravitreal injections of the anti-VEGF agents ranibizumab or aflibercept significantly improve visual and anatomic outcomes in patients with macular edema secondary to CRVO.[5–9]

Intravitreal aflibercept (historically known in the scientific literature as VEGF Trap-Eye; Regeneron Pharmaceuticals, Inc, Tarrytown, NY, and Bayer Healthcare Pharmaceuticals, Berlin, Germany) is a fusion protein of key domains from human VEGF receptors 1 and 2 with the

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constant region (Fc) of human immunoglobulin G that binds to multiple VEGF-A isoforms with a higher affinity than ranibizumab and bevacizumab.[10] Studies of intravitreal aflibercept injections in patients with neovascular age-related macular degeneration (AMD) demonstrate that aflibercept given monthly for 3 initial administrations and then once every 2 months improves visual and anatomic outcomes as effectively and safely as monthly ranibizumab over a 1-year period.[11] The efficacy and safety of intravitreal aflibercept for the treatment of macular edema secondary to CRVO was investigated in 2 parallel trials performed in Europe and in the Asia Pacific region (GALILEO) and in the United States (COPERNICUS).[5,7,9] The primary efficacy end point of the GALILEO study was at week 24 and was published previously.[9] Herein, we report the 52-week results of the GALILEO study.

Methods

Study Design

The GALILEO study is an 18-month, randomized, double-masked, phase 3 study comparing the efficacy and safety of intravitreal aflibercept with sham for the treatment of macular edema secondary to CRVO. The study protocol was approved by the institutional review board or ethics committee 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 across 63 sites in Europe and the Asia Pacific region in compliance with ethical guidelines from the Declaration of Helsinki and International Conference on Harmonization. Data for this 52-week report were collected between October 2009 and July 2011.

The design and eligibility criteria for the GALILEO study have been described previously.[9] Only 1 eye from each patient was included in the study. Patients were randomized in a 3:2 ratio to receive 2 mg intravitreal aflibercept (IVT-AFL 2Q4) or sham injections in the study eye once every 4 weeks for 20 weeks, for a total of 6 doses (Fig 1). From weeks 24 to 52, patients in the aflibercept group were evaluated monthly and received aflibercept as needed (pro re nata [PRN]; IVT-AFL 2Q4 + PRN) if they had more than a 50-μm increase in central retinal thickness (CRT) compared with the lowest previous measurement, new or persistent cystic changes within the neurosensory retina or subretinal fluid, persistent diffuse edema of 250 μm or more in the central subfield, loss of 5 letters or more from the best prior measurement in conjunction with any increase in CRT, or an increase of 5 letters or more in best-corrected visual acuity (BCVA) from the most recent visit, potentially suggesting further improvements on a subsequent injection. If none of the retreatment criteria were met, patients received a sham injection to maintain masking. Patients in the sham group continued to receive sham injections at all visits through week 52. 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 fundus. Given that there was no approved treatment for CRVO when the GALILEO study was designed, no other rescue treatment was prespecified. The GALILEO study design included a full year of treatment with sham based on the request from health authorities. However, considering this long duration of sham treatment, the visual acuity and other ocular findings were monitored carefully by a team of masked medical reviewers. If, at any time, this review team had the impression that a patient may not benefit from further study participation or would be treated more adequately outside the study, the investigator was queried and asked to provide a reassessment of the patient. Investigators then used their medical judgment ultimately to determine whether it would still be beneficial for the patient to continue the study.

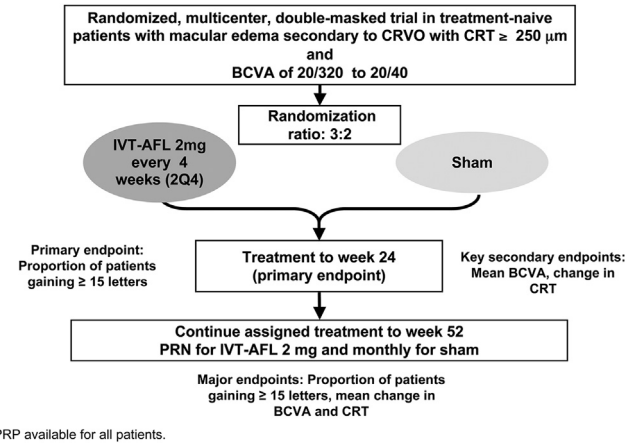

Figure 1. Diagram showing the GALILEO study design. BCVA = best-corrected visual acuity; CRT = central retinal thickness; CRVO = central retinal vein occlusion; IVT-AFL = intravitreal aflibercept; PRN = pro re nata (as needed); PRP = panretinal photocoagulation; 2Q4 = every 4 weeks.

Outcome Measures

The primary efficacy end point of the GALILEO study was the proportion of patients achieving a gain of 15 letters or more in BCVA from baseline to week 24, which was published previously.[9] Herein, we report the 52-week results of the GALILEO study. Efficacy end points at week 52 all were exploratory and included the proportion of patients who gained 15 letters or more in BCVA; mean change from baseline 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 25-item National Eye Institute Visual Function Questionnaire total and subscale (distance activities, near activities, and vision dependency) scores.

The efficacy and safety end points were assessed as described previously.[9] The BCVA and CRT were assessed at baseline and every 4 weeks afterward to week 52. Fundus photography and fluorescein angiography were performed at screening (days −21 to −1) and weeks 12, 24, 36, and 52. Retinal perfusion status was determined by fluorescein angiography. Perfused and nonperfused retinas were defined as those with less than 10 disc areas and 10 disc areas or more, respectively, of capillary nonperfusion on fluorescein angiography. Vision-related quality of life was assessed at baseline and weeks 24 and 52 using the 25-item National Eye Institute Visual Function Questionnaire, which was administered by masked site personnel before intravitreal injections.

Statistical Analyses

The efficacy end points were analyzed in the full analysis set (FAS), which included all randomized patients who received any study treatment and had a baseline and at least 1 postbaseline BCVA assessment. In a prespecified analysis of proportions of patients who gained 15 letters or more at week 24 (the primary efficacy end point), patients who discontinued before week 24 were

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considered to be nonresponders. In a prespecified analysis of proportions of patients who gained 15 letters or more at week 52, the missing values were imputed by the last-observation-carried-forward method. Between-group differences in the proportion of patients who gained 15 letters or more 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. The last-observation-carried-forward approach was used to impute missing values. For sensitivity, additional analyses were performed using observed values at week 52. The proportion of patients with neovascularization by week 52 was analyzed using a Cochran-Mantel-Haenszel test. Safety from baseline to week 24 was analyzed in the safety analysis set, which included all randomized patients who received any study treatment. Safety from weeks 24 to 52 was analyzed in week 24 completers within the safety analysis set.

Results

Of 240 patients screened, 106 patients were randomized to the IVT-AFL 2Q4 + PRN group, and 71 patients were randomized to the sham group. A total of 104 (98.1%) patients in the IVT-AFL 2Q4 + PRN group and 68 (95.8%) patients in the sham group were treated in the study and were included in the safety analysis set. One patient did not have any postbaseline BCVA value, and therefore was excluded from the FAS. Thus, the FAS included 103 patients in the IVT-AFL 2Q4 + PRN group and 68 patients in the sham group. Overall, 15 (14.2%) patients in the IVT-AFL 2Q4 + PRN group and 19 (26.8%) patients in the sham group discontinued the study before week 52. Major reasons for discontinuation in the IVT-AFL 2Q4 + PRN group were protocol violation (5 patients [4.7%]), withdrawal of consent (4 patients [3.8%]), and adverse events (4 patients [3.8%]). Major reasons for discontinuation in the sham group were lack of efficacy (6 patients [8.5%]), withdrawal of consent (6 patients [8.5%]), and adverse events (4 patients [5.6%]). No patient in the IVT-AFL 2Q4 + PRN group discontinued the study treatment because of a lack of efficacy.

Demographics and baseline disease characteristics of patients were similar in both treatment groups.[9] Approximately half of patients had CRVO for less than 2 months (53.4% in the IVT-AFL 2Q4 + PRN group and 51.5% in the sham group, FAS). Most patients had a perfused retina (86.4% in the IVT-AFL 2Q4 + PRN group and 79.4% in the sham group) and a baseline BCVA of 35 letters or better (>20/200; 83.5% in the IVT-AFL 2Q4 + PRN group and 82.4% in the sham group).[9]

Visual Outcomes

At week 24, the proportion of patients who gained 15 letters or more in BCVA was 60.2% and 22.1% in the IVT-AFL 2Q4 and sham groups, respectively (patients who discontinued before week 24 were considered to be nonresponders; $P < 0.0001$).[9] At week 52, the proportion of patients who gained 15 letters or more in BCVA was 60.2% in the IVT-AFL 2Q4 + PRN group versus 32.4% in the sham group (last observation carried forward; Fig 2A). More patients in the sham group had 15 letters or more of improvement in BCVA at week 52 compared with week 24 (32.4% vs. 22.1%, respectively). At week 52, patients treated with IVT-AFL 2Q4 + PRN maintained the improvements in BCVA achieved at week 24.

The proportion of patients who gained 10 or more letters and 30 or more letters or those who lost more than 0, more than 10, and more than 15 letters at week 52 are shown in Table 1. Overall, higher proportions of sham patients lost more than 0, more than 10, and more than 15 letters compared with patients treated with IVT-AFL 2Q4 + PRN at week 52 (Table 1).

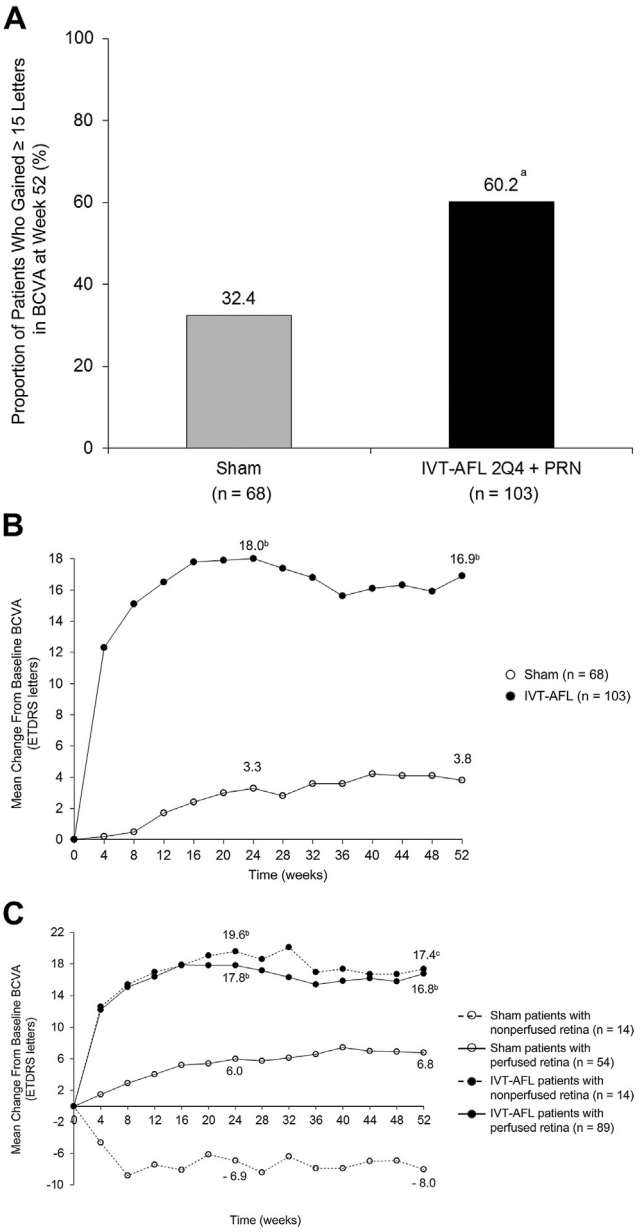

Figure 2. Graphs showing visual outcomes during the 52 weeks of the study: (**A**) percentage of patients who gained 15 letters or more at week 52, (**B**) mean change from baseline best-corrected visual acuity (BCVA), and (**C**) mean change from baseline BCVA by the status of retinal perfusion at baseline. Treatment frequency with intravitreal aflibercept (IVT-AFL) was every 4 weeks (2Q4) and pro re nata (PRN; as needed), respectively, before and after week 24. [a]$P = 0.0004$ vs. sham; [b]$P < 0.0001$ vs. sham; [c]$P < 0.001$ vs. sham. ETDRS = Early Treatment Diabetic Retinopathy Study.

The mean change from baseline BCVA in the IVT-AFL 2Q4 + PRN and sham groups was 18.0 versus 3.3 letters at week 24 and 16.9 versus 3.8 letters at week 52 ($P < 0.0001$ for both; Fig 2B). When stratified by the baseline retinal perfusion status, patients treated with IVT-AFL 2Q4 + PRN had a similar mean ± standard deviation (SD) change from baseline BCVA in the perfused and nonperfused subgroups (+16.8±14.7 letters vs. +17.4±16.1

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Table 1. Patients with Vision Gain and Loss at Week 52

	Week 52	
	Sham (n = 68)	*Intravitreal Aflibercept Injection Monthly from Baseline to Week 24 plus Pro Re Nata Treatment from Weeks 24 to 52 (n = 103)*
Vision gain, n (%)		
≥30 letters	5 (7.4)	15 (14.6)
≥15 letters	22 (32.4)	62 (60.2)
≥10 letters	26 (38.2)	74 (71.8)
Vision loss, n (%)		
>0 letters	30 (44.1)	11 (10.7)
>10 letters	16 (23.5)	1 (1.0)
>15 letters	10 (14.7)	1 (1.0)

letters, respectively; Fig 2C). In contrast, eyes with a perfused retina in the sham group gained a mean ± SD of 6.8±17.5 letters, whereas those with a nonperfused retina lost a mean of 8.0±15.8 letters at 52 weeks (Fig 2C). Regardless of the treatment group, patients with a baseline BCVA of 20/200 or worse had a greater BCVA gain than those with a baseline BCVA of better than 20/200 (9.4 vs. 2.5 letters for sham and 21.1 vs. 16.0 letters for IVT-AFL 2Q4 + PRN, respectively). Patients who had the disease for less than 2 months in the sham and IVT-AFL 2Q4 + PRN groups gained a mean of 2.1 letters and 19.5 letters from baseline, respectively, whereas those having the disease for 2 months or more gained a mean of 5.5 letters and 13.7 letters from baseline, respectively.

Anatomic Outcomes

At week 24, the mean CRT reduction from baseline was 448.6 μm and 169.3 μm in the IVT-AFL 2Q4 and sham groups, respectively ($P < 0.0001$). With the start of PRN dosing at week 24, CRT slightly increased in the IVT-AFL 2Q4 + PRN group, but then remained stable through week 52 (Fig 3). At week 52, the mean CRT reduction from baseline was significantly greater in the IVT-AFL 2Q4 + PRN group than in the sham group (423.5 μm vs. 219.3 μm, respectively; $P < 0.0001$). Regardless of the retinal perfusion status, patients treated with IVT-AFL 2Q4 + PRN had a greater CRT reduction (±SD) than those treated with sham (412.4±238.1 μm vs. 201.2±226.4 μm for the perfused subgroup and 494.6±318.4 μm vs. 294.3±258.6 μm for the nonperfused subgroup, respectively). During the 52-week study, 6 (5.8%) patients in the IVT-AFL 2Q4 + PRN group and 6 (8.8%) patients in the sham group developed neovascularization. In each group, 3 patients had a nonperfused retina at baseline, and 5 had disease duration of less than 2 months at baseline. In the IVT-AFL 2Q4 + PRN group, 4 patients demonstrated anterior segment neovascularization, 1 patient demonstrated neovascularization elsewhere in the fundus, and 1 patient demonstrated neovascularization both in anterior segment and elsewhere in the fundus. In the sham group, 4 patients demonstrated neovascularization of elsewhere in the fundus, 1 patient demonstrated anterior segment neovascularization, and 1 patient demonstrated neovascularization of optic disc. Panretinal photocoagulation was performed for 3 (4.4%) of the sham patients and 2 (1.9%) of the IVT-AFL 2Q4 + PRN patients.

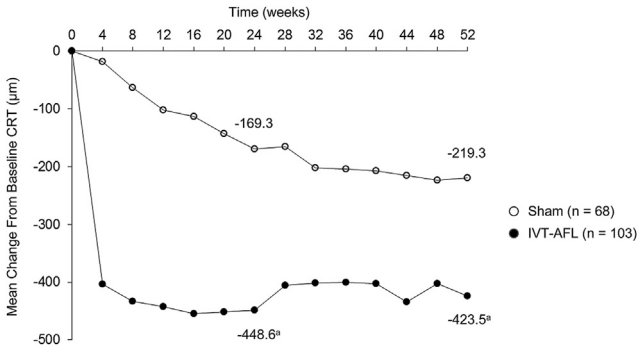

Figure 3. Graph showing the mean change from baseline central retinal thickness (CRT) during the 52 weeks of the study. Treatment frequency with intravitreal aflibercept (IVT-AFL) was every 4 weeks and pro re nata (as needed), respectively, before and after week 24. [a]$P<0.0001$ vs. sham.

Patient-Reported Outcomes

A clinically relevant improvement in the mean 25-item National Eye Institute Visual Function Questionnaire total score (≥4-point increase) was observed in both IVT-AFL 2Q4 + PRN group (7.8 points) and sham group (4.5 points) at week 52 (Table 2). The mean change from baseline to week 52 in near activities subscore was the highest among subscales, with IVT-AFL 2Q4 + PRN patients reporting a mean change of 12.2 points versus sham patients reporting a mean change of 5.0 points. No difference was noted between the 2 groups in the dependency subscale.

Study Drug Injections

During the 52 weeks of treatment, the mean (±SD) number of injections was 11.8±2.8 in the IVT-AFL 2Q4 + PRN group and 10.5±4.2 in the sham group. Most IVT-AFL 2Q4 + PRN patients (64 of 91 patients completing week 52 [70.3%]) received 3 or fewer IVT-AFL injections during weeks 24 to 52, with a mean ± SD of 2.5±1.7 injections during the PRN phase of study (Table 3). Patients who received 3 PRN injections or fewer had relatively higher BCVA gains than those who received 4 to 6 injections (Table 3). The median time to the first PRN intravitreal aflibercept injection was 83 days (95% confidence interval, 62−88 days).

Safety

The percentage of patients experiencing at least 1 ocular treatment-emergent adverse event (TEAE) in the sham and intravitreal aflibercept groups was 64.7% and 54.8% from baseline to week 24 and 50.9% and 69.1% from week 24 to week 52, respectively. The most common ocular TEAEs reported for the study eye in the intravitreal aflibercept group as compared with the sham group were eye pain (11.5% vs. 4.4%, respectively), increased intraocular pressure (8.7% vs. 5.9%, respectively), and conjunctival hemorrhage (8.7% vs. 4.4%, respectively) from baseline to week 24 and worsening of macular edema (35.1% vs. 10.5%, respectively), increased intraocular pressure (13.4% vs. 3.5%, respectively), and reduced visual acuity (11.3% vs. 1.8%, respectively) from weeks 24 to 52. All adverse events of intraocular pressure elevation were mild, except for 1 severe event that occurred in a sham patient before week 24. Ocular treatment-emergent serious adverse events (SAEs) are shown in Table 4. 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 SAEs.

The incidence of nonocular TEAEs was similar in the sham and intravitreal aflibercept groups from baseline to week 24 (54.4% and 45.2%, respectively) and from weeks 24 to 52 (50.9% vs. 51.5%, respectively). Nasopharyngitis was the most commonly reported nonocular TEAE in both the sham and intravitreal aflibercept groups from baseline to week 24 (8.8% vs. 7.7%, respectively) and from weeks 24 to 52 (19.3% vs. 9.3%, respectively). Nonocular SAEs occurred in a small group of patients with a similar frequency in both the sham and intravitreal aflibercept groups from

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Table 2. Change from Baseline to Weeks 24 and 52 in the National Eye Institute 25-Item Visual Function Questionnaire Score

	Baseline to Week 24*				Baseline to Week 52†			
	Mean Change				Mean Change			
	Sham	Intravitreal Aflibercept Injection Monthly from Baseline to Week 24	Difference in Least Square Mean Change (95% Confidence Interval)	P Value	Sham	Intravitreal Aflibercept Injection Monthly from Baseline to Week 24 Plus PRN Treatment from Week 24 to 52	Difference in Least Square Mean Change (95% Confidence Interval)	P Value
Total score	3.5	7.5	4.2 (1.7−6.8)	0.0013	4.5	7.8	3.6 (1.1−6.0)	0.0049
Distance activities subscore	2.4	6.3	3.5 (−0.3 to 7.2)	0.0689	3.9	8.4	4.2 (0.4−7.9)	0.0283
Near activities subscore	1.6	10.4	8.6 (4.0−13.2)	0.0003	5.0	12.2	6.9 (3.1−10.8)	0.0005
Dependency subscore	2.4	3.7	2.1 (−1.6 to 5.8)	0.2552	3.1	3.8	1.6 (−1.7 to 4.8)	0.3423

PRN = pro re nata (as needed).
*n = 65 for sham and n = 96 for intravitreal aflibercept injection monthly from baseline to week 24.
†n = 67 for sham and n = 97 for intravitreal aflibercept injection monthly from baseline to week 24 plus PRN treatment from week 24 to 52 (except for the total score, which was n = 98).

baseline to week 24 (7.4% and 5.8%, respectively) and from weeks 24 to 52 (8.8% and 6.2%, respectively). None of the nonocular SAEs were reported for more than 1 patient from baseline to week 24. During weeks 24 to 52, nonocular SAEs reported for more than 1 patient were pneumonia (1 patient in each treatment group) and syncope (2 patients in the sham group and 1 patient in the aflibercept group). No adverse event was adjudicated as an Anti-Platelet Trialists' Collaboration-defined arterial thromboembolic event during the course of study. There were no deaths during the 52 weeks of this study.

Discussion

The findings of the current study demonstrate that the improvements in BCVA and CRT achieved with monthly intravitreal aflibercept injections in the first 24 weeks of treatment largely were maintained during the PRN (as-needed) phase of study, with monthly monitoring and a mean of 2.5 injections from weeks 24 to 52. Of note, there was also a marked improvement in BCVA with aflibercept in a subgroup of patients with nonperfused retinas at baseline, in contrast to a particularly poor response in the sham group. The visual improvements with aflibercept enhanced vision-related quality of life, particularly in near visual activities. In this study, aflibercept generally was well tolerated, and the most common adverse events were those typically associated with intravitreal injections or the underlying disease. The increase in macular edema seen in aflibercept patients during the PRN dosing phase suggests that some patients would have benefited from more regular dosing, rather than being treated in response to the recurrence of disease.

The sister study of GALILEO, the COPERNICUS study, demonstrated comparable improvements in BCVA and CRT with intravitreal aflibercept injections.[5,7] However, the sham groups in the 2 studies were not comparable during weeks 24 to 52 because, in the COPERNICUS study, sham patients received aflibercept PRN starting from week 24, whereas in the GALILEO study, sham patients continued to receive sham treatments through week 52. In the COPERNICUS study, patients receiving sham plus IVT-AFL PRN

Table 3. Distribution of Pro Re Nata Injections during Weeks 24 through 52 and Best-Corrected Visual Acuity Gains at Week 52 in Patients Treated with Intravitreal Aflibercept Injection Every 4 Weeks from Baseline to Week 24 and Pro Re Nata from Weeks 24 to 52

No. of Pro Re Nata Injections	Intravitreal Aflibercept Patients, n (%; n = 91*)	Change (Standard Deviation) from Baseline in Best-Corrected Visual Acuity at Week 52,† No. of Letters
0	13 (14.3)	19.8 (11.4)‡
1	12 (13.2)	
2	18 (19.8)	21.1 (12.8)§
3	21 (23.1)	
4	17 (18.7)	13.1 (13.5)‖
5	3 (3.3)	
6	7 (7.7)	

BCVA = best-corrected visual acuity; SD = standard deviation.
*Patients completing week 52.
†Because of the small number of patients in each injection category, BCVA gains at week 52 were shown for patients who received 0 to 1, 2 to 3, and 4 to 6 injections. The mean BCVA ± SD at baseline was 58.2±15.5 letters, 49.4±15.9 letters, and 55.4±15.0 letters for patients who received 0 to 1, 2 to 3, and 4 to 6 injections, respectively.
‡For both 0 and 1 injection categories.
§For both 2 and 3 injections categories.
‖For 4 to 6 injections categories.

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